B6

From: Huma Abedin [redacted]
Sent: Sunday, February 22, 2009 12:16 AM
To: humamabedin [redacted]
Subject: PrFw:

RELEASE IN PART B6

-----Original Message-----
From: H <hdr22@clintonemail.com>
To: Huma Abedin
Sent: Sat Feb 21 23:48:07 2009
Subject: Fw:

Pls print.
------Original Message------
From: Bill Owens
To: 'hdr22@clintonemail.com'
Sent: Feb 21, 2009 6:38 PM
Subject:

Dear Hillary,

I think your "listening tour" has been inspiring to all of us who have cared about our relationships with Asia. I had dinner last night in Beijing with about a dozen very well placed senior generals and politicians. You would have liked their comments about your visit. I'm proud of what you're doing and always here to help when I can. It was very nice to see you at the Embassy. After such an arduous trip, I thought you were great with the staff/Marines/Peace Corps (and the kids!).

I hope you'll have a chance to think about the "complementary engagement" one pager on mil/econ/political friendships (which I'm afraid I too quickly passed to you). I think the effort is helpful to what you're doing on a more formal level.

Warm best wishes, I'm cheering for you, Bill Owens

From: Huma Abedin [redacted] B6
Sent: Sunday, February 22, 2009 12:16 AM
To: humamabedin [redacted]
Subject: PrFw: Fwd: a second memo
Attach: McHale Memo II to SecState 02.19.09.doc

RELEASE IN PART B6

-----Original Message-----
From. H <hdr22@clintonemail com>
To: Huma Abedin
Sent: Sat Feb 21 23 48.38 2009
Subject: Fw Fwd: a second memo

P <<McHale Memo II to SecState 02.19.09.doc>> ls print.

From: williamsbarret [redacted]
Date Sat, 21 Feb 2009 18:28:16 -0500
To: <hdr22@clintonemail.com>, <cmills [redacted]
Subject Fwd a second memo

This is second memo prepared by Judith - follow up to the first. m

---

From: Roy Spence [redacted] B6
Sent: Sunday, February 22, 2009 4:45 PM
To: hdr22@clintonemail.com
Cc: Hillary Clinton <hr15@att.blackberry net>
Subject: Madame Sis-Your trip was incredible. Of course I was not there...

RELEASE IN PART
B6

But the look and feel and the out pouring of "love and respect for you" and your core purpose of standing for the ideal that everyone should have the opportunity to live up his or her god-given potential-may not spoken-but from the visuals and the blogs ---was deeply displayed...especially with the women and young women. I simply do not know quite how you keep doing all the good you do...but I thank God for you [redacted]

[redacted] Maggie/Cheryl and team is moving the Gallup world poll stuff forward-Judy and I met with them 2 times. The data is stunning.
Like you...

Love you-your devoted Bro!!!

RS
Ride at Dawn

From: H <hdr22@clintonemail.com>
Sent: Sunday, February 22, 2009 6:39 PM
To: Maggie Williams [redacted] B6
Subject: Re: Fwd. a second memo

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B6

I just landed and will have these printed I'd like to set up a time to meet w you and Judith soon Hope all is well

From: williamsbarrett[redacted]
Date: Sat, 21 Feb 2009 18:28 16 -0500
To: <hdr22@clintonemail.com>; <cmill[redacted]
Subject: Fwd a second memo

This is second memo prepared by Judith - follow up to the first. m

From: Strobe Talbott [redacted]
Sent: Sunday, February 22, 2009 7:51 PM
To: HRC <hr15@att.blackberry.net>
Subject: an early rave review is already in...

B6

RELEASE IN PART B6

Andrea Mitchell came by our house straight from Andrews (to pick up Alan who was here for a book party), and she was exceedingly positive about how the trip played within the press corps in the back of the plane. And she's not a pushover on such things. So by that standard, as well as others, feel good. And welcome home. S.

==========

Strobe Talbott
President, The Brookings Institution
1775 Massachusetts Avenue NW
Washington, DC 20036
[redacted]

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B6

RELEASE IN PART
B6

From: H <hdr22@clintonemail.com>
Sent: Sunday, February 22, 2009 9:31 PM
To: Cheryl Mills
Subject: Re: Can we talk tonight?

Great. Are you calling secure?
------Original Message------
From: Cheryl Mills
To: hdr22@clintonemail.com
Sent Feb 22, 2009 8:58 PM
Subject: Re: Can we talk tonight?

I can do now

-----Original Message-----
From. H <hdr22@clintonemail.com>
To: Cheryl Mills
Sent: Sun Feb 22 18:37:51 2009
Subject Can we talk tonight?

I just landed and will be home shortly We can try a secure call at your convenience. Let me know what time works.

From: H <hdr22@clintonemail com> B6
Sent: Sunday, February 22, 2009 9:54 PM
To: Cheryl Mills
Subject: Re: Can we talk tonight?

RELEASE IN PART
B6

I'm holding on a secure line. Are you also trying to get on?
------Original Message------
From: Cheryl Mills
To: hdr22@clintonemail.com
Sent: Feb 22, 2009 9 39 PM
Subject: RE. Can we talk tonight?

they were supposed to connect us - I called some time ago to do a secure call with you -- call them and ask them to try the connection

-----Original Message-----
From. H [mailto:hdr22@clintonemail com]
Sent: Sunday, February 22, 2009 9 39 PM
To: Cheryl Mills
Subject: Re Can we talk tonight?

Are you calling me? What #? I called ops and they gave me your "secure" cell which I just tried but only got a long high pitched whining sound
------Original Message------
From: Cheryl Mills
To: hdr22@clintonemail.com
Sent: Feb 22, 2009 8.58 PM
Subject: Re Can we talk tonight?

I can do now

-----Original Message-----
From. H <hdr22@clintonemail com>
To: Cheryl Mills
Sent: Sun Feb 22 18:37:51 2009
Subject Can we talk tonight?

I just landed and will be home shortly We can try a secure call at your convenience. Let me know what time works.

From: Cheryl Mills [redacted] B6
Sent: Sunday, February 22, 2009 10:02 PM
To: hdr22@clintonemail.com
Subject: Re: Can we talk tonight?

RELEASE IN PART
B6

I just spoke to ops and called you reg line - we have to wait until we see each other b/c thje technology is not working

-----Original Message-----
From. H <hdr22@clintonemail.com>
To: Cheryl Mills
Sent: Sun Feb 22 21:38:46 2009
Subject. Re: Can we talk tonight?

Are you calling me? What #? I called ops and they gave me your "secure" cell which I just tried but only got a long high pitched whining sound.
-----Original Message-----
From: Cheryl Mills
To: hdr22@clintonemail com
Sent Feb 22, 2009 8.58 PM
Subject: Re Can we talk tonight?

I can do now

-----Original Message---
From. H <hdr22@clintonemail.com>
To· Cheryl Mills
Sent: Sun Feb 22 18:37:51 2009
Subject: Can we talk tonight?

I just landed and will be home shortly We can try a secure call at your convenience [redacted] Let me know what time works.

From: H <hdr22@clintonemail.com> B6
Sent: Sunday, February 22, 2009 10:08 PM
To: Cheryl Mills [redacted]
Subject: Re: Can we talk tonight?

RELEASE IN PART
B6

Pls try again- [redacted]

From: "Cheryl Mills"
Date: Sun, 22 Feb 2009 22:02:23 -0500
To: <hdr22@clintonemail.com>
Subject: Re: Can we talk tonight?

Just did - no answer

-----Original Message-----
From: H <hdr22@clintonemail.com>
To: Cheryl Mills
Sent: Sun Feb 22 22:01:52 2009
Subject: Re Can we talk tonight?

I give up Call me on my home #.
------Original Message------
From: Cheryl Mills
To: hdr22@clintonemail.com
Sent: Feb 22, 2009 9:39 PM
Subject: RE: Can we talk tonight?

they were supposed to connect us - I called some time ago to do a secure call with you -- call them and ask them to try the connection

-----Original Message-----
From: H [mailto:hdr22@clintonemail.com]
Sent: Sunday, February 22, 2009 9:39 PM
To: Cheryl Mills
Subject: Re Can we talk tonight?

Are you calling me? What #? I called ops and they gave me your "secure" cell which I just tried but only got a long high pitched whining sound.
------Original Message------
From: Cheryl Mills
To: hdr22@clintonemail.com
Sent: Feb 22, 2009 8:58 PM
Subject: Re Can we talk tonight?

I can do now

-----Original Message-----
From H <hdr22@clintonemail.com>
To Cheryl Mills
Sent: Sun Feb 22 18:37:51 2009
Subject: Can we talk tonight?

I just landed and will be home shortly We can try a secure call at your convenience. [redacted] Let me know what time works.

HA 09/01/2015

From: Huma Abedin
Sent: Sunday, February 22, 2009 10:56 PM
To: humamabedin
Subject: PrintFw: Hearing and Gaza

B6

RELEASE IN PART B6

-----Original Message-----
From: H <hdr22@clintonemail.com>
To: Huma Abedin
Sent: Sun Feb 22 22:24:00 2009
Subject: Fw: Hearing and Gaza

Pls print

From: "Mark Hyman, MD"
Date: Mon, 16 Feb 2009 10:43:24 -0500
To: Hillary Clinton<hr15@att.blackberry.net>, Hillary Clinton<hdr22@clintonemail.com>
Subject: Hearing and Gaza

Dear Hillary,

Thinking of you a lot these days in gratitude for opening the door to the Senate and allowing the perspective of Functional medicine to be heard – the hearing is set for February 26th. If you want to connect while I am in DC from the 24th to the 28th for the IOM meeting and the hearing– let me know

When I finish writing my testimony I will send it to you – if you have a few minutes (which I realize is unlikely) I would welcome any input or advice.

The main reason I wanted to touch base was to forward this email from James Gordon about his work in Gaza.. Considering what is ahead of you I thought his perspective from the ground might be helpful.

His contact info is below if you want to contact him

Fondly,

Mark

------ Forwarded Message
From: James Gordon
Date: Mon, 16 Feb 2009 10:21:47 -0500
To: Mark Hyman
Subject: Re: Updated Plan

I'd like to talk with Hillary about the situation in Gaza and the very real prospects for peace that I believe are there, possibilities that we have for a variety of reasons ignored or dismissed or allowed to be "taken off the table." It's time for a fresh perspective and a deep, informed commitment to peace and I believe she can bring these, and I can be of help to her.

I've made over a dozen visits to Gaza in the last 7 years, know quite a bit about the populations's state of mind: We've worked intensively with 20,000 traumatized children and adults and have interacted with some of the major families (tribes) as well as the government. UN and NGO bureaucracies. I've also met with political leadership from Hamas and Fatah (in both Gaza and the West Bank) as well as independent intellectuals. I have too a pretty good understanding of the various Israeli perspectives and state of mind and have worked with every segment of Israeli society from UltraOrthodox to militantly secular, from the settlers removed from Gaza to the soldiers and government officials who removed them. Finally, our major funder for this work (Tom Harkin had helped us obtain some seed money from the CDC) is Chuck Feeney who helped with the Irish peace process and is potentially interested in economic development in Gaza as well as in our humanitarian and mental health work.

I feel I can help Hillary seize this moment of crisis and turn it into an extraordinary opportunity. There is, underneath the understandable fear and anger and the posturing so much yearning for peace, and perhaps I can help her find ways to use it creatively and effectively.

Thanks so much for being willing to contact her.

Jim

James S. Gordon, M.D.
www.jamesgordonmd.com <http://www.jamesgordonmd.com>

Founder and Director
The Center for Mind-Body Medicine
5225 Connecticut Avenue, NW, Suite 414
Washington, DC 20015

www.cmbm.org <http://www.cmbm.org>

------ End of Forwarded Message

From: Abedin, Huma <AbedinH@state.gov>
Sent: Monday, February 23, 2009 7:02 AM
To: humamabedin [redacted] B6
Subject: Marina print
Attach: 022309 Press Briefing.doc; 022309 Press Clips.doc

RELEASE IN PART B6

From: Bishop, Christopher W
To: Abedin, Huma
Cc: S_SpecialAssistants; Macmanus, Joseph E; Sullivan, Jacob J
Sent: Mon Feb 23 07:01:36 2009
Subject: Morning Press

Good Morning Huma,

Let us know if you need anything else.

Christopher

Christopher W. Bishop
Special Assistant to the Secretary of State
202-647-9573

From: Rattner, Steven [redacted]
Sent: Monday, February 23, 2009 1:48 PM
To: hr15@att.blackberry.net
Subject: My news

B6

RELEASE IN PART B6

Hillary:

Just to let you know that it's now official For whatever it's worth, here is the official description of my responsibilities:

Steven Rattner is joining the Treasury Department as Counselor to the Secretary. In that capacity, he will advise Secretary Timothy Geithner regarding a variety of economic and financial matters and will lead the team advising Secretary Geithner and National Economic Council Director Lawrence Summers on the automobile sector.

Thanks for all your support and offers of help while I was working through this.

Steve

Steven Rattner
Managing Principal

Quadrangle Group LLC
375 Park Avenue
New York NY 10152
[redacted]
www.quadranglegroup.com

From: Eric Bederman [redacted] B6
Sent: Monday, February 23, 2009 5:21 PM
To: Lauren Jiloty <jilotylc@state.gov>; Huma Abedin [redacted]
Subject: RE: Mort Zuckerman

RELEASE IN PART B6

TY Will do.

Subject: RE: Mort Zuckerman
Date: Mon, 23 Feb 2009 17:17:35 -0500
From: JilotyLC@state.gov
To: eric[redacted]; humamabedin[redacted]

Mine is fine.
Thanks eric.

From: Eric Bederman[redacted]
Sent: Monday, February 23, 2009 5:17 PM
To: Jiloty, Lauren C; Huma Abedin
Subject: Mort Zuckerman

Got a message from Amy at Mort Zuckerman's office asking what the best email address would be for Mort to send a message to HRC? Assume it should go to one of you gals?

- Eric B.

From: Huma Abedin
Sent: Monday, February 23, 2009 7:30 PM
To: humamabedin
Subject: PrintFw: One of your people at State. Fw: Global Partnership Center Website

B6

RELEASE IN PART B6

-----Original Message-----
From: H <hdr22@clintonemail.com>
To: Huma Abedin
Sent: Mon Feb 23 17:14:39 2009
Subject: Fw: One of your people at State. Fw: Global Partnership Center Website

Pls print.
-----Original Message-----
From: "Burns Strider"

Date: Mon, 23 Feb 2009 17 02:59
To: <hdr22@clintonemail.com>
Subject: One of your people at State. Fw Global Partnership Center Website

See comments below from Robert . He's been an active volunteer, doing online faith blogging for me for a couple of years and is in your Global Partnership office. Incredible young man.

-----Original Message-----
From: Lalka, Robert T <LalkaRT@state.gov>
To: bstrider
Sent: Mon Feb 23 16:42:26 2009
Subject: FW: Global Partnership Center Website

Burns,

I just realized that tonight's when the Delta State reception is happening and I'm hoping to make it. Just in case, I wanted to write to let you know that I had the chance to meet the Secretary for the first time today. She was visiting the East Asia and Pacific Affairs Office to thank them for their work on her first trip abroad; and, man, the folks here just seem to love her...

I also haven't sent you a link to the Global Partnership Center's website as promised, so I have enclosed the link with the quotes we are using in the "read more" boxes you'll see on the right side of the page.

Hope to see you again tonight,

Best,
Rob

http://www.state.gov/s/d/rm/partnerships/
"Diplomacy is primarily a government mission. But there are lots of ways that nongovernment actors, like corporations, like religious organizations, like charities and foundations, are actually building relationships with foreign governments and foreign people all the time, which, if done in the right way, are really value added to who we are as a nation and what we can achieve " -Secretary of State Hillary Clinton
"I think it's a real opportunity for us if we can figure how best to better coordinate and facilitate the private sector and the not-for-profit and religious community of the United States on behalf of humanitarian and commercial efforts."
- Secretary of State Hillary Clinton
"The State Department will be firing on all cylinders to provide forward-thinking, sustained diplomacy in every part of the world, applying pressure wherever it may be needed, but also looking for

opportunities, exerting leverage, cooperating with our military and other agencies of government, partnering with nongovernmental organizations, the private sector, and international organizations, using modern technologies for public outreach, empowering negotiators who can protect our interests while understanding those of our negotiating partners. Diplomacy is hard work. But when we work hard, diplomacy can work, not just to defuse tensions, but to achieve results that advance our security interests and values "
- Secretary of State Hillary Clinton
"I want more partnerships . .I don't think there's any substitute for having seasoned, experienced professionals and experts leading our efforts on diplomacy and development and working, where possible, in partnership and coordination with the private sector and the not-for profit sector."
-Secretary of State Hillary Clinton
"You know, right now in Rwanda, a number of foundations, a number of churches, a number of private sector actors are all working to try to build that country back up. So I would hope that when we look at the State Department, we think of the role of foreign policy, diplomacy, and development as involving not just those who are the Foreign Service officers and the Civil Service professionals and the development experts, but really it's all hands on deck We have a lot of work to, in my view, kind of repair damage and get out there and present America as we know we are "
-Secretary of State Hillary Clinton

Also, I remember mentioning this study to you:
http://www.brookings.edu/reports/2008/~/media/Files/rc/reports/2008/07_national_security_brainard/07_national_security_brainard.pdf Check out the sections on development and human rights (pages 17 and 18), and if it's something you'd like to read more on, there are a number of good reads, including one I just finished called Security By Other Means, which I would be happy to lend to you.

Robert Tice Lalka
Work: 202.647.3408 | Fax: 202.647.3311

Public-Private Partnerships Liaison
at the Global Partnership Center

http://www.state.gov/s/d/rm/partnerships

US Department of State
2201 C Street NW Suite 3800
Washington, DC 20520
United States of America

From: Cheryl Mills [redacted] B6
Sent: Tuesday, February 24, 2009 4:58 AM
To: hdr22@clintonemail com
Subject: FW: From my father-in-law who is in Japan on business...

RELEASE IN PART
B6

FYI below

New York University
70 Washington Square South
New York, NY 10012

From: Maya Seiden [redacted]
Sent: Monday, February 23, 2009 10:21 AM
To: Sean Maloney
Cc: Cheryl Mills
Subject: Re: From my father-in-law who is in Japan on buisness...

The colliquial translation is 'Isn't Hillary awesome?'

Quite a statement from men in a culture that is not exactly known for its advancement of women.

On Feb 23, 2009, at 10:01 AM, "Sean Maloney" [redacted] wrote:

> P.S. Maya will have to translate the Japanese for you.
> *Also, in case Cheryl wants to know, everyone in Japan loves Hirari-san. Her trip was extraordinarily successful. Everyone has been talking about her with great fondness and admiration. Every taxi driver (nearly) has said something like "Hirari-san wa segoii desu ne!"*
> Sean Maloney, New York University
> [redacted]

HA 09/01/2015

From: Abedin, Huma <AbedinH@state.gov>
Sent: Tuesday, February 24, 2009 6:40 AM
To: humamabedin [redacted] B6
Subject: Marina print
Attach: 022409 State Clips.doc; 022409 State Briefing.doc

RELEASE IN PART B6

From: Davis, Jennifer L (S Staff)
To: Abedin, Huma
Cc: S_SpecialAssistants
Sent: Tue Feb 24 06:35:45 2009
Subject: Morning Press, 2/24/09

Good morning, Huma.

From: Berger, Samuel R.
Sent: Tuesday, February 24, 2009 1:29 PM
To: hdr22@clintonemail.com
Subject:

B6

RELEASE IN PART B6

HRC: The Chinese see a new era of cooperation. By throwing away the old talking points, you have changed the landscape. Sensational trip Sandy

From: Burns Strider [redacted] B6
Sent: Tuesday, February 24, 2009 6:34 PM
To: hr15@att.blackberry.net
Subject: What the Bible Says about Federal Budgets..
Attach: Scripture on the Budget- Part 1.doc

RELEASE IN PART B6

Three of eight posts are up at www.faithfuldemocrats.com from the updated *Primer on Scripture and the Budget for 2009.*

The second posting is also attached: *The Responsibility of the Nation and Its Government to "the Least of These"*

Over the next week at Faithfuldemocrats.com, we are going to publish each section of the updated *Primer on Scripture and the Budget for 2009*, which is organized by theme Our hope is that you will use this resource, share it with friends, and discuss it in the comment section...and that together we can make a positive contribution to the upcoming budget debates that will shape our country's priorities and demonstrate where its heart truly lies.

The sections and future posts are titled:

The Responsibility of the Nation and Its Government to "the Least of These"
The Policy Implications of Praying, "Thy Kingdom Come..."
On Corruption and the Exploitation of Workers
The Sin of Helping the Rich at the Expense of the Poor
The Blessedness of the Poor and Our Christian Responsibility to Them
Wealth, Materialism, and the Bible's View of an "Ownership Society"
Countering the Right's Pharisaical Approach to Moral Legalism
Concluding Thoughts: Applying Scripture in a Pluralistic Society

Back in 2006, the budget debate followed immediately on the heels of Congressional consideration of the Marriage Amendment. As a result, there was a desire by a number of Democratic leaders for a reference guide that would more easily allow Democrats to authentically speak out against the extreme and selective use of scripture by the Republicans and their allies on the Right. The first "Guide to Scripture and the Budget" that included scriptural references and simple talking points to help equip Christian Democrats in their response to Republican budget arguments was distributed shortly before the 2006 budget debate.

My underlying assumption in writing and continuing to update this document is that Democrats should not cede the prophetic language of scripture and its ability to inspire and frame issues in a moral context to the other side. Many traditional Democratic positions are rooted in the teachings of scripture, and it is time Democrats stopped losing on the Bible.

The language of scripture is a language that calls people to turn their attention away from selfish desire and personal gain and to focus instead on serving God and their neighbors. Furthermore, it is a language that speaks with moral clarity and purpose. Therefore it speaks with authority to the policy debates currently underway in our country. In short, it is a language Democrats cannot afford to ignore.

One aspect of the Democratic response to the upcoming Republican budget attacks must be a willingness by "faithful Democrats" to discuss budget and tax policies from a moral perspective and to challenge Republicans to apply the same moral codes to kitchen table issues that they so eagerly embrace on bedroom issues...because we all know that ***as soon as we start talking about budget and taxes, the Republicans will put away their Bibles and turn to Darwinian social and economic theories to support their policy positions.***

The first chapter of the Book of Isaiah begins with the prophet cataloguing the decline of the city of Jerusalem into injustice, where its former greatness is besmirched by its obsession with materialism and wealth. It is important to remember that the prophets are speaking against the government "rulers" and the nation as a whole. The prophets in scripture are not calling for individual piety and charity but for systemic societal/governmental reform. And they specifically challenge government leaders to remember that the nation's leaders are called to help the powerless and those in greatest need, not those with the most power and money.

Isaiah clearly states what God expects of leaders: "Wash yourselves; make yourselves clean; remove the evil of your doings from before my eyes; cease to do evil, learn to do good, seek justice, rescue the oppressed, defend the orphan, plead for the widow" (Isaiah 1:16-17). [note: he does not say, "cut federal funding for state child services"]

Here is what a true "Justice Sunday" should focus on from Jeremiah's exhortation of the king about his responsibility as head of government: "Did not your father eat and drink and do justice and righteousness? Then it was well with him. 16He defended the cause of the poor and needy, and so all went well. Is that not what it means to know me?" declares the Lord. 17"But your eyes and your heart are set only on dishonest gain, on shedding innocent blood and on oppression and extortion" (Jeremiah 22:15-17).

Taken together with Micah 6:8, this forms the core of the prophetic message: To know God as a nation means to take care of the poor and ensure that justice is done on behalf of the needy: "He has showed you, O man, what is good. And what does the Lord require of you? To act justly, to love mercy, and to walk humbly with your God" (Micah 6:8).

There are obvious parallels between ancient Jerusalem and the role that big donors and lobbyist played in setting government priorities in Washington that contributed to the ouster of the GOP from Congress and the White House in the 2006 & 2008 elections respectively: "Everyone loves a bribe and runs after gifts. They do not defend the cause of the fatherless. The widow's cause does not come before them."(Isaiah 1:23)

"The Lord takes his place in court and rises to judge his people. He enters into judgment against the elders and leaders of his people saying, "It is you who have ruined my vineyard; the plunder from the poor is in your houses" (Isaiah 3:14).

"You seem eager for God to come near you. Yet on the day of your fasting, you do as you please and exploit all your workers. Yet is not this the kind of fasting I, your Lord, have chosen. to loose the chains of injustice...to share your food with the hungry and to provide the poor wanderer with shelter—when you see the naked, to clothe them?" (Isaiah 58: 2-7).

"He who oppresses the poor shows contempt for their Maker, but whoever is kind to the needy honors God" (Proverbs 14:31).

"If you do away with the yoke of oppression, with the pointing finger and malicious talk, 10and if you spend yourselves in behalf of the hungry and satisfy the needs of the oppressed, then your light will rise in the darkness, and your night will become like the noonday. 11 The Lord will

guide you always; he will satisfy your needs" (Isaiah 58: 9-11).

Nehemiah (who rebuilt Jerusalem after the Babylonian exile) enforces social justice through the power of the state and addresses an insidious problem that sadly still plagues us to this day (predatory lending): "Still others were saying, "We have had to borrow money to pay the king's tax on our fields and vineyards. 5 Although we are of the same flesh and blood as our countrymen and though our sons are as good as theirs, yet we have to subject our sons and daughters to slavery…we are powerless, because our fields and our vineyards belong to others." 6 When I heard their outcry and these charges, I was very angry. 7 I told the [nobles and government officials], "You are exacting usury from your own countrymen!" So I called together a large meeting to deal with them 8 and said… "What you are doing is not right…let the exacting of usury stop! 11 Give back to them immediately their fields, vineyards, olive groves and houses, and also the usury you are charging them—the hundredth part of the money, grain, new wine and oil." 12 "We will … do as you say," they replied. Then I summoned the priests and made the nobles and officials take an oath to do what they had promised." (Nehemiah 5:1-13)

From the New Testament: "Mercy triumphs over judgment! What good is it, my brothers, if a man claims to have faith but has no deeds? Can such faith save him? 15Suppose a brother or sister is without clothes and daily food. 16If one of you says to him, "Go, I wish you well; keep warm and well fed," but does nothing about his physical needs, what good is it? 17In the same way, faith by itself, if it is not accompanied by action, is dead"(James 2: 14-17).

Scripture sets a very high bar for public morality as well as for private behavior. Although we can easily rationalize why alternatives to the commands of Scripture might be more "sensible" and "realistic," if people are going to insist on applying scripture to the bedroom, they must be willing to apply it to the boardroom as well. The Bible leaves no room for trickle-down economics. Jesus and the Prophets do not say, "Help the widow and orphan by supporting businesses in an effort to prop up the stagnant economy"! On the contrary, when a rich young man asks Jesus what he must do to inherit the Kingdom of God ("go to heaven" in today's terminology), "Jesus answered, "If you want to be perfect, go, sell your possessions and give to the poor, and you will have treasure in heaven. Then come, follow me" (Matthew 19:21—note Jesus says this is what the man must do before he can follow Christ). The Bible's call repeated throughout the Old and New Testament is for direct action by government leaders on behalf of the least of these…nothing less.

HA 09/01/2015

From: Cheryl Mills [redacted]
Sent: Tuesday, February 24, 2009 10:05 PM
To: hr15@att.blackberry.net; hdr22@clintonemail.com
Subject: just called your house twice - but keep getting hang up - was calling to check in - I'm on [redacted]

B6

RELEASE IN PART
B6

From: Mark J. Penn [redacted] B6
Sent: Tuesday, February 24, 2009 10:16 PM
To: hr15@att.blackberry.net
Subject: pretty good speech

RELEASE IN PART
B6

Basically a copy of all the techniques we used – well done and certainly what he needed. Serious, patriotic and always appearing to bring people together. Very much the kind of stuff that works.

You have been getting good reviews on your tours – I always liked having a leadership track and a human track and you have been doing both, but I would be careful about seeming too silly as it could make you look irrelevant. Obama has serious, direct, and powerful leadership style.

My biggest worry would be that the policies may not work.

From: H <hdr22@clintonemail.com>
Sent: Wednesday, February 25, 2009 8:23 AM
To: Tamera Luzzatto [redacted] B6
Subject: How are you?

RELEASE IN PART
B6

I tried calling you at all your numbers Let me know when we can talk and what # to call?

From: jkcanc[redacted] B6
Sent: Wednesday, February 25, 2009 9:04 AM
To: Hillary Clinton <hdr22@clintonemail.com>
Subject: Welcome Back

RELEASE IN PART
B6

Hillary,
Sent you a message to your old address by mistake Lauren will provide you a hard cy. Welcome back, all the best, Jack
Sent via BlackBerry by AT&T

From: Huma Abedin [redacted] B6
Sent: Thursday, February 26, 2009 6:26 AM
To: hdr22@clintonemail.com
Subject: Re. Calls

RELEASE IN PART
B6

China call confirmed for 7 30
Lavrov will be later this morning.

-----Original Message-----
From: H <hdr22@clintonemail.com>
To: Huma Abedin
Sent: Wed Feb 25 23:52:18 2009
Subject. Re Calls

Ok
------Original Message------
From: Huma Abedin
To: hdr22@clintonemail com
Sent: Feb 25, 2009 11:50 PM
Subject: Calls

Call with foreign minister yang has been confirmed for tomorrow morning at 7:30am while u r with isabelle. Lavrov will be right after probably.

HA 09/01/2015

From: Gary Gensler [redacted] B6
Sent: Thursday, February 26, 2009 8:37 AM
To: hr15@att.blackberry.net
Subject: Harkin plans to suppport

RELEASE IN PART B6

Hillary,

My Senate confirmation hearing today went well. Senator Harkin said afterward that he planned to poll the committee shortly but saw no opposition at this time and would try to schedule a committee vote next week. The newswire story below suggest his support now.

Senators Mikulski & Cardin along with former Senator Sarbanes introduced me today.

Off the Committee, both Senators Feinstein and Senator Levin have signaled their support as well.

Your call to Senator Harkin and following your specific advice on how to address my past in the Clinton Administration was of the greatest help.

Thank you once again for all of your support.

Gary

Sen. Harkin Plans To Support CFTC Nominee *Gensler*

DOWJONES Newswires factiva

Source. Dow Jones News Service
Date: 02/25/2009
By Sarah N. Lynch
Of DOW JONES NEWSWIRES

WASHINGTON (Dow Jones)--Senate Agriculture Chairman Tom Harkin signaled Wednesday that he intends to support the nomination of Gary ***Gensler*** to chair the U S. Commodity Futures Trading Commission despite some lingering concerns

Harkin's support came after ***Gensler***, at a hearing Wednesday, sought to reassure the Iowa Democrat and other senators on the panel that his views on swaps regulation have evolved since his tenure at the Treasury Department during the Clinton administration.

"I think that Mr. ***Gensler*** was very forthright in saying his views have changed over the years," Harkin said. "I will be polling the committee, but I don't expect any opposition. I assume that we will be moving his name forward." If the committee approves ***Gensler***'s nomination, ***Gensler*** will face a confirmation vote from

the full Senate.

Harkin had previously raised concerns about ***Gensler***'s involvement in talks over the Commodity Futures Modernization Act, passed in 2000, which deregulated swaps. At the time, ***Gensler*** was a senior Treasury official.

Harkin hit ***Gensler*** with a tough first question at ***Gensler***'s confirmation hearing Wednesday, recalling testimony ***Gensler*** gave in 1999. Quoting ***Gensler*** as saying he "positively, unambiguously" agreed with former Treasury Secretary Lawrence Summers in opposing additional regulations for over-the-counter derivatives, Harkin pressed ***Gensler*** on whether or not his beliefs have changed.

Gensler responded: "Looking back now, it is clear to me that all of us that were involved at the time, and certainly myself, should have done more to protect the American public through aggressive regulation."

"We should have fought harder for some of the things we raised with Congress at the time," he added.

Since President Barack Obama first nominated ***Gensler*** to the CFTC late last year, ***Gensler*** has worked hard behind the scenes to convince Harkin and other lawmakers that he would be a tough regulator if confirmed as the agency's chairman. ***Gensler*** has said he didn't participate in discussions on the Commodity Futures Modernization Act at certain times in 1998, when he was recused, but he did get involved after that recusal period expired.

His efforts have paid off in winning over key lawmakers like Sen. Dianne Feinstein, D-Calif., who has been critical of the CFTC's oversight in the past. Feinstein indicated late Tuesday that she plans to support the nomination.

Sens. Benjamin Cardin and Barbara Mikulski, both Democrats from ***Gensler***'s home state of Maryland, also urged the Senate Agriculture Committee to support ***Gensler*** on Wednesday.

Responding to questions from the committee, ***Gensler*** said that he wished he had fought harder for uniform regulation for all physical commodities when he served at Treasury. At the time, he said, those in favor of uniform regulations were unable to get it into the legislation. If confirmed, ***Gensler*** pledged to take the issue up again.

He also said he would support a regulatory regime for derivatives dealers. As an example of why such reforms are needed, he cited the unit at American International Group (AIG) which issued credit-default swaps without having the collateral to back the provisions in those contracts.

Sen. Kent Conrad, D-N.D., a member of the committee, said Wednesday he deeply regrets supporting the deregulation of swaps in 2000, adding that ***Gensler*** also shares some of the blame for it.

"At least for some of that, you gave us bum advice," Conrad said.

Gensler said he believes it's clear the regulatory system failed, and he pledged to push for tough new reforms If confirmed, he said, he will support mandating clearing for standardized over-the-counter products as well as putting some of those derivatives on regulated exchanges For customized products that don't lend themselves to clearing, ***Gensler*** said he would push to enact strict reporting and record-keeping requirements.

He also reiterated Wednesday he believes speculation and index investing did contribute in part to the run-up in agricultural and energy commodities last summer and he would do more to prevent excessive speculation if confirmed That would entail re-examining the rules governing hedge exemptions, which allow traders to get around position limits if they are hedging a business risk

"I am a proud believer in financial reform, tough regulation and enforcement," ***Gensler*** said.

-By Sarah N Lynch, Dow Jones Newswires; 202-862-6634; sarah.lynch@dowjones com [02-25-09 1743ET]

From: Abedin, Huma <AbedinH@state.gov>
Sent: Friday, February 27, 2009 7:03 AM
To: humamabedin[redacted] B6
Subject: Marina print
Attach: 022709 State Briefing docx, 022709 State Clips docx

RELEASE IN PART B6

From: Bishop, Christopher W
To: Abedin, Huma
Cc: S_SpecialAssistants; Macmanus, Joseph E; Sullivan, Jacob J
Sent: Fri Feb 27 07:02:18 2009
Subject: Morning News Clips

Good Morning Huma,

Please let us know if you need anything else.

C

Christopher W. Bishop
Special Assistant to the Secretary of State
202-647-9573

Testimony of Mark Hyman, M.D.

Founder and Medical Director

The UltraWellness Center

Vice-Chairman, Institute for Functional Medicine

SENATE HEALTH REFORM TESTIMONY
INTEGRATIVE CARE: A PATHWAY TO A HEALTHIER NATION
Senate Committee on Health, Education, Labor and Pensions

Chairman: Senator Edward M. Kennedy

Ranking Member: Senator Michael B. Enzi

Senator Tom Harkin & Senator Barbara Mikulski

United States Senate

Senate Dirksen Building

Washington, DC

February 26, 2009

Reforming the United States Health Care System:
Mastering the Challenge of Chronic Disease

Executive Summary: Testimony of Mark Hyman, MD

Effective Health Care Reform: Addressing the Drivers of Costs and Chronic Disease

- The current medical and scientific paradigm of acute care medicine has been unable to effectively address the epidemic of chronic disease and its associated costs.
- There is a new paradigm which addresses the fundamental underlying causes of chronic disease, and can form the basis for a more effective model of medical education, practice, and research that over time will generate dramatic cost savings.
- There are specific initiatives and strategies based on this new paradigm that can help transform our sick care system into a health care system.

The Right Solution for the Problem of Chronic Disease

- This new paradigm is personalized, preventive, participatory, predictive, and patient centered. It is proactive rather than reactive. It is based on addressing the causes of disease and optimizing biologic function in the body's core physiologic systems, not only treating the symptoms.
- It based on systems biology or medicine That model exists today, and is called ***Functional Medicine.***
- Functional medicine is a system of personalized care, a **new "operating system"** that directly addresses **how environment and lifestyle influence our genes to create imbalances in our core biologic systems that, over time, manifest as disease.** It is this kind of medicine that is needed to create real successes in 21st century medicine.
- Even if we get everything else right in health care reform, it won't matter unless we address the underlying causes of illness that drive both costs and the development of chronic disease.

Clinical Examples: Systems Medicine in the Clinic

- Case examples of Functional medicine in chronic disease in autoimmune, digestive, behavioral, and hormonal disorders illustrating the power and implications for transforming the quality of our health care and reducing the economic burden of chronic disease.
- Report on pilot program for children using functional medicine showing a 16-fold reduction in costs from dramatically better health outcomes with integrated health care teams based on Functional medicine.

Key Avenues for Change: Recommendations

1. Re-tooling medical education and research to match the science of systems medicine. This would involve funding the development of training programs in medical schools and residencies, and supporting initiatives for certification and training in functional medicine for existing practitioners through establishing a fully funded university affiliated Institute for Lifestyle and Systems Medicine
2. Creation of Functional medicine demonstration projects in federally funded community health centers, with integrated health care teams focusing on treating chronic disease and providing

education about lifestyle and wellness. These would form the foundation for the development of clinical practice networks of Functional medicine for education and research.

Reforming the United States Health Care System:
Mastering the Challenge of Chronic Disease

Testimony of Mark Hyman, MD
Before the Senate Committee on Health, Education, Labor and Pensions
February 26, 2009

Chairman Kennedy, Ranking Member Enzi and distinguished members of the Committee: Thank you for this opportunity to share the dramatic changes in medical thinking and practice that must be the central focus of health care reform. My name is Dr. Mark Hyman. I am a practicing physician and vice chair of the Board of Directors of the Institute for Functional Medicine. As a practicing functional medicine physician, I am on the front lines of a scientific medical revolution.

Effective Health Care Reform: Addressing the Drivers of Costs and Chronic Disease

My testimony will show that:

- The current medical and scientific paradigm of acute care medicine has been unable to effectively address the epidemic of chronic disease and its associated costs.
- There is a new paradigm which addresses the fundamental underlying causes of chronic disease, and can form the basis for a more effective model of medical education, practice, and research that over time will generate dramatic cost savings and improved health outcomes.
- There are specific initiatives and strategies based on this new paradigm that can help quickly transform our sick care system into a health care system.

Even if we get everything else right in health care reform, it won't matter unless we address the underlying causes of illness that drive both costs and the development of chronic disease. This innovative approach to chronic disease cannot only prevent but also more effectively TREATS chronic disease.

We must change not only the WAY we do medicine, but also the medicine we DO. We must improve not only financing and delivery of health care, but also our fundamental scientific approach to chronic disease—an epidemic that now affects 133 million Americans and accounts for 78% of health care costs.

This way of doing medicine, or Functional medicine, is a system of personalized, patient centered care based on **how our environment and lifestyle choices act on our genes to create imbalances in our core biologic systems. Those imbalances show up as the signs and symptoms we call disease.**

It is best solution for our health care crisis. The solution is not our current acute care model, which though extremely effective for acute disease, leads to worse outcomes and higher costs when applied to chronic disease because it doesn't address WHY people are sick.

This new paradigm is personalized, preventive, participatory, predictive, prospective, and patient centered It is proactive rather than reactive. It is based on addressing the causes of disease and optimizing biologic function in the body's core physiologic systems, not only treating the symptoms. It based on systems biology or medicine. That model exists today, and is called ***Functional Medicine***.

The Right Solution for the Problem of Chronic Disease

Our current model of medicine is unsustainable because it cannot stem the rising tide of chronic disease. Relying only on reforms in access, financing, electronic records, malpractice, reduction in medical errors, coordination of care, and research on new drug therapies – while retaining the acute-care model – will be untenable. These reforms are necessary but not sufficient to avoid the collapse of our health care system that may soon mirror our current financial crisis. These reforms do not alter the fundamental approach to prevention and treatment. If we focus on improving the way we practice the medicine of the past, we will still have the medicine of the past. If we improve the wrong type of care, then we will simply be doing the wrong things better.

Acute-care medicine is designed for acute illness, trauma, and end-stage disease for which it is the best in the world. It is disease-, drug- and procedure-based. Our current medical education focuses on sickness rather than health; journals publish about disease management not causality. Disease based acute care medicine is the WRONG model to address chronic illness, because it doesn't address WHY people are sick, or the underlying mechanisms and biologic causes. That is why we spend more than any other industrialized nation and are near the bottom of the list for all major health outcomes, and are witnessing a decline in life expectancy for the first time in history.

Functional medicine is not a new treatment, test, or procedure but a new **"operating system"** or method for problem solving and processing complex clinical information. It is a fundamentally different WAY OF THINKING about the origins and mechanisms of illness. It encompasses all the TOOLS of healing and medicine, both conventional and integrative. And it provides a common language, a map or GPS system for navigating through the puzzle of chronic illness. A growing coalition of practitioners, educators, and scientists is dedicated to advancing this model. We have introduced 20,000 physicians and health care providers to functional medicine since 1991, and we wrote the *Textbook of Functional Medicine* in 2005 to describe both the underlying science and the practical clinical strategies and tools that comprise this new model.

We have begun a certification program in functional medicine and are building key educational programs for residencies throughout the country. We are partnering with Harvard

in strategic research to document the extent and scope of practice as well as the efficacy of this model as a better roadmap for chronic disease.

Through a scholarship program funded by one of my patients, we have trained over 50 academic faculty and fellows from major institutions who are part of the Consortium of Academic Health Centers for Integrative Medicine (funded by the Bravewell Collaborative) including Harvard, Yale, Duke, Johns Hopkins, USCF, and the University of Arizona. We are also collaborating with the American Academy of Family Practice and the American Dietetic Association. We collaborate and advance the foundational work of James Gordon, MD at the Center for Mind Body Medicine and Dean Ornish, MD at the Preventive Medicine Research Institute

Clinical Examples: Systems/Functional Medicine in the Clinic

Let me illustrate how this works with real people.

A Pilot Program For Functional Medicine: Reducing Costs 16 Fold in Sick Children

At the University of Minnesota, Dr. Anne Kelly developed a model of care based on Functional medicine called the *U Special Kids* program It was for the 5% of the sickest children who generated 60% of the total costs, mostly from unplanned hospitalizations. In one year, the costs incurred by that population dropped from $4 million to $250,000, or more than $50,000 per enrollee, or a 16-fold decrease in costs. Yet the program was cancelled in November 2008 after one year because less than 10% of the high science, low tech, and high touch approach was reimbursable.

We cannot control costs by reducing access to effective programs. We must increase access to integrated health care teams that include a variety of health professionals, all of whom are trained in the appropriate chronic disease model. Both the science and methodology exist to utilize functional medicine for such teams on a wide scale.

Reform must also encompass re-structuring financing and financial incentives to prioritize health care, not just sick care. We cannot afford incremental change. The health our nation, our future generations, and the health of our economy depend on addressing the explosion of chronic disease and associated health care costs.

A Woman with Treatment Resistant Autoimmune Disease

Cris Scoufos, a 40-year-old woman came to see me after 5 years of uncontrolled ulcerative colitis with bloody diarrhea, joint pain and cystic acne, which started after 4 rounds of antibiotics for respiratory infections. She was treated unsuccessfully at the Mayo Clinic with the most advanced, dangerous and expensive immunosuppressive therapies. Just before returning to Mayo to start a new investigational drug, she saw me. We simply eliminated common food sensitivities, treated yeast infections, and normalized the function of her digestive tract with probiotics, digestive enzymes, fish oil, and vitamin D. After just 6 weeks of treatment she went back to Mayo and was found to have a completely normal bowel, and

her joint pain, fatigue, and cystic acne resolved by treating the upstream triggers instead of the downstream symptoms. We cannot get to the solution for chronic disease with our current methods of diagnosis and treatment.

Here is her email to me shortly after her visit to Mayo Clinic. Her before and after photos are attached.

Dear Dr. Hyman,

I am so thankful for all that you are helping me with. I prayed for God to guide me to someone who could show me how to properly care for my body so that I could heal and that the honor and glory would belong to Him. Instead of asking for God to just heal me, like I had for four and a half years, I asked for guidance on what I needed to do.

After failing all conventional drug treatments I was told I would have to go into an investigational drug study next. My trip to Mayo Clinic had been planned and I was nervous about the choices I was going to have to make. My colonoscopy in April 2008 showed 45cm of ulceration.

The trip to see you the last week of August was planned in one week and everything fell together so easily. It seems like it was meant to be. I started following your recommendations right away, even though I haven't incorporated all of the supplements in yet, the change has been amazing.

My colonoscopy at the Mayo Clinic in Rochester, Minnesota was last Monday, October 13th. My physician Dr. Sandborn, who is highly regarded in the gastroenterology field as one of the best in the country, told me that there is no ulceration left in my large intestine and there was only some scarring. I have completely healed! It is amazing! I was still bleeding just two months ago and now I am completely healed. It has been a very long five years and I thought you would want to know just how much your help has made in my life. Thank you very much. You have been the instrument that God has sent into my life for healing.

Unending blessings to you and your loved ones,

Cris Scoufos

A Doctor with Autoimmune Arthritis

A 57-year-old vascular surgeon was seen with debilitating autoimmune psoriatic arthritis that had been unsuccessfully treated with Humira, methotrexate, and NSAIDs; he also had migraines, reflux, constipation, and fatigue. He was symptom free and off all medications only 6 weeks after changing his diet, fixing nutritional deficiencies, and addressing imbalances in his digestive system, which is home to more than 70% of the immune system

A Woman with Multiple Chronic Diseases

A 46-year-old woman, having seen a dozen doctors over a dozen years, came to me with 29 different diagnoses, including depression, hypertension, obesity, polycystic ovarian syndrome, migraines, heavy uterine bleeding, asthma, sinusitis, irritable bowel syndrome, fibromyalgia, osteoarthritis and psoriasis. Each disease was treated with the best available conventional treatment. But she was still sick, despite 9 medications

Of course, she didn't have 29 separate diseases. She had imbalances in a few core networks of physiologic function – digestive, immunologic, and hormonal – that gave rise to all her symptoms. The underlying cause of all her "diseases" was an autoimmune response to gluten, leading to autoimmune thyroid disease and severe vitamin D deficiency because of malabsorption. Six weeks after eliminating gluten, improving her diet, replacing thyroid hormone and vitamin D, her 29 diseases were completely gone, along with 21 pounds.

A Boy with Attention Deficit Disorder and Asthma and Allergies

Clayton Lampert was a 12-year-old boy with severe attention deficit hyperactivity disorder, behavior problems, and poor school performance on Ritalin for years. He also had illegible handwriting or dysgraphia. He also had apparently "unrelated" problems of asthma, allergies, hives, stomachaches, headaches, insomnia, muscle cramps, and anxiety. He had a history frequent infections and antibiotics. He had seen 5 specialists (lung, GI, allergist, psychiatrist and neurologist) and was on 7 medications for allergies, asthma, pain, and ADHD. No one asked how everything was connected, or how his diet of junk food and sugar made him sick.

His immune system was activated, his digestion not working and he was nutritionally deficient in zinc, omega 3 fats, magnesium and vitamin B6. We simply normalized his function by removing impediments to health (junk food diet, food sensitivities, overgrowth of yeast, and lead) and providing the ingredients necessary for optimal biologic function - whole foods diet, additional nutrients including B6, magnesium, zinc, omega 3 fats and probiotics. In two months he returned without any physical or psychiatric symptoms and was off all his medication. How many children suffer needlessly when we have the solutions to these problems? Here is his mother's email to me about his progress. And below is his handwriting sample before and two months after treatment.

Dear Dr. Hyman,

We had a 504 meeting at Clayton's school this morning (where the teachers, school counselor, parents, and principal all get together to review "the plan" for kids with special educational needs—in Clayton's case prompted by the ADHD diagnosis). This was the first time in his entire schooling history that everything seems to be going well. The input from his teachers was that he is "a different kid" than they saw in the first half of the year and that they're amazed by the difference. The school nurse hasn't seen him since March (and he used to be in her office several times a week). The school psychologist said his social skills are very good, age appropriate, and that she sees no problems at all. She also noted that Clayton seems very proud of himself and his new health and that he's taking good ownership of all the

changes in his diet. He even seems to be shrugging it off when the other kids at school tell him he's an "alien" because he doesn't drink soda.

This was just such a fantastic meeting and I wanted to pass along the good news and say Thank You!

Recovery from Dementia

The power of this approach is that it can be often applied without the intervention of a trained professional. Below is the story of a woman's whose husband recovered from dementia by following the principles of Functional medicine. This recovery was likely due to a reversible nutritional cause. Other causes of dementia, which is not a homogenous disease, may respond differently, however the social and economic impact of this method can no longer be ignored.

Eight years ago, at the age of 42, I met and married the love of my life, Robert Foster. We both have felt that "we" were absolutely "meant to be together". Two years ago I began worrying whether or not the "moments" of forgetfulness meant the beginning of dreaded Alzheimer's disease. I began to educate myself obsessively, and came to the conclusion that the traditional route of pharmaceutical drugs was the wrong approach to combat this beast. I would not accept that the "only" outcome was a horrible death sentence. My beloved husband's cognitive function took a sudden and alarming spiral downward this past fall. The formal diagnosis of "Alzheimer's" was no less heartbreaking, but I felt lucky to have had those two years to do the precious research and reading, where I was given the extraordinary gift of awareness and respect for Functional Medicine.

Knowing instinctively that this was the only answer to the war we needed to fight – it was here that I sought help. I was made aware of Dr. Hyman by another Functional Medicine doctor a couple of years ago, and have followed his work and have read several of his books. Having a program to follow, was the answer to a prayer.....literally. The actual "turnaround" has been so dramatic that I have been hesitant to share the results, not wanting to offer unwarranted "hope" to others, as it sounds "too good to be true". I do not want this to sound like "hype" – or as the "magic pill" that cured Alzheimer's, but I do think it would be irresponsible not to share our astounding results.

The bottom line--five days after starting the program, my husband had gone from not being able to hold a thought, constantly misplacing any number of objects, repeating questions and thoughts, and not being able to drive (as he would get lost), to the normal functioning man I married. The "comeback" is NOT 100%-- it IS over 90%. He is able to hold his concentration on a project for hours at a time. He is able to get into the car and run errands flawlessly. He carries out a conversation and relates to it hours or days later. He is able to recall telephone numbers and addresses. I have my husband back. I have no doubt the change in diet, addition of specific supplements, the detox program, and the addition of regular exercise, are responsible for these results. I pray that the miraculous results are multiplied a million times over, and others feel the joy and relief that I have had. Dr. Hyman – our eternal thanks and gratitude.

Key Avenues for Change: Recommendations

While there are many questions still to be answered, and research to be done, it is time to act. Based on the aforementioned considerations, I submit that public and private sector investment must be made in the following areas:

1. Re-tooling medical education and research to match the science of systems medicine. I recommend the establishment a sustainably funded university affiliated ***Institute for Lifestyle and Systems Medicine/Functional Medicine***. This would be the national center and prototype for the development of training programs in medical schools, residencies, and postgraduate certification and training in Functional medicine for existing practitioners and ancillary health professionals. Sixty seven percent of the 250,000 primary care doctors are currently dissatisfied with medicine and 80% are seeking new ways to practice based on this emerging model of medicine. The goal should be 20,000 fully trained practitioners in five years.

2. Creation of Functional medicine ***demonstration projects in federally funded community health centers***, with integrated health care teams focusing on treating chronic disease and providing education about lifestyle and wellness. These would form the foundation for the development of clinical practice networks of Functional medicine for education and research.

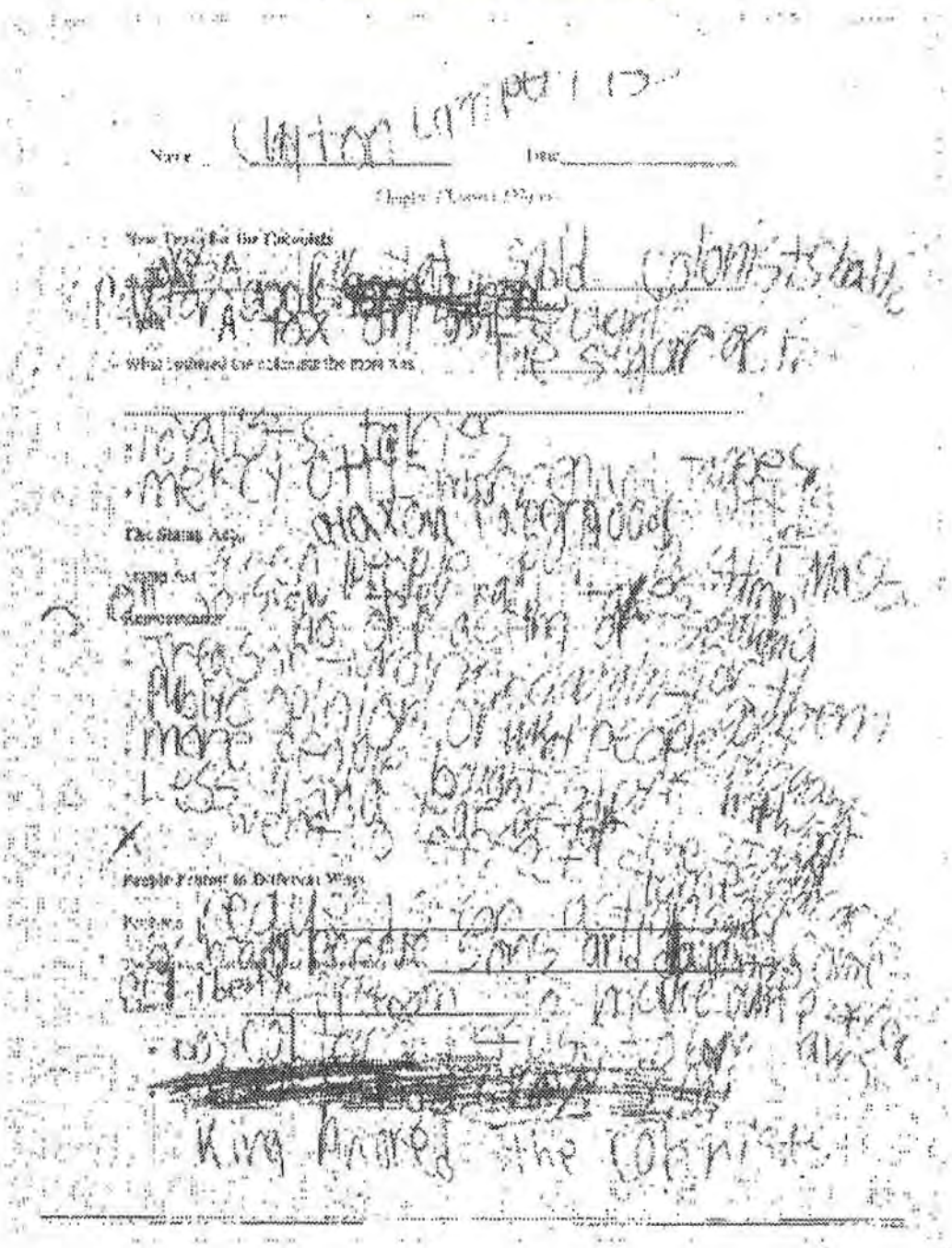
3. The establishment of a ***White House and/or Congressional Office for Health and Wellness*** to coordinate all efforts in this area as detailed in the WIN proposal submitted by Dr. Wayne Jonas.

Conclusion

Most chronic disease today is not necessary. While conventional medicine has been great for acute disease, Functional medicine is the model for easing the heavy burden of chronic disease from which our society—indeed, the whole world—suffers today.

Thank you.

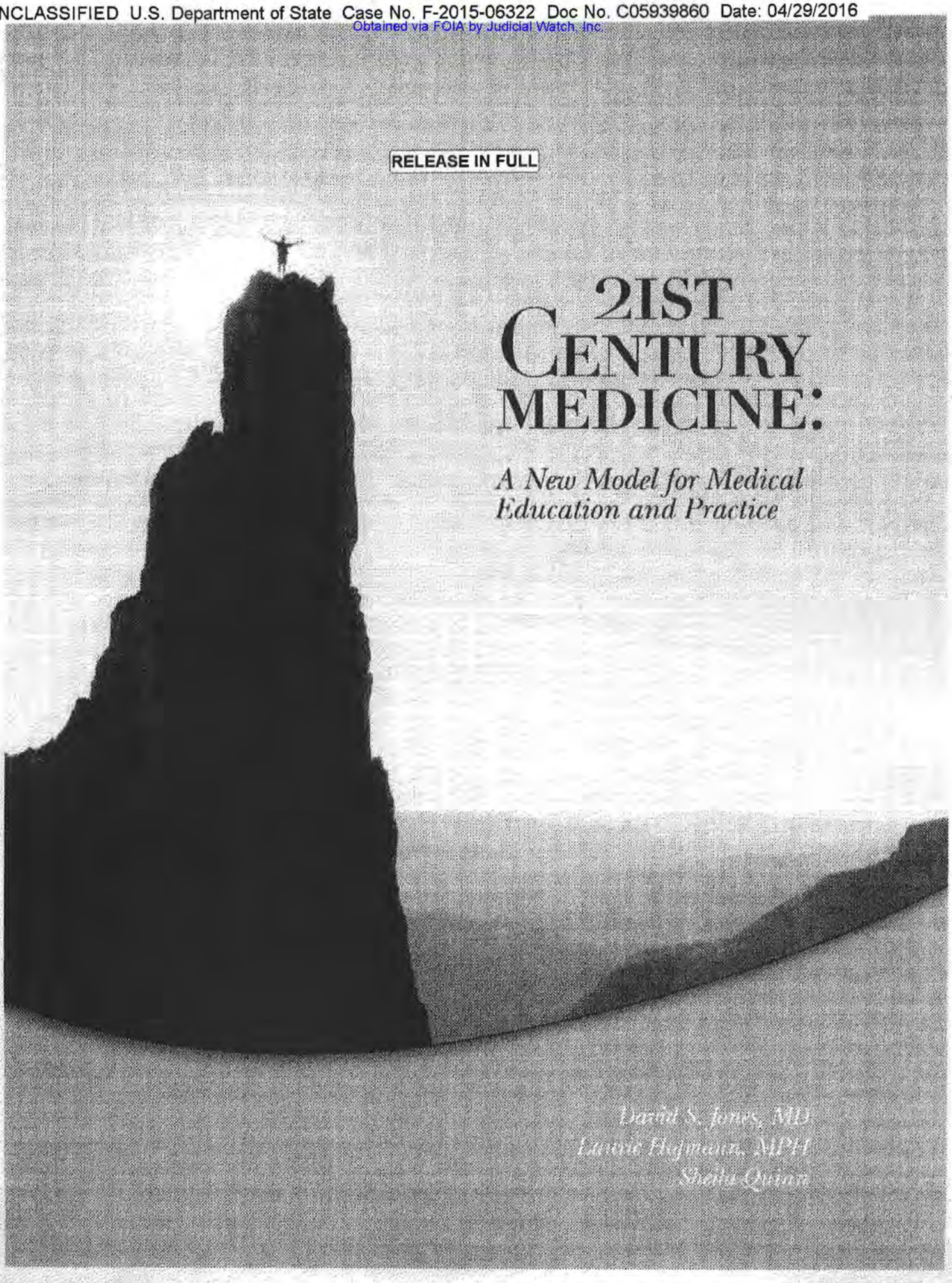
Mark Hyman, MD
Institute for Functional Medicine
45 Walker Street
Lenox, MA 01240
(413) 637-9991
mark@drhyman.com



CLAYTON LAMPERT

Clayton Lampert 136

1. I wrote this sentence.
2. I have several radios.
3. Since when do you have an x box?
4. I am thinking of something.
5. I am better at math than my sister.
6. Though the cat was old, it was still very playful.
7. We're all in this together.
8. The water was calm until the alligator attacked.
9. Usually it is quiet in my room.
10. I am very happy most of the time.
11. While you were at school, I went skiing.
12. You ate the whole cake!!!
13. I went on a cruise on the English canal.
14. I am good at mathmatics.
15. I listen to music alot.
16. My Dad took a physical.
17. I have an education.
18. The old man was not very



21ST CENTURY MEDICINE:

A New Model for Medical Education and Practice

David S. Jones, MD
Laurie Hofmann, MPH
Sheila Quinn

4411 Pt Fosdick Dr NW, Ste 305
Gig Harbor, WA 98335

21ST CENTURY MEDICINE:
A New Model for Medical Education and Practice

Table of Contents

Preface

Beginning a Journey of Discovery

The document you are about to read emerged from a systematic process of inquiry and intentionality about some of the most critical issues in health care today. While there are many vital structural factors to be addressed elsewhere (reimbursement practices, insurance coverage, electronic medical records, and the medical home concept), our attention and expertise are here focused on the content and process of care. The path we followed to conceive of, research, and write this white paper on 21st century medicine can be traced back to 2006, when the Fountainhead Foundation approved a grant to The Institute for Functional Medicine (IFM) to establish and manage a scholarship program for medical schools and residency programs to send selected faculty, students, and residents to learn about functional medicine. Over a two-year period, 43 scholarships were awarded, representing 15 medical schools and six residency programs. The impact and opportunities that have grown out of this seed funding have been significant, immediate, and wide-ranging across academic medicine, clinical programs, fellowships, and residency programs.

Our interviews, meetings, and follow-up discussions with scholarship recipients and their colleagues underscored the fact that IFM needed to provide a rationale and methodology for facilitating a more systematic and widespread introduction of functional medicine into these diverse institutions and programs. It is very arduous to modify both the process and content of medical education. There must be a compelling reason and a clear path toward the goal. Our journey, therefore, involved documenting the urgent need for a major shift in medical education, and then describing a model of care that can be adapted to the teaching needs of medical (and other health professions) schools and residency programs. In so doing, we provide both the justification for, and a description of, the change that must occur to equip clinicians to adapt successfully to the healthcare demands of the 21st century.

We looked first at relevant major themes in health care today (Chapters 2 and 3): the epidemic of chronic disease; the evolution of evidence-based medicine; the poor performance of the acute-care model in a chronic-care environment; the emergence of new paradigms such as systems biology, integrative medicine, and personalized care; and the lack of consensus on how to address these issues in a systematic way. This journey took us deep into the literature of costs vs. performance, science vs. art, research vs. clinical practice, and the many ideas about how to consolidate the gains of the 20th century without losing flexibility or constraining the promise of new information and new models of care for the future.

With this background in place, we began to explore how all of this looks and feels to the individual clinician who is immersed in the daily demands of clinical practice (Chapters 4 and 5). This, of course, is where the rubber meets the road. We found that not only have we failed to materially assist most primary care practitioners in understanding how to make better use of evidence, and in translating new tools and ideas into their clinical practice, but we have left clinical medicine poorly equipped to address two critical elements: (1) managing the uncertainty that is inherent in

clinical practice, and (2) creating a healing partnership with patients. We found that clinicians are no longer taught how to integrate the science and the art of medicine—indeed, the art of medicine has all but disappeared as a subject of teaching. From the evidence-based medicine (EBM) perspective, all you really need to do is gather data, focus the data toward securing the diagnosis, and then research the evidence about the best molecule (Rx) or procedure to treat that diagnosis. Doctors in the EBM, acute-care model have almost become technicians. Converging pressures have reinforced this model by forcing doctors to focus their office visits more and more narrowly, and to deliver care in less and less time (often for less and less money).

If that model worked, we wouldn't have had grounds for writing this paper. Unfortunately, the model has failed spectacularly to help stem the rising tide of chronic disease (Chapter 2). Fortunately, however, there is plenty of evidence that this is not the only way forward. Physicians and other practitioners can be taught to shift into a personalized, systems-medicine approach that is much better adapted to the complex demands of chronic disease. They can learn to gather and analyze patient data differently. They can twist the kaleidoscope and apply critical thinking to the use of evidence. And they can create healing partnerships that allow both patients and practitioners to achieve insight and then to evaluate that insight in the light of knowledge and experience.

The Institute for Functional Medicine has developed a model of comprehensive care and primary prevention for complex, chronic illness that is grounded in both the science (the Functional Medicine Matrix Model™) and the art (the healing partnership in the therapeutic encounter) of clinical medicine. We call this model functional medicine, and we have taught it for many years. It is not a separate discipline or specialty—it is an approach to clinical care that is comprehensive and patient-centered, personalized and grounded in science. It can be taught to and practiced by any health practitioner who has a background in the basic medical sciences and clinical practice, and it can adapt quickly and easily to emerging evidence. It can also provide a common language, shared principles and organizing tools, and a consistent analytic process to support and facilitate integrated health care.

Reintegrating the Science and Art of Medicine

There are always two deeply powered processes at work in any life-changing endeavor. Human beings require both denotative and connotative information for mastery—that is, we need both data and intuition, science and art. Brain scientists have made great progress in illuminating the deep creative processes by which our "minds" make use of the "matter" of our brains.[1,2,3,4,5,6] Clinicians, particularly, need to bring to the therapeutic encounter the unique qualities of both right- and left-brain function that have been emerging from brain science research. In the last decade, wider use of functional imaging technology has delivered a much clearer picture of coordinated brain function—why and how it occurs.

Jill Bolte Taylor, PhD was a neuroanatomist at Harvard Medical School when she sustained an aneurismal stroke in the primary speech areas of the left brain. In her video presentation to the TED (Technology, Entertainment, Design) group,[7] she describes the integrated functionality of the two sides of the brain in a way that can inform our understanding about a comprehensive patient-care model that respects and integrates both the science and the art of medicine. Her articulation of her "stroke of insight"[8] vividly illustrates important aspects of the new pattern that we must weave together:

...when you look at the brain, it's obvious that the two cerebral cortices are completely separate from one another. For those of you who understand computers, our right hemisphere functions like a parallel processor. While our left hemisphere functions like a serial processor. The two hemispheres do communicate with one another through the corpus collosum, which is made up of some 300 million axonal fibers. But other than that, the two hemispheres are completely separate. Because they process information differently, each hemisphere thinks about different things, they care about different things, and dare I say, they have very different personalities.

Our right hemisphere is all about this present moment. It's all about right here right now. Our right hemisphere thinks in pictures and it learns kinesthetically through the movement of our bodies. Information in the form of energy streams in simultaneously through all of our sensory systems. And then it explodes into this enormous collage of what this present moment looks like. What this present moment smells like and tastes like, what it feels like and what it sounds like. I am an energy being connected to the energy all around me through the consciousness of my right hemisphere. We are energy beings connected to one another through the consciousness of our right hemispheres as one human family.

My left hemisphere is a very different place. Our left hemisphere thinks linearly and methodically. Our left hemisphere is all about the past, and it's all about the future. Our left hemisphere is designed to take that enormous collage of the present moment. And start picking details and more details and more details about those details. It then categorizes and organizes all that information. Associates it with everything in the past we've ever learned and projects into the future all of our possibilities. And our left hemisphere thinks in language. It's that ongoing brain chatter that connects me and my internal world to my external world. But perhaps most important, it's that little voice that says to me, "I am. I am." And as soon as my left hemisphere says to me "I am," I become separate. I become a single solid individual separate from the energy flow around me and separate from you.

Continuing the Journey

We find ourselves at the beginning of the 21st century faced with a healthcare system in disarray on many levels. We must reassemble the disparate pieces of this baffling puzzle into a new and more coherent pattern. The intention of this document is to establish the need for a new model of care, and to make conscious, transparent, and usable the functional medicine model. We will show how this integrated model can better meet the needs of a population afflicted with steadily increasing rates of chronic disease. We believe that these changes will also help physicians establish a more satisfying basis for clinical practice.

The diligent work and thinking of 20th century clinicians and scientists have brought us to this moment with many tools and key concepts, including:

- the art and science of clinical medicine
- systems biology and personalized, systems medicine
- prospective health care
- patient-centered health care
- the chronic-care model and the chronic-care team
- integrative medicine
- nutrigenomics, pharmacogenomics, proteomics, metabolomics
- evidence-based medicine (EBM)
- right and left brain functionality and the healing partnership
- the science and practice of creating insight as part of the therapeutic encounter
- the process of managing the uncertainty inherent in the clinical encounter

Ultimately, we will transform medical education and clinical care for chronic disease only if we can elucidate both the urgency of and the pathway toward a new model. We will succeed as 21st century physicians only if we attack the underlying drivers of chronic disease and rising costs—the complex, lifelong interactions of lifestyle, environment, and genetics. We will create an integrated healthcare system only if we provide a common set of principles, concepts, and practices that can be taught to and used by all members of the healthcare team. To these ends, we have used our time, expertise, and commitment to synthesize a model of health care for the 21st century that cogently integrates the best components of both established and emerging knowledge and practices. We describe in these pages a healing partnership that can readily adapt to new approaches and new evidence, that engages all parts of the brain, and that strengthens the bodies, minds, and spirits of both physicians and patients as they share the path toward improved health.

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Chapter 1

INTRODUCTION

Opportunity

If done right, the development of a health care system that focuses on personalized health planning will be every bit as transformational as the coupling of science to medicine was in the early 20th century.

—RALPH SNYDERMAN, MD, AND R. SANDERS WILLIAMS, MD[9]

Throughout the medical system, the heartbeat of impending change has been heard with increasing intensity since the turn of the century. Concepts such as prospective health care, personalized medicine, systems biology, nutritional genomics, integrative medicine, the chronic-care model, and others represent diverse aspects of the impetus to devise a substantively different way of approaching health care in the 21st century. The shift in prevalence from acute to chronic disease[10,11], and a growing recognition of the inherent limitations and consequences of shaping medicine primarily around an acute-care model[12] are among the most powerful forces that are driving change. The context of uncertainty that pervades the realm of clinical care[13] demands a comprehensive and flexible model that can integrate evidence relevant to the individual without forcing physicians and other practitioners to manage complex, chronic disease using an acute-care model that is ill-suited to the task. Transformation is imminent—the opportunity is now.

The "next next transformation" will change the paradigm to focus on health—positively defined and measured as something other than the "absence of disease"; conceived as an integrated function of biology, environment, and behavior; and measured as a product of physical, mental, social, and spiritual variables.

—MICHAEL JOHNS, MD, AND KENNETH BRIGHAM, MD[14]

As we come to the close of the first decade of the 21st century, the opportunity to influence the strategic decisions that will redirect medical education and practice for the foreseeable future will encounter many challenges. Philosophies of health and disease, exciting new models of delivery and management of care, practitioner diversity and interrelationships, emerging perspectives on science and evidence, and the teaching of analytical thinking and clinical reasoning are all under pressure to evolve. Resistance to change and eagerness for it exist simultaneously within all established systems; both perspectives represent important issues that must be addressed successfully to ensure that changes are purposeful, practical, and effective. Educational programs and leaders will be called upon to set the pace of change, identify the best models, integrate those models into existing curriculums, and advocate for widespread adoption.

We can facilitate this process by taking into account the substantial common ground that already exists among many of the leading innovative paradigms, even when they are not directly comparable in intent or in practical applications. Congruent elements can be identified, extracted, and synthesized to inform a comprehensive new model that will be compatible with both established and emerging approaches to health education and practice. In addition, there are important principles and practices that can provide a solid foundation for synthesizing these congruent elements into a workable new model.

Visualizing and implementing a fresh approach to health and disease will require collaborative efforts and systems that work to the benefit of patients and practitioners alike. In this paper, we will describe how certain key forces and concepts are critical components of a dedicated effort to achieve productive and lasting improvements in our healthcare system. We will demonstrate how the common themes in these overlapping paradigms represent fertile terrain for synthesizing a comprehensive new model. We will identify elements that must be added to the common themes to create an effective model for teaching and practice. And we will describe that new model and advance suggestions about how to strengthen and implement it. The ideas are (metaphorically) bursting out of the literature, essential tools are being developed, and the pivotal technologies are rapidly advancing—the moment is ripe with promise.

Purpose

Our overarching purpose in writing this paper is to illuminate a path toward health and vitality for patients—not an easy or straightforward task in a world of increasing complexity and epidemic levels of chronic disease (Chapter 2). ***The intention of this document is to establish the need for a new model of care and to make conscious, transparent, and usable the functional medicine model.*** We offer to academic medicine leaders, practicing physicians, and other health professionals a model that we believe will substantially improve management of disease risk and assessment—as well as treatment for the millions of patients who already suffer from complex, chronic disease—using personalized, systems-oriented, cost-effective approaches. Blending the foundational principles and practices of functional medicine with the substantial common ground that already exists in emerging models clarifies a more comprehensive and effective model of teaching and practice for medical schools, residency programs, and eventually other health profession schools. Such an ambitious goal will succeed only if the plans rest upon a solid foundation that resonates strongly with leaders and early adopters in medical education and the health professions. Strategic objectives and effective tools to guide action steps appropriately will be required. The need for change and the matching of solutions to problems must be clear and persuasive. This paper will analyze emerging trends and needs and address the power of this synthesized model to shape those trends and meet critical needs in order to help improve the education and effectiveness of healthcare practitioners and offer their patients a better path toward lifelong health.

Emerging Models

From among the creative and fascinating new paradigms, we will address six that have emerged as leaders and already claim many adherents. They share a great deal of common ground that is critical to a synthesized, comprehensive model for 21st century medicine. Each of these new models, while incomplete in itself, contains elements that help to ensure compatibility and integration

into an overarching approach. These will be discussed in much greater detail in Chapter 3, but here we introduce the key concepts of each model. (There are other models of note, of course, including the Future of Family Medicine project and the Medical Home project; information on both of these is provided in the Appendix. In the body of this paper, however, we have narrowed our discussion to the models that appear to have the greatest potential impact on the actual content of care, rather than the structure of care.)

A graphic representation of some of the common themes and key concepts in these six models can be seen in Figure 1.

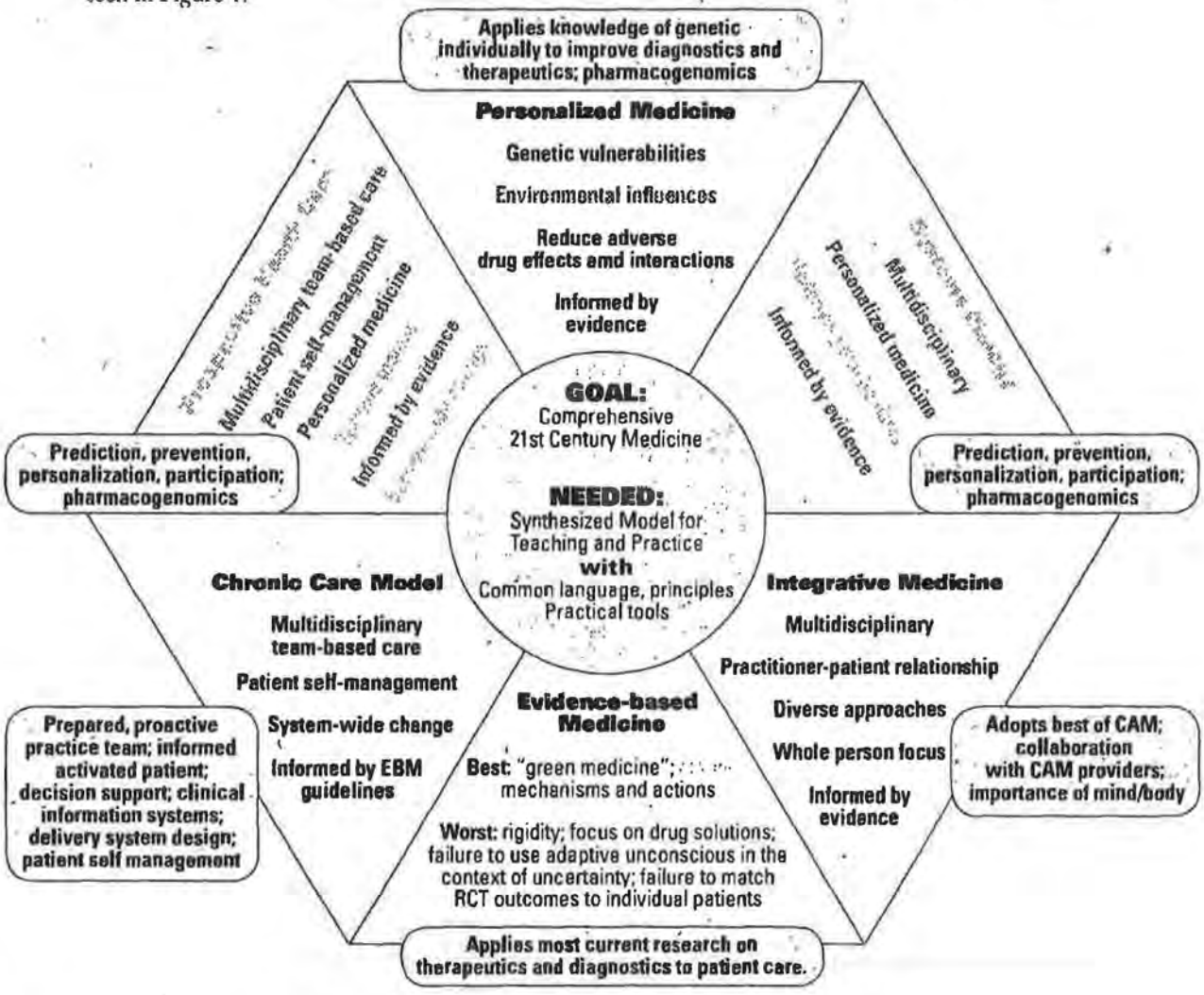


Figure 1: Common Themes and Key Concepts Among Emerging Models in Medical Education and Clinical Practice

1. Personalized medicine

Personalized medicine is often rather narrowly defined to comprise primarily the development of genetic tests to identify risk factors for adverse or unpredictable drug effects and to identify individuals who are most appropriate for certain kinds of drug therapies or diagnostic procedures.[15, 16] This kind of assessment should certainly help to improve the matching of drugs and diagnostics to individual patients and, as a result, may also help to reduce death, disability, and costs associated with individual differences in the biotransformation of drugs and other substances.[17] However, under the rubric of personalized medicine lie many other complex issues relevant to biochemical, physiological, genetic, and environmental individuality that must also be attended to if we hope to reverse the modern epidemic of chronic disease and assist patients toward healthier lives. This broader model of personalized care has already become an explicit component of systems biology and prospective health care, and it is implicit in the chronic-care model and integrative medicine as well. Personalized medicine is critical to the future of health care.

2. Prospective health care

A bold new model for 21st century medicine called prospective health care was proposed in 2003 by Snyderman and Williams.[18] Pilot projects have been initiated and are being tested now at Duke University. In a 2006 article,[19] Snyderman and Langheier described their rationale in terms completely consistent with the focus of functional medicine for the past two decades:

> Chronic diseases develop as a consequence of an individual's baseline susceptibility coupled with their exposure to environmental factors. These may trigger initiating events, leading to the accumulation of pathological changes and the onset and progression of chronic disease. Today, most health-care expenditure is focused on the later stages of this process, long after the development of many underlying pathological changes. Until recently, it could be argued that the focus on treating disease was justified because the ability to predict, track, and prevent its onset was not technically feasible. This is no longer the case, and the emerging sciences of genomics, proteomics, metabolomics, medical technologies and informatics are revolutionizing the capability to predict events and enable intervention before damage occurs. Personalized risk prediction and strategic health-care planning will facilitate a new form of care, which we have called "prospective health care."

Including the same four elements as systems biology (prediction, prevention, personalization, and participation), prospective health care offers a much broader perspective, describing structural and procedural transformations that must also occur in reimbursement, research, risk management assessment, record keeping, and the delivery of care.[20] The thrust of these changes is "toward managing disease risk and providing personalized care for chronic and acute disease."[21]

3. Chronic-care model

The full chronic-care model (CCM), first conceived in 1998, was formally presented in a 2nd publication by Wagner et al.[22] Since that time, it has undergone serious study, implementation, and revision to accommodate experiences in clinical settings and findings from research. Emerging evidence has shown fairly conclusively that patient outcomes in a variety of chronic conditions can be improved whenever substantive progress is made on integrating the elements of this model into clinical practice. Core elements include:

- Productive interactions between informed, activated patients and prepared practice teams
- Effective patient self-management strategies
- Delivery system redesign (team approach; multidisciplinary, planned interventions instead of acute, reactive interventions; use of case managers; regular follow-up)
- Decision support (integration of evidence-based guidelines into the flow of clinical practice so that information to support clinical decision making is readily available)
- Clinical information system (the use of a database and other resources that bring timely, relevant information to both physicians and patients)
- Community resources and policies

CCM has in common with prospective health care a strong emphasis on redesigning the systems that support and shape clinical practice. Both have explicit emphases on a team approach to chronic care, the necessity of patient self-management, and the urgent need to involve community resources and attract the attention of policymakers.

4. Evidence-based medicine

Evidence-based medicine (EBM) is "the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients." The practice of EBM means integrating individual clinical expertise with the best available external clinical evidence from systematic research."[i]

We include EBM in the analysis of emerging models because of its growing influence on clinical practice and medical education. Although it is not, in and of itself, a type of medical education or clinical practice, at its best it can provide practitioners and healthcare delivery organizations with more current and focused decision support through the integration of relevant research findings into clinical decision making. Although EBM is intended to reduce uncertainty and improve the consistent use of best practices in patient care, experimental designs have not yet caught up with the complexity of chronic disease, the multiple needs and diverse presentations of patients in the clinical setting, and the multifactorial interventions that are required to address such diversity and

[i] Used with permission of the Centre for Evidence-based Medicine. A more expanded definition of Evidence-based medicine is included in the Appendix.

complexity.[23] EBM cannot replace analytical thinking, clinical reasoning, and clinical experience,[24] although sometimes it is presented as doing just that. Improperly applied, EBM can place patients in serious jeopardy.[25] Ideally, it can be used to increase practitioner effectiveness if its strengths are appropriately utilized and its limitations are clear: "The methods of EBM do not supply 'correct' answers but rather information that can improve clinical judgment."[26] Ultimately, the appropriate use of EBM relies on a more precise definition of what constitutes relevance and best evidence for each individual patient encounter.

5. Systems biology

The Institute for Systems Biology in Seattle, Washington, identifies four factors that comprise its field: prediction, prevention, personalization, and participation. Although elsewhere systems biology is not defined quite so broadly, it is useful to consider it through this wide-angle lens, for it makes readily apparent the interconnections with integrative medicine, prospective health care, and personalized medicine that open the door to a synthesized model. Systems biology as currently pursued focuses primarily, as does personalized medicine, on genetic mechanisms in drug responses, but given a broad vision—and the will and funding to execute on that vision—it could become the scientific engine driving clinical medicine toward the model we are proposing. A more detailed description from the Institute for Systems Biology's Web site is provided in the Appendix.

6. Integrative medicine

In the years since 1990, when eight academic medical institutions first met to discuss the emerging field of integrative medicine, active participation among academic medical centers has grown dramatically. Now more than 40 institutions[b] are members of the Consortium of Academic Health Centers for Integrative Medicine (CAHCIM), comprising many of the most medical schools in the country, with several having endowed centers or foundations to support expanded development in the field. Their collective mission is:

> ...to help transform medicine and health care through rigorous scientific studies, new models of clinical care, and innovative educational programs that integrate biomedicine, the complexity of human beings, the intrinsic nature of healing and the rich diversity of therapeutic systems. [27]

Their definition of integrative medicine is:

> ...the practice of medicine that reaffirms the importance of the relationship between practitioner and patient, focuses on the whole person, is informed by evidence, and makes use of all appropriate therapeutic approaches, healthcare professionals and disciplines to achieve optimal health and healing.

[b]See list of CAHCIM members in the Appendix.

Several elements of integrative medicine are highly relevant to the model proposed in this paper:

- The openness to new diagnostic and therapeutic strategies (e.g., nutrients, botanicals, mind-body interventions, acupuncture) and to cooperation with health professionals from other disciplines signals an important readiness to develop a fully integrated healthcare model—one in which the patient is the central focus and all practitioners have in common certain critical elements of language, philosophy, and clinical practice.
- The commitment to adopt innovative approaches in education is essential to the transformation of medicine.
- The emphasis on the value of practitioner-patient relationships and the focus on the whole person will play a significant role in the medicine of the future. These values—formerly so intrinsic a part of medicine that they went almost unnoticed—are receiving renewed attention now that their disappearance from much of medical care has become apparent. They are absolutely vital components of a transformed approach to health care.

Summary

In this white paper, we will establish the need for a new model of education and care; we will address forces that may represent obstacles to change; and we will explore the key concepts and elements already present in science and medicine that are ripe for synthesis into a new, more comprehensive model. Our goal is to make improvement in medical education programs and clinical practice *feasible* – not in an abstract or ideal sense, but in the real world with all its resistance to change and discomfort with emerging concepts. To that end, funding has already been secured for the development of a pilot project for adapting the model to medical education. Before being finalized, each phase of the project will be reviewed by a small group of leaders within academic medicine who are interested in achieving a major shift in medical education, so that we tailor our recommendations to the audience with as close a fit as possible. Our aim is nothing short of inspiring system-wide change—the transformation of medicine is imminent, it is urgently needed, and it is entirely possible.

Chapter 2

THE CHANGING MEDICAL ENVIRONMENT

Background

There are, literally, innumerable facts and statistics available with which to describe and analyze health and health care. Any discussion must of necessity be based on a selected subset of the data and, thus, subject to the bias of the authors. We have, for example, omitted such critical issues as the reimbursement structure, governmental regulatory influences, health disparities, environmental degradation, and the uses of technology—all topics on which reams of important material have been written. Our goal here is not to cover everything that is either problematic or of value within the medical environment, but to concentrate our thinking on well-established data that help to illuminate an overarching problem—that we are losing the battle against chronic disease and that fundamental change will be required to improve our performance.

Global and economic issues

The healthcare system is influenced by increasingly complex and varied issues. Although many of these are beyond the scope of this paper, we would be remiss if we did not at least acknowledge their importance:

- The growing ethnic diversity of the U.S. population poses challenges of communication, varied beliefs and preferences about treatment, and the adverse impact of the standard American diet (SAD) on genetically vulnerable populations. [An excellent overview of emerging global health issues that are brought to the U.S. by immigrant populations can be found in the July/August 2008 issue of *Health Affairs*, which focuses on India and China. These articles demonstrate unequivocally that health issues in the developing countries parallel those of the developed world, as affluence, sedentary lives, and fragmentation of communities increase while food quality and diversity decrease.]
- The transmissibility of new diseases (e.g., avian flu) between species and across the world's continents poses a special challenge to both acute and chronic care.[28]

- Economic shifts that are strongly affected by global markets could have profound effects on the U.S. model of healthcare financing, an issue that has been under considerable scrutiny for many years already. Increasingly, the evidence identifies our patchwork approach to reimbursement as a considerable barrier to equitable and effective care.[29]
- Importation and transportation of foods, prescription drugs, botanicals, and nutraceuticals among countries with widely differing quality control and environmental standards will affect virtually every citizen over time.

While we focus in this paper on models for clinical practice and medical education, we should keep the above issues in mind, because they will continue to influence both the healthcare system and individual health

The pharmaceutical and acute-care models

The acute-care model is characterized by rapid differential diagnosis aimed at prescribing a drug (or procedure) that will ameliorate the patient's presenting symptoms and avert the immediate threat.[30] It minimizes the involvement of the patient, who functions as a mostly passive recipient of the procedure or prescription.[31] It is not a model that reimburses the practitioner for looking into why the patient became ill, or whether she/he will be back many times for continuous of the same underlying problem.[32] Instead, it prioritizes quick solutions to the most pressing problems. It is, of course, absolutely essential in emergency and hospital-based care, but difficulties arise when this model is applied to ongoing, community-based care, a process that accelerated under the managed-care movement (which turned out to be far more about managing costs than managing care) and the direct-to-patient advertising of drugs. With hindsight, it seems as though everything has been pushing the system toward this narrowed focus, regardless of it (Figure 2).

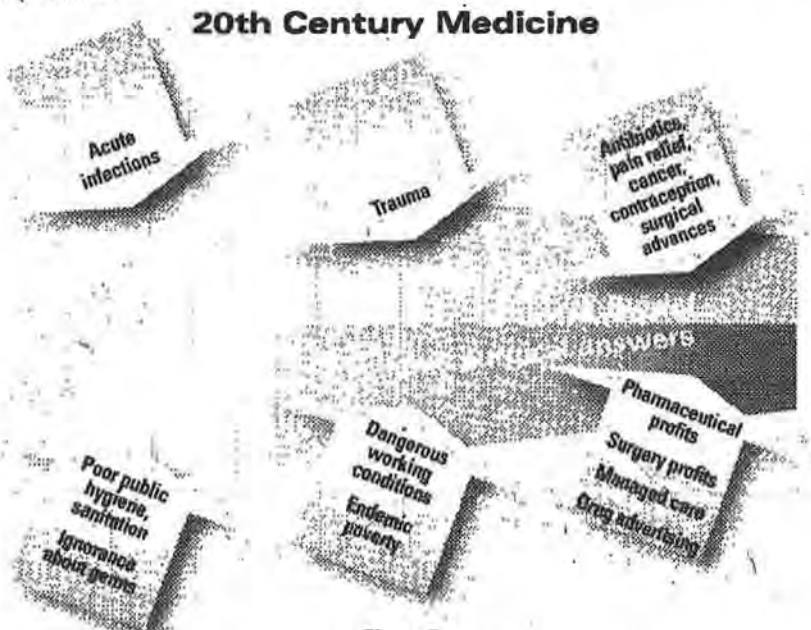


Figure 2:
Forces Narrowing the Focus of 20th Century Medicine

The advances achieved by drugs in curing acute infections and managing some of the most threatening diseases mankind has faced were dramatic in the last century. The extended romance with pharmaceutical medicine, which first blossomed in the early 1930s when penicillin began to cure previously intractable infectious diseases, has now dominated medicine and medical education for more than seven decades. From depression to diabetes, from heart disease to asthma, the search for therapeutic compounds that can be patented as drugs continues unabated. The accompanying financial incentives have attracted (and perhaps distracted, see **Sidebar**) some of the best minds and most influential leaders in research and medical education, including those engaged in the development of systems biology and personalized medicine, both of which are primarily focused on pharmacogenomics at this time (see Chapter 3 and the Appendix for more information on these models).

Costs and Performance in the Battle for Health

It is discouraging to note that among the vast array of peer-reviewed medical research reports published every year, there is so little that addresses whether the overall health of the population shows an adequate positive response to current medical treatment. Thousands upon thousands of studies compare one drug to another without ever acknowledging that Americans are far less healthy—at far greater cost—than their counterparts in the rest of the industrialized world. The reduction in deaths from, for example, heart disease is emphasized,[39] while the fact that we have failed to prevent CVD—even while reducing, through drugs, the prevalence of CVD risk factors such as hypertension and high cholesterol[40] —is too often ignored. In fact, we must turn primarily to philanthropic or governmental agencies for data and analyses that reveal the scope of the failure. "The Milken Institute recently estimated that the most common chronic diseases cost the economy more than $1 trillion annually, mostly from lost worker productivity, which could balloon to nearly $6 trillion by the middle of the century."[41] If nothing else, that estimate alone should galvanize us to action!

Research Bias: The Pharmaceutical Hegemony in Funding and Focus

Opportunities lost are perhaps the greatest concern in the dominance of the pharmaceutical research model. Too often, the search for drugs that will pay off for investors and executives of pharmaceutical companies determines the research agenda.[35] Rather than being driven by patient needs, public health priorities, or scientific curiosity about mechanisms and pathways, the profit motive is the driver of the research agenda, and the gains to science and health are collateral outcomes, not central purposes. Lest we think this is trivial, consider that 70% of the money for clinical drug trials in the U.S. comes from the pharmaceutical industry.[34]

"Scientifically, a neutral or negative trial is as valuable as a positive one," although commercially this is clearly not the case."[35] Unless all results are available to the scientific community, the evidence record about those drugs that are investigated can be significantly skewed by the absence of negative or neutral findings. The value to academic researchers (and their institutions) of bringing in large clinical trials with drug company funding may be very significant; promotions, recognition, and supplemental income provide a triple-threat incentive that is virtually impossible to ignore when considering research priorities.[36, 37]

Many studies have shown a bias toward positive results when the research was funded by the drugs' manufacturers.[38]

The broad education in science and clinical arts that physicians experience today is expressed in clinical practice through a constricting and linear process that is primarily aimed at naming a drug of choice for the patient at hand.[42] Unfortunately, 50 years of such practices have failed to stem the rising tide of chronic diseases among both young and old,[43] while related problems have emerged to cause great concern:

- The **cost of care** is unmanageably high and rising,[44] driven by the high costs of hospitalization[45] and drugs,[46, 47] but also fueled by increasing prevalence of complex, chronic disease at all ages of the population.[48, 49] It is estimated, for example, that more than half of all Americans suffer from one or more chronic diseases,[50] and that the 8 million Medicare beneficiaries who have five or more chronic conditions accounted for over two-thirds of the program's $302 billion in spending in 2004.[51]

> The Milken Institute report, *An Unhealthy America* (October 2007), provides the following food for thought:
>
> "To quantify the potential savings from healthier lifestyles and plausible but modest advances in treatment, we compared a "business-as-usual" baseline scenario with an optimistic scenario that assumes reasonable improvements in health-related behavior and treatment. The major changes contemplated here are weight control combined with improved nutrition, exercise, further reductions in smoking, more aggressive early disease detection, slightly faster adoption of improved therapies, and less-invasive treatments....
>
> "Across the seven diseases, the optimistic scenario would cut treatment (direct) costs in 2023 by $217 billion.... And the cumulative avoidable treatment costs from now through 2023 would total a whopping $1.6 trillion. Note that this would be a gift that keeps on giving, saving hundreds of billions annually in the years beyond 2023.
>
> **"All told, our analysis implies that modest reductions in avoidable factors—unhealthy behavior, environmental risks, and the failure to make modest gains in early detection and innovative treatment—will lead to 40 million fewer cases of illness and a gain of over $1 trillion** annually in labor supply and efficiency by 2023. Compared to the costs we project under the business-as-usual scenario, this represents a 27 percent reduction in total economic impact."

- Table 1 displays the **bookends of health: rankings on infant mortality and life expectancy**. The U.S. makes a very poor showing on both, particularly for a country whose citizens have been taught to believe they have the best health care in the world. The U.S. spends twice the median per-capita costs calculated by the Organization for Economic Cooperation and Development (OECD),[52] has extraordinarily poor outcomes for such a massive investment,[53] and does not even provide coverage for all its citizens (an estimated 47 million currently uninsured[54]; 75 million under- and uninsured combined[55]).

Table 1. Infant Mortality and Life Expectancy Rankings of the United States

Ranking	Country	Infant Mortality[1]	Country	Life Expectancy[2]	Ranking
1	Sweden	2.8	Japan	81.4	1
2	Japan	3.2	Switzerland	80.6	2
3	Finland	3.5	Sweden	80.6	3/4
4	Norway	3.6	Australia	80.6	3/4
5	Czech Republic	3.9	Canada	80.3	5
6	Germany	4.1	Italy	79.9	6/7
7	France	4.2	France	79.9	6/7
8	Spain	4.3	Spain	79.8	8
9	Switzerland	4.3	Norway	79.7	9
10	Austria	4.5	Israel	79.6	10
11	Denmark	4.5	Greece	79.4	11
12	Australia	4.6	Austria	79.2	12
13	Canada	4.6	New Zealand	79.0	13/14
14	Portugal	4.9	Germany	79.0	13/14
15	United Kingdom	5.0	United Kingdom	78.7	15
16	Ireland	5.2	Finland	78.7	16
17	Greece	5.3	United States	78.0	17/18/19
18	Italy	5.7	Denmark	78.0	17/18/19
19	New Zealand	5.7	Cyprus	78.0	17/18/19
20	Korea, South	6.1			
21	United States	6.4			

1. Infant deaths per 1,000 live births.
2. Life expectancy at birth, in years, both sexes.
Source: U.S. Census Bureau, International Database
From http://www.infoplease.com/ipa/A0004793.html

- The **"quick fix" mentality** that drug dependence has fostered in patients creates an unhealthy cycle that drives further drug dependence. Sensible and distinguished voices calling for major long-term investments in helping people establish healthy behaviors and in ensuring a healthy planet have heretofore been mostly ignored in the struggle for attention and funding. And yet, with only a few exceptions, the development of chronic disease is predominantly influenced by multiple interactions between genes and environment experienced over many years; neither factor alone is enough—the genes must be plunged into an adverse environment to express disease and they must be rescued from such environments to restore health (not just suppress symptoms):

- **Walter Willett:** "For most diseases contributing importantly to mortality in Western populations, epidemiologists have long known that nongenetic factors have high attributable risks, often at least 50 or 90%, even when the specific etiologic factors are not clear."[56]
- **Kenneth Thorpe:** "Health behavior such as overconsumption of food, lack of exercise, smoking, and stress accounts for 40% to 50% of morbidity and mortality."[57]
- **Robert Heaney:** "Discerning the full role of nutrition in long-latency, multifactorial disorders is probably the principal challenge facing nutritional science today. The first component of this challenge is to recognize that inadequate intakes of specific nutrients may produce more than one disease, may produce diseases by more than one mechanism, and may require several years for the consequent morbidity to be sufficiently evident to be clinically recognizable as 'disease.'"[58]

- Drug-resistance phenomena,[59] **adverse drug reactions**,[60] and adverse interactions between drugs and foods,[61] drugs and botanicals,[62] and drugs and other drugs[63] now affect millions of lives each year and are a cause of death in unprecedented numbers.[64] Rates of visits to provide care for adverse drug reactions increased by one-third between 2001 and 2004.[65]

On a deeper level, the drug paradigm—and the most rigid part of the evidence-based movement that supports it—may adversely affect clinical judgment. To minimize time spent with patients, physicians are forced to focus on prescribing the "right" drug. Very often, however, the evidence about the "right" drug rests on studies that do not reflect a real patient population as seen in clinical practice[66]; multiple comorbidities, for example, are usually excluded from RCTs.[67, 68] Until very recently, nearly all clinical trials failed to account for variations in individual biochemistry and physiology, as well.[69, 70]

This shift toward rapid prescribing results in a de-emphasis on establishing therapeutic relationships and exploring the patient's story. Time pressures applied by reimbursement entities make it very difficult to do the analytical thinking that develops broad pattern-recognition abilities. Immensely valuable clinical skills for managing complex, chronic disease and multiple comorbidities are thus being sidelined; as that happens, fears about innovation and creativity surface, a retreat to dogma and linearity becomes apparent, and the idea that the job of medicine is to find the right drug(s) for the most pronounced diagnosis preoccupies mainstream thought. Such forces separate the physician from many analytical and inferential skills that are likely to be extremely useful in the search for common underlying pathways of chronic disease and for new approaches designed to intervene where such disease actually originates—in the patient's unique mix of biochemistry, genetics, and environment.

The focus on drugs could be considered both cause and effect of the dominance of the acute-care model that has come to characterize medicine today. As the challenges of infectious disease and trauma gave ground to advances in drugs and surgery, startling successes strengthened the belief that modern medicine would eventually conquer most diseases with those tools. A perspective that only intensified as the profits to be made from drugs and surgery became a magnet for both individuals and institutions. Few scientists or physicians in the 1950s and 60s foresaw a moment when the challenge of chronic disease would swamp the healthcare system and prove resistant to the miracles of 20th century medicine.

Now, however, in the 21st century, we are fully aware that **complex, lifelong interactions between our genes and environmental degradation,[71] unhealthy diets[72] (fueled by changes in both eating habits and food supply[73]), stress,[74,75,76] sedentary lives,[77] and social fragmentation of families and communities[78] have surged to the forefront as interwoven causes of chronic disease that are not amenable to treatment with an acute-care model.** (Figure 3 depicts the pressures that are forcing a broader process of clinical thinking and care.) With an aging population, these effects are present through many more years of life and thus become impressive cost drivers (see, for example, the Medicare data in Figure 4). The system must expand to address these interconnected trends. Broad-based pattern-recognition and communications skills will be needed to prevent, treat, and reverse the declining function associated with these pervasive influences. We must transform our system of health care through new models for medical education, acute and chronic disease management, research, health insurance, and fiscal responsibility.

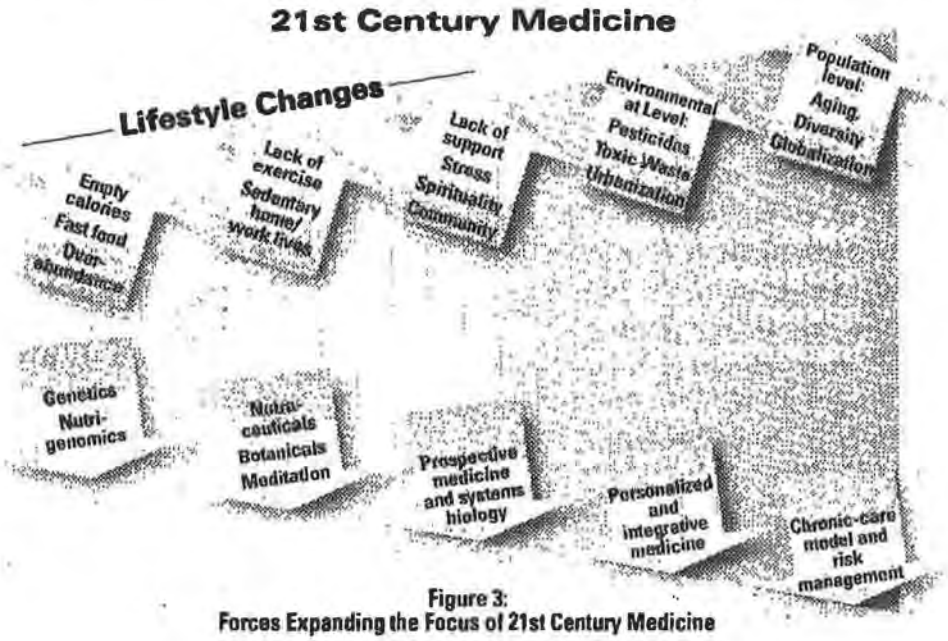


Figure 3:
Forces Expanding the Focus of 21st Century Medicine

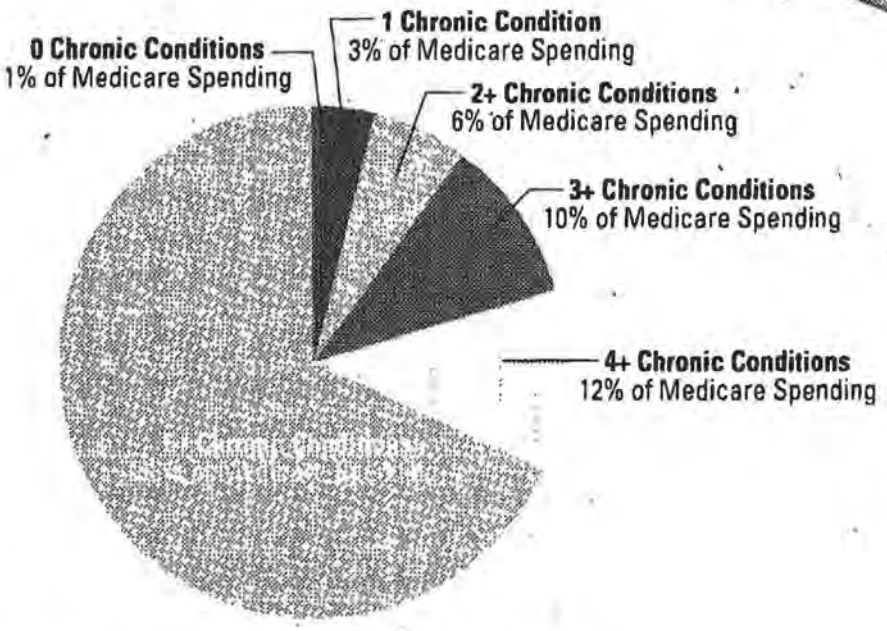


Figure 4:
Medicare Spending as a Function of Number of Chronic Conditions

Data from Chronic Conditions: Making the Case for Ongoing Care. Johns Hopkins University and The Robert Wood Johnson Foundation: Partnership for Solutions, September 2004.

The seemingly intractable poor performance of American medicine on a wide range of health measures[79, 80] forces us to pose some critical questions:

- Does the investment in a paradigm that identifies drugs as the treatment of choice across a broad array of diagnoses still produce the same returns on investment that were achieved in earlier decades?
- Is a system that seeks to reduce doctor-patient face time to the fewest possible minutes, and that measures effectiveness by how little time and money are spent, going to enable us to address population-wide health needs in the century ahead?
- Does the acute-care model respond appropriately to the needs of patients already suffering from complex, chronic disease and multiple comorbidities, as well as to the exigency of preventing those diseases for currently healthy people and future generations?

We suggest that not only is the evidence persuasive that the answer to those questions is "no," but that the continued almost exclusive reliance on pharmaceutical answers to an epidemic of complex, chronic disease may constitute an unintended rejection of some practices critical to improving our response to today's urgent problems.

Changing Patterns: From Acute to Chronic Disease

The changes in mortality and morbidity in the United States over the last century have been described as a shift from an age of "pestilence and famine" to an age of "degenerative and man-made diseases."[81] In other words, infections and undernutrition as relatively straightforward causes of illness and (often early) death have been overwhelmingly superseded by chronic, degenerative conditions caused by multiple, complex influences. In addition to the discovery and development of antibiotics, the great achievements of the public health system[82]—vaccinations; safety in municipal water and sewage systems, foods, medicine, workplace, highways and motor vehicles; prenatal and pediatric care; reduction in smoking—were among the most critical factors in making this shift, particularly in the first half of the 20th century.

Medicine's focus on the development of a sophisticated and multifaceted pharmaceutical war chest to cope with infectious disease achieved many notable successes. Unfortunately, infectious disease still has an uncomfortable persistence—a way of breaking out in a different guise just when it was thought to be under control—witness the emergence of AIDS, the ability of bacteria and viruses to become resistant to drug treatments, and the ever-evolving influenza virus, to name a few examples. There is no question, however, that pneumonia, influenza, tuberculosis, and diarrhea/enteritis (the leading causes of death in the United States in the early 1900s) have been replaced by heart disease, cancer, and cerebrovascular disease at the top of the mortality list.[83]

The tremendous advantage of this shift is that we can live much longer with chronic than acute diseases.[ii] Cardiovascular disease (CVD), for example, is the biggest killer,[iii] even though three of its four primary risk factors (hypertension, hypercholesterolemia, smoking) have been significantly reduced.[84] Unfortunately, the fourth, diabetes, has increased.[85] Pharmaceutical and surgical interventions have evolved to address both secondary prevention and symptom management. The upshot of this massive, long-term effort is that people with CVD are living longer and the incidence of death from this disease has substantially decreased.[86]

We could stop there and declare victory, but that would be tragically shortsighted. Although we have reduced the mortality associated with many serious chronic diseases, the prevalence of, for example, cancer, diabetes, asthma, and heart disease—and the conditions that precede and perpetuate them—has grown, rather than diminished. Rising disease prevalence is complex, of course, composed of at least three primary factors: "...a rise in the population prevalence of disease, changes in clinical thresholds (and awareness) for treating and diagnosing disease, and new technologies that allow physicians to treat additional patients with a particular medical condition. A rise in total disease prevalence (both diagnosed and undiagnosed) is associated with changing population risk factors such as obesity. For instance, among adults ages 20–74, obesity prevalence increased from 14.5% (1976–1980) to 30.4% 20 years later (1999–2000). During the same period, total diabetes prevalence, which is clinically linked to obesity, increased 53%, and diagnosed (treated) diabetes prevalence increased 43%."[87]

[ii] In the last century, overall life expectancy has risen from 51 to 79.4 years for women and from 48 to 73.9 years for men. Source: Chapter on Human Health, EPA Report on the Environment, 2003. Available at http://www.epa.gov/roe/roe/html/roeHealthSt.htm

[iii] "According to the NCHS, if all forms of major CVD were eliminated, life expectancy would rise by almost seven years. If all forms of cancer were eliminated, the gain would be three years." Heart Disease and Stroke Statistics—2008 Update, American Heart Association. Cited source: U.S. Decennial Life Tables for 1989-91, Volume 1, No. 4. Eliminating Certain Causes of Death, 1989-91. NCHS, September 1999.

The current (and growing) dominance of chronic and degenerative diseases in the population is accompanied by many grave problems in addition to shortened life expectancy for today's children: increasing disability over time, lowered quality of life, and far greater costs—both for direct treatment and as a result of important factors such as lowered productivity, reduced income due to early disability, and the cost of supporting disabled people in society for many years. As discussed above, the cost of simply treating—with all the tools and expertise at our command—the current epidemic of chronic disease threatens to either bankrupt us or to displace resources needed for other urgent priorities such as education, infrastructure, social security, defense, research, and countless other vital activities.

We also know with greater certainty that longer life without vitality and health imposes a considerable burden in addition to the costs of treatment:

- Depression is strongly associated with chronic disease; it has become one of the world's most common conditions and results in severely decreased quality of life and increased direct and indirect costs.[99]
- Overall health-related quality of life (HRQOL) has gone down as chronic disease rates have risen. The Mortality and Morbidity Weekly Report Surveillance Summaries reported that "during 1993-2001, the mean number of physically unhealthy days, mentally unhealthy days, overall unhealthy days, and activity limitation days was higher after 1997 than before 1997. ...Adults increasingly rated their health as fair or poor and decreasingly rated it as excellent or very good."[100]
- Prolonged stress is exerted on families that provide care for disabled elders. "An estimated 16 million Americans—more people than live in all of New England—find themselves 'sandwiched' between two generations, struggling to raise their kids while caring for an aging loved one. That number is about to explode: In 25 years, there will be 60 million Americans between the ages of 66 and 84, many of them needing full- or part-time care."[101]

The Role of Obesity in Chronic Disease

Focusing on the role of obesity in chronic disease could pay untold dividends. "[O]ne of the most heritable of human traits,"[88] obesity is also profoundly influenced by lifestyle and environment.[89] It fuels (and can be exacerbated by) chronic diseases with high morbidity as well as mortality—cancer, diabetes (now projected to touch 30-40% of all Americans during their lifetimes), heart disease, and depression. As an outcome of the rise in diabetes and other obesity-driven diseases, Olshansky et al. made the shocking projection in 2005 that "... the steady rise in life expectancy during the past two centuries may soon come to an end."[90] In other words, if current trends continue unchecked, future generations will have shorter and less healthy lives than the adults of today.

The urgency of this situation is underscored in many compelling—and poignant—scientific papers that highlight some of the profound effects of the obesity epidemic on all age groups:

- **Elderly:** "Obese seventy-year-olds will live about as long as those of normal weight but will spend more than $39,000 more on health care. Moreover, they will enjoy fewer disability-free life years and experience higher rates of diabetes, hypertension, and heart disease."[91]
- **Adults:** "Two-thirds of adults in the United States today are obese or overweight."[92] "...the prevalence of diagnosed type 2 diabetes mellitus continued to increase concurrently

- Creativity and innovation are lost to underemployment or unemployment and the shrinking work force must support an increasingly disabled aging population for many more years.

We can and should feel grateful that the threat of acute disease decreased so substantially over the last century and, concomitantly, that our life expectancy increased dramatically. We must also recognize, however, the urgent need to redirect some of our healthcare dollars, energy, expertise, and time toward stopping and ultimately reversing the spread of chronic disease. While it is certainly true that we all must die of something, and conquering acute disease made space for chronic diseases to rise to the top of the mortality charts, we cannot allow our much longer lives to be increasingly haunted by unprecedented rates of chronic disease and its accompanying disability, depression, and sharply rising costs. Instead of spending all our resources on managing symptoms and secondary prevention, we must turn our attention to causal factors. We know with steadily increasing confidence and knowledge that the primary driver of chronic disease is the interaction among genes, activities of daily living (lifestyle), and the environment. Describing a model that folds that very general awareness into actual clinical practice, enabling physicians to acquire effective skills and tools for addressing the unique pattern of each individual patient's life and health, is the ultimate goal of this paper.

Improving the Response to Chronic Disease

Chronic disease is now the principal cause of disability and use of health services and consumes 78% of health expenditures. (p. 1057 in the publication cited) [D]eveloping a different way to practice medicine for chronic disease is at the heart of any solution to the problem.
(p. 2975, a reply to letters generated by the cited publication)

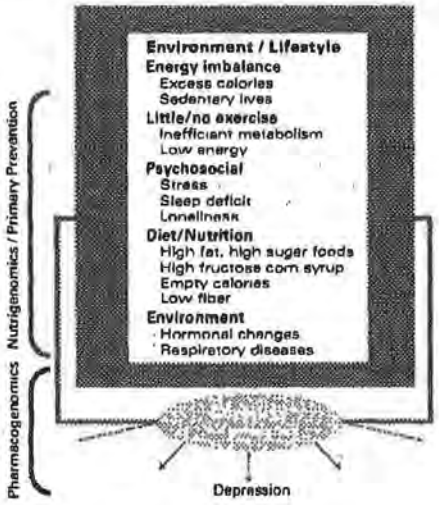
—Halstead Holman, MD, JAMA, 2004[107]

The burden of harm conveyed by the collective impact of all of our health care quality problems is staggering. It requires the urgent attention of all the stakeholders: the health care professions, health care policymakers, consumer advocates and purchasers of care. The challenge is to bring the full potential

with increases in obesity."[94]

- **Adolescents:** "...extrapolation from current data suggests that adolescent overweight will increase rates of CHD among future young and middle-aged adults, resulting in substantial morbidity and mortality ... more than 100,000 excess cases of CHD attributable to the increased obesity."[94]
- **Children:** Type 2 diabetes, previously almost unheard of in children, "...has become common among the pediatric age population, accounting for ~40% of all diabetes diagnosed."[95]

A (highly simplified) model of the multiple, complex influences that create obesity and associated chronic diseases:



If we concentrate our resources at the bottom of the diagram, on pharmacogenomics, we have already lost the battle; chronic disease is already entrenched and the costs of treating it will only rise.

benefit of effective health care to all Americans while avoiding unneeded and harmful interventions and eliminating preventable complications of care. Meeting this challenge demands a readiness to think in radically new ways about how to deliver health care services and how to assess and improve their quality. Our present efforts resemble a team of engineers trying to break the sound barrier by tinkering with a Model T Ford. We need a new vehicle or perhaps, many new vehicles. The only unacceptable alternative is not to change.

—Mark Chassin, MD, MPH; IOM National Roundtable on Health Care Quality, JAMA, 1998[103]

The three arenas in which fundamental change is required in order to improve both prevention and treatment of chronic disease are medical education, clinical care (which is conditioned by medical education), and consumer/patient behavior. This paper focuses primarily on clinical care.

Medical education

The Institute of Medicine report, *Crossing the Quality Chasm*, in the chapter on "Preparing the Workforce" (p. 213) observes: "Despite changes that have been made, the fundamental approach to medical education has not changed since 1910."[104] The report also addresses some of the factors that make changing medical education very difficult. However, it does not directly address the imperative to integrate creative and innovative approaches to chronic disease into the process. Medical education must teach physicians to quickly and skillfully differentiate situations requiring an acute-care intervention from those presenting the very different challenge of complex, chronic disease. Once that differentiation is achieved, then physicians must be given new tools, information, and skills with which to address the common comorbidities and complexities of chronic disease. Key concepts that underlie and will facilitate these fundamental changes are presented in Chapters 4 and 5 of this paper.

Clinical care

Changes in the roles of both patients and clinicians are critical to transforming our healthcare system. Chapter 4 addresses "The Clinician's Dilemma": how to practice in such a way that both the continuing advances of science

It is important to note, however, that there is no precise, predictive formula. One person's obesity is not identical in cause, signs and symptoms, or secondary outcomes to another's, and thus both treatment and prevention must be individualized to accommodate the genetics, lifestyle, and environment of each patient. Any model for managing chronic disease that does not address all of these components will fall short in comprehensiveness and effectiveness. In a 2008 publication in *Circulation*,[96] the American Heart Association described a comprehensive population-based approach to preventing obesity, including the following key strategies (among others):

- Prevention at the population level, with emphasis on key risk subgroups
- Differentiating environmental and policy approaches from clinically-based interventions
- Use of an ecological model that "includes multiple layers of influences on eating and physical activity across multiple societal sectors"

Often in medicine the marshaling of substantial and focused resources to fight a public health problem wears upon the research agenda. While there are many questions yet to be answered about how and why obesity develops and how and why it is such a risk factor for other serious diseases, it is a long and expensive process to test and verify strategies for prevention and treatment.[97] We cannot afford that delay; there are far too many lives at stake. Dr. Richard Horton, editor-in-chief of *The Lancet*,

and the essential art of medicine are integrated seamlessly into clinical practice, neither overshadowing the other. Clinicians must improve their capacity to incorporate important emerging evidence into a personalized, systems-oriented model of care, within the context of a strong healing partnership with patients. Chapter 5 presents the functional medicine model and methods that facilitate this evolution as well as an approach to establishing and strengthening the healing relationship. Two cases that exemplify the process are presented.

Consumer (Patient) needs and preferences

The growth and sustained energy of consumer interest in alternative and complementary medicine over the last quarter century is one indicator of the desire patients have for a different kind of healthcare system. Although not addressed directly in this paper, healthcare consumers must be assisted to take a lifelong interest in the forces that push each of us toward health or disease. As difficult as it is for physicians and other health practitioners to alter their mode of practice, that's how difficult it is for patients to alter their mode of living to maximize the prospects of health and minimize the risks of disease. These changes represent a major undertaking and we will not be successful unless both consumers and providers of health care commit to a long-term, sustained effort.

addressed this issue in an editorial titled, "The Precautionary Principle":

We must act on facts, and on the most accurate interpretation of them, using the best scientific information. That does not mean we must sit back until we have 100% evidence about everything. Where the state of the health of the people is at stake, the risks can be so high and the cost of corrective action so great, that prevention is better than cure. We must analyze the possible benefits and cost of action and inaction. Where there are significant risks of damage to the public health, we should be prepared to take action to diminish those risks even when the scientific knowledge is not conclusive, if the balance of likely costs and benefits justifies it.[90]

We must act in concert with emerging research, being willing and able to adapt as new information becomes available. That is why we need a model of care that is comprehensive, yet flexible; science-based but not rigidly bound to an imperfect and incomplete evidence base; personalized and holistic. That model will be presented and discussed in Chapters 4 and 5.

Chapter 3

PERSONALIZED MEDICINE

If it were not for the great variability among individuals, medicine might as well be a science, not an art.

—SIR WILLIAM OSLER, 1892

What is it?

Personalized medicine can be described as the effort to define and strengthen the art of individualizing health care by integrating the interpretation of patient data (medical history, family history, signs, and symptoms) with emerging "-omic" technologies—nutritional genomics[v], pharmacogenomics[vi], proteomics[vii], and metabolomics[viii].[105] Developing these strategies is critical to enabling physicians to match individual patients to the best diet, environment, nutraceuticals, and pharmaceuticals for their genetic make-up—a process that will eventually revolutionize medicine. Such a comprehensive individual fingerprint is still many years away from being feasible in research or clinical practice. It is not too early, however, to begin learning about it and applying key concepts and early data to patient care in incremental steps as the evidence base advances.

To date, the research underlying personalized medicine has concentrated mostly on pharmacogenomics. The knowledge that "a relatively large number of patients treated for cancer, infectious disease, psychiatric

[v] **Nutritional genomics or, as commonly used, nutrigenomics:** The study of how different foods may interact with specific genes to increase the risk of common genetic diseases such as type 2 diabetes, obesity, heart disease, stroke, and certain cancers. Nutrigenomics also seeks to provide a molecular understanding of how common chemicals in the diet affect health by altering the expression of genes and the structure of an individual's genome. The premise underlying nutrigenomics is that the influence of diet on health depends on an individual's genetic make-up. (From MedicineNet.com)

[vi] "...**pharmacogenomics** includes identifying candidate genes and polymorphisms, correlation of polymorphisms with therapies, prediction of drug response and clinical outcomes, reduction in adverse events, and selection and dosing of drugs based on genotype." (Issa, 2007)

[vii] **Proteomics:** The study of the proteome, the complete set of proteins produced by a species, using the technologies of large scale protein separation and identification. The term proteomics was coined in 1994 by Marc Wilkins who defined it as "the study of proteins, how they're modified, when and where they're expressed, how they're involved in metabolic pathways and how they interact with one another." (From MedicineNet.com)

[viii] **Metabolomics/Metabonomics:** The study of metabolic responses to drugs, environmental changes and diseases. Metabonomics is an extension of genomics (concerned with DNA) and proteomics (concerned with proteins). Following on the heels of genomics and proteomics, metabonomics may lead to more efficient drug discovery and individualized patient treatment with drugs, among other things. (From MedicineNet.com)

illnesses, respiratory diseases and cardiovascular conditions are not responding to the drugs they are given"[106] has been one of the key drivers of the field. The process of developing new drugs specifically designed for personalized applications involves many phases: identification and screening of candidate genes; detection and description of various polymorphisms that affect drug response (e.g., slow or rapid metabolizers); the correlation of each polymorphism with possible therapeutic targets; and the evaluation of clinical outcomes with large enough study sizes to create confidence in the efficacy of the new strategy. All of these steps must occur before selection of a drug and specification of therapeutic dosage can be based on genotype.[107] Once the drug development process is complete, the transformation of research-based data into a new tool for clinical practice must await a cost-effective screening test for patients (a process that involves many challenging and time-consuming phases—see **Sidebar**), delineation of which patients should be screened and at what stage in their care, and long-term follow-up to check for possible adverse effects of therapy. The identification of drugs already in the pharmacopeia that have inter-individual variability in dosing, efficacy and/or side effects that would make them amenable to a pharmacogenomics approach will also be a lengthy and expensive process, as there are thousands of drugs that could be tested for such personalized applications. Screening tests to detect various polymorphisms must also be developed and they must be cost effective if they are to be utilized routinely in clinical care. Pharmacodiagnostic tests that enable clinicians to quickly and cost effectively identify patients who are at risk for adverse drug responses "must possess high sensitivity and specificity with regards to their predictive performance."[108]

A couple of examples will indicate the incalculable potential—and the complexity and costliness—of pharmacogenomics as a clinical strategy:

- **New drug development:** Herceptin® (trastuzumab) is a monoclonal antibody developed to treat breast cancer that over-expresses HER2 (human epidermal growth factor receptor 2). This characteristic "is associated with an aggressive phenotype, high recurrence rate and reduced survival"[110] and it affects approximately 25-30% of breast cancer patients.[111] Before a drug could even be conceptualized, the HER2 protein

Integrating Pharmacogenomic Testing in Clinical Practice

McKinnon et al.[109] describe a general process for developing pharmacogenomics tests that can be used in clinical practice. Each of these steps represents a point at which poor outcomes may completely stall the development of an affordable and effective clinical test:

1. Identify circumstances in which knowledge of inter-individual variation in drug response is likely to improve clinical (or financial) outcomes)
2. Find a significant genotype-phenotype association
3. Determine reproducibility across ethnic populations
4. Propose model of how genotyping would guide clinical practice
5. Collect data on cost effectiveness of new pharmacogenomic profile vs. current practice
6. Educate stakeholders on appropriate use
7. Implement testing in a staged manner

had to be detected and reliably identified, and many breast cancers had to be analyzed to discover the proportion with overexpressed HER2. Then, the search for a drug targeted to this trait could begin. Ultimately, trastuzumab was developed, tested, and validated in research trials as an effective treatment for breast cancers that over-express HER2; its ability to work with other chemotherapeutic agents was also assessed. Two cost-effective screening tests were developed and are now available—immunohistochemistry (IHC—appropriate as a general screening tool for all breast cancer) and fluorescence in situ hybridization (FISH—used as further screening for patients with 2+ and 3+ IHC scores).[112] And "...five recent adjuvant breast cancer trials have demonstrated an astonishing and highly reproducible benefit in halving the recurrence rate and reducing mortality in patients with this phenotype."[113]

- **Existing drug specifications:** Warfarin, an effective anticoagulant in use for many decades, has "a narrow therapeutic range because of both genetic and environmental factors,"[114] and has been under-prescribed because of "historically high rates of drug-associated adverse events."[115] Understanding these factors sufficiently well to alter dosing appropriately would enable this cost-effective drug to be used more widely. Studies assessing the role of patient demographics and known variants in CYP2C9 alleles and VKORC1 genotypes have been performed, and therapeutic response to warfarin is now known to vary among Jewish (both Ashkenazi and Sephardic origins), African American, and Asian patients.[116, 117, 118] In 2005, "the U.S. FDA Clinical Pharmacology Sub-Committee (CPSC) of the Advisory Committee for Pharmaceutical Science voted to re-label the dosing of warfarin to take into consideration the new information."[119] It is not known how many patients already on warfarin have undergone testing to re-evaluate their dosage since the prescribing recommendations were changed. However, at least one study has determined that "prospective application of a multivariate CYP2C9 gene-based warfarin dosing model is feasible,"[120] and another reported that "a quantitative dosing algorithm incorporating genotypes for 2C9 and VKORC1 could substantially improve initial warfarin dose-selection and reduce related complications."[121]

The incorporation of nutrigenomics (the effect of diet on gene expression), nutrigenetics (effect of genetics on response to diet, foods, or nutrients), proteomics, and metabolomics into the personalized medicine model has moved much more slowly,[122, 123] perhaps simply as a reflection of the marked dominance of drug treatments that characterizes our healthcare system and shapes the funding priorities (see Sidebar in Chapter 2). However, much that is learned in pharmacogenomics will drive the knowledge base in these related fields as well because the underlying principle is common to all: individual genetic variations affect our physiological and biochemical response to virtually everything we are exposed to. This represents a fundamental alteration in our understanding of health and disease. The knowledge of how to identify and manage these individual differences is acutely needed for lifelong prevention of chronic disease. It won't be enough to say "Eat more vegetables and less fat and sugar." We will need to be able to individualize healthy diets, add targeted nutraceuticals, prescribe specific exercise programs, advise stress reduction efforts, plan to avoid certain pollutants, all based on individual genetic variations. Ultimately, personalized medicine will not be fully realized until all the influences, effects, and interactions are researched

and described in such a way that practitioners are able to bring them to bear on an individual patient's health and on lifelong prevention of chronic disease.

Strengths and weaknesses

The ultimate promise of personalized medicine is its potential to uncover "the causes of the causes" of disease.[124] From the unlocking of the human genome to the development of proteomics (wherein we begin to understand how the proteins made by genes behave[125]), scientists can now demonstrate how individualized both health and disease really are. It's a powerful and exciting model that is already beginning to affect both research and clinical practice. Its strength is the rapidly developing science (all the –omics) that opens new vistas and new possibilities for dramatically increasing the effectiveness of individualized prevention and treatment strategies.

On the other hand, the many challenges of transferring this model to clinical practice are daunting; they include:

- The "clinical complexity of genomic-based diagnostics and treatment."[126] A recent NIH report phrases the complexity question clearly: "An enormous scientific challenge now presents itself: What are the best ways to understand, prevent, and treat common, chronic diseases like heart disease, cancer, addiction, and mental illness when it is apparent that they are the result of interactions between individuals—in all their biological complexity—and their ever-changing physical, behavioral, and societal environments?"[127]
- Excessive cost[128]
- Regulatory issues[129, 130]
- Ethical concerns[131]
- The need for new information technology[132]

At the level of patient care, additional complex challenges arise that may take decades to resolve:

- Devising accurate and cost-effective genomic and/or proteomic screening tools
- Identifying biomarkers that will indicate whether/when an active adverse process is in play for specific conditions in a given patient
- Testing and validating diagnostic tools across many populations
- Selecting appropriate patients for screening and demonstrating the usefulness of screening in improving patient outcomes through long-term clinical trials
- Convincing third-party payers to reimburse for screening tests (likely to happen only when the results from long-term trials demonstrate cost-effectiveness)
- Interpreting individual patient screening reports appropriately
- Devising and validating effective interventions based on individual screening results

Common ground with other emerging models

As shown in Figure 1 (Chapter 1), personalized medicine shares many features with other emerging models: the emphasis on discovering individual patients' genetic vulnerabilities, the vision of individualized diagnoses and treatment, and the reliance on a powerful (and still emerging) scientific evidence base. It also shares with other models the absence of a clear and practical method of integrating emerging information into medical education and practice. Nor does it address structural and multidisciplinary issues in clinical practice that are part of the chronic-care model and integrative medicine.

Role in a synthesized, comprehensive model of 21st century medicine

Despite the rapidly evolving research base, therefore, personalized medicine does not (yet) have a robust, consistent architecture for clinical applications, nor does it describe a clear pathway toward achieving that goal. Research designs are still in development, and research findings do not specify how personalized medicine may (or may not) contribute to a new model of care for chronic disease. Even when a gene mutation, or SNP, can be identified, we may still be "six degrees of separation removed from the functional aspects of the disease,"[133] because gene analysis does not tell us which protein and protein pathways are affected and what the aberrant protein is doing. "Proteins are actually the drug targets; analysis of genes and gene expression just gives an indication of whether or not the proteins may be present."[134] The same can be said of the effects of diet, environmental toxins, psychosocial influences, and many other lifestyle and environmental factors on gene expression and protein function. For these reasons, it is difficult to plan for the integration of this model into medical education in a systematic way in the near future.

It will be necessary, therefore, to ensure that whatever transformative model is used, it will allow clinicians to integrate new and useful information from personalized medicine as and when it becomes available, and will also empower them to respond effectively now to the urgent need for improved prevention and management of complex, chronic disease. Perhaps the single most valuable portion of the personalized medicine model at the moment is the transparency it brings to the concept of patient individuality. The evidence clearly reveals that each patient is a unique individual—one whose gene expression patterns are constantly in flux and whose complex and ever-changing response to treatment, environment, and lifestyle will challenge physicians to listen differently, see differently, and respond differently than taught by the linear model of acute care.

Prospective Medicine

"The ability to identify those individuals most at risk for developing chronic diseases and to provide a customized means to prevent or slow that progression are emerging competencies and provide the foundation for prospective care."

—Ralph Snyderman, MD and R. Sanders Williams, MD [19]

What is it?

A relatively new concept introduced in 2003, prospective medicine is a descriptive rather than a prescriptive term, encompassing "personalized, predictive, preventive, and participatory medicine."[136] Snyderman argues persuasively that a comprehensive system of care would address not only new technologies (e.g., identification of biomarkers, use of electronic and personalized health records), but also delivery systems, reimbursement mechanisms, and the needs of a variety of stakeholders (government, consumers, employers, insurers, and academic medicine). Prospective medicine does not claim to stake out new scientific or clinical territory; instead, it focuses on creating an innovative synthesis of technologies and models—particularly personalized medicine (the "-omics") and systems biology—in order to "determine the risk for individuals to develop specific diseases, detect the disease's earliest onset, and prevent or intervene early enough to provide maximum benefit. Each individual would have a personalized health plan to accomplish this."[137]

Strengths and weaknesses

A very compelling element of prospective medicine is the call for fundamental change in clinical practice—from treating people only when they are sick enough to visit the doctor's office to prospectively examining individual risks and developing comprehensive preventive strategies based on the best available evidence at the time. This would, indeed, revolutionize medicine; not only would it shift the focus of primary care, but it would establish a serious partnership between patient and clinician aimed at lifelong health. Snyderman emphasizes the need for clinical medicine and the emerging genomic models to integrate their respective knowledge and skills to create the best outcomes for patients. He discusses some diagnostic and risk-assessment tools that are already available, such as the following examples:

- Know Your Number®, a program that "uses … synthesis modeling to quantify an individual's risk of developing chronic, preventable, obesity-related diseases such as diabetes, chronic obstructive pulmonary disease, and heart disease. In addition, KYN calculates what modifiable factors are contributing to that risk so that individuals can take steps to improve their overall risk profile."[138] Although Know Your Number is not available directly to consumers, other similar programs are. One example is Navigenics Health Compass,[139] offering "A scan of your whole genome, carried out by a government-certified laboratory that captures data on 1.3 million of your genetic risk markers." For $2500, individuals can obtain an analysis of their "genetic predisposition for a variety of common health conditions, and the information, support and guidance to know what steps you can take to prevent, detect or diagnose them early." For $250 per year, they will have a subscription that entitles them to regular updates.
- Biomarkers can be assessed through an analysis of 250 serum proteins ($3400). According to the company's Web site: "Biophysical250 … measures 250 different biomarkers that may indicate the presence of diseases and conditions often before symptoms appear. Unlike standard physicals that measure only up to 40 biomarkers, Biophysical250 simultaneously assesses hundreds of biomarkers used by 12 different medical specialties."[140]
- Two gene-expression assays that predict recurrence of breast cancer in patients with stage I or II node-negative breast cancer. These tests can be used to individualize follow-up treatment by helping to determine "the need for systemic adjuvant therapy in such patients."[141]

Also compelling is the call to involve a broad range of stakeholders to "work together to develop innovative applications of new technologies and appropriate delivery models."[142] It is certainly true that reimbursement strategies and academic training practices will have to evolve to encompass such a broad-based new model of care, and retraining existing practitioners must become a high priority.

What's missing? Like the other emerging models we are discussing, prospective medicine does not provide a clear road map for integrating these new technologies into clinical practice. Precisely how, one wonders, will the 500,000+ MDs and DOs already in practice be retrained? How will academic medicine evolve? How many patients can spend $2500-$3500 on laboratory tests to assess risk biomarkers? How much new and expensive testing is actually necessary compared to how much risk is already clear when a comprehensive history is taken and a thorough examination including (mostly) standard laboratory tests is performed? And what, exactly, will change in clinical practice once expanded information is in hand from these new technologies? Will doctors still be in the same position they are in today—suggesting better diet, losing weight, and reducing stress without knowing how to help their patients make all of that happen?

The big missing piece in prospective medicine (at least as described thus far in the literature) lies in the absence of a clear, practical, and systematic method for altering clinical practice. Recognizing that the interactions between doctor and patient and between patients and their lifestyle-environment exposures and choices are where real change happens, Johns and Brigham,[143] offer this commentary on a post-prospective medicine world:

> *This "next next transformation" will identify "healthy" biologic processes (i.e., homeostatic) and provide tools for measuring early deviations from health ("unhealth") that are not necessarily disease specific but that predict dire outcomes and warrant health-focused interventions. For example, many chronic diseases (diabetes, atherosclerosis, autoimmune diseases) share inflammation as a common mechanism. Characterizing an individual inflammatory phenotype may be a potent health predictor. And inflammatory responses to stress can be modified by behavior. Such health-focused treatment is the logical step beyond the "next transformation" that Snyderman and Yoediono advocate.*

Common ground with other emerging models

Prospective medicine urges the integration of the developing sciences of personalized medicine and systems biology with the skills and knowledge of clinicians, and describes recommendations for revisions in reimbursement mechanisms and medical education that will be required in order to implement a comprehensive new system of care. It clearly relies on the emerging evidence base, but not to the exclusion of other important information. It does not specifically address the chronic-care model, nor issues of integrated care or integrative medicine; neither diagnostic approaches nor treatment strategies appear to include a multidisciplinary model of care.

Role in a synthesized, comprehensive model of 21st century medicine

Because prospective medicine relies on personalized medicine and systems biology for the science of risk-assessment, many of its strengths and its limitations are found in those two models. It is, however, more comprehensive in sweep than either of them, incorporating not only technologies such as electronic health records but also acknowledging the need for simultaneous reform of the reimbursement structure and the training of future physicians. Thus, it is an important step forward, but it still lacks a robust, consistent architecture for clinical applications.

Chronic-Care Model

What is it?

The chronic-care model (CCM) is briefly outlined in Chapter 1 and fairly thoroughly described in the Appendix, where extensive material from the Improving Chronic Care Web site is included. The primary focus of this model is to include "...the essential elements of a healthcare system that encourage high-quality chronic disease care.... the community, the health system, self-management support, delivery system design, decision support and clinical information systems. Evidence-based change concepts under each element, in combination, foster productive interactions between informed patients who take an active part in their care and providers with resources and expertise."[144] The CCM is a response to powerful evidence that patients with chronic conditions often do not obtain the care they need, and that the healthcare system is not currently structured to facilitate such care (see **Sidebar**).

Strengths and weaknesses

The chronic-care model has the advantage of having been around for more than a decade; it has undergone considerable testing and revision. Implementation trials have indicated that, when enough of the model can be implemented, compliance with current algorithms and guidelines can be improved for conditions such as diabetes,[146, 147] depression,[148] and tobacco cessation.[149] The CCM is a structure-of-care (or process-of-care) more than a content-of-care model; it describes a multidisciplinary, multi-stakeholder approach to delivering care that will improve both patient and practitioner compliance with current evidence-based best practices. For this reason, integrating new technologies, such as those emerging from personalized medicine, are not explicitly addressed; one might assume that as those tools make their way into clinical guidelines and algorithms, they will become part of the CCM as well. However important improving the structure of care may be—and we certainly agree that it is important—the care thus provided will still be limited to the current medical model, which does not address individualizing care, lifelong primary prevention, or reversal of chronic disease, and which is primarily pharmaceutical in nature. We could

The Institute of Medicine's report, *Crossing the Quality Chasm*,[145] comments extensively on the unmet needs of those with chronic conditions:

- **Page 4:** "... there remains a dearth of clinical programs with the infrastructure required to provide the full complement of services needed by people with heart disease, diabetes, asthma, and other common chronic conditions (Wagner et al., 1996). The fact that more than 40% of people with chronic conditions have more than one such condition argues strongly for more sophisticated mechanisms to communicate and coordinate care (The Robert Wood Johnson Foundation, 1996)."
- **Page 9:** "Care for the chronically ill needs to be a collaborative, multidisciplinary process."
- **Page 28:** "In a population increasingly afflicted by chronic conditions, the health care delivery system is poorly organized to provide care to those with such conditions."
- **Page 29:** "Thus the American health care system does not have well-organized programs to provide the full complement of services needed by people with such chronic conditions as heart disease, cancer, diabetes, and asthma."
- **Page 89:** "Common chronic conditions should serve as a starting point for the restructuring of health care delivery because, as noted in Chapter 1, chronic conditions are now the leading cause of illness, disability, and death in the United States, affecting almost half

imagine implementing, for example, personalized medicine using the chronic-care model, but no mechanism for achieving that is described. In fact, just implementing the full CCM itself is a very difficult proposition that encounters many barriers (e.g., no consensus on the value of the changes, limited change management skills within organizations, too many competing priorities, and failure to engage the commitment of physicians).[150] The Academic Chronic Care Collaborative, representing 22 academic medical centers, has reported some initial promising outcomes from their experiences with implementing aspects of the CCM.[151] It is worth noting that these institutions were committed to providing effective leadership and resources for the change process. The Agency for Healthcare Research and Quality provides an extensive *Toolkit for Implementing the Chronic Care Model in an Academic Environment.*[152]

Common ground with other emerging models

The CCM shares with integrative medicine an emphasis on a multidisciplinary care model, the use of evidence-based best practices, and engagement of the patient in self-care. It does not address biochemical and physiological individuality, any of the emerging genomic technologies, or the influence of underlying mechanisms of disease. It shares with prospective health care a focus on structural, system-wide change, although the two models emphasize different aspects of structural change.

Role in a synthesized, comprehensive model of 21st century medicine

The CCM advances our knowledge of how to improve the structure or process of care for chronic disease using standard approaches, but it does not advance our ability to select more effective strategies for actually improving both treatment and prevention. Still lacking is a robust, consistent architecture for selecting the most effective clinical applications for each unique patient.

of the population and accounting for the majority of health care resources used (Hoffman et al., 1996)."

- **Page 94:** "Four chronic conditions (cardiovascular disease, cancer, chronic obstructive pulmonary disease, and diabetes) account for almost three-quarters of all deaths in the United States (Centers for Disease Control and Prevention, 1999)."
- **Page 211:** "The ability to plan care and practice effectively using multidisciplinary teams takes on increasing importance as the proportion of the population with chronic conditions grows, requiring the provision of a mix of services over time and across settings.... A changing relationship between clinicians and their patients also calls for new skills in communication and support for patient self-management, especially for patients with chronic conditions. Collaborative management requires collaboration between clinicians and patients in defining problems, setting goals, and planning care; training and support in self-management; and continuous follow-up (Von Korff et al., 1997). Patients with chronic conditions who are provided with knowledge and skills for self-management have been shown to experience improvements in health status and reduced hospitalizations (Lorig et al., 1999). Clinicians need to have skills to train patients in techniques of good self-management."

Evidence-based Medicine (EBM)

What is it?

EBM is a tool for improving clinical practice. Its stated goal is to ensure that clinical decision making is grounded in the best available evidence. Despite its many limitations, it wields a great deal of power over medical training, clinical practice, and—increasingly—reimbursement decisions and legal determinations.[153, 154] We include it in our discussion of emerging models because of its multifaceted influences on patient care. Although it is beyond the scope of this paper to explore EBM in depth, it is critical to the future of health care to understand its strengths and weaknesses. To that end, we provide a brief description of this evolving paradigm.

Since the late 1970s, various efforts have been made to systematize the use of research findings in clinical decision making.[155] Rather than expecting each practitioner to establish and maintain a constant surveillance over a rapidly expanding evidence base, and to know which studies should generate the highest level of confidence, specific guidelines have been proposed concerning the interpretation of evidence that influences clinical decision making. There have been many definitions and ratings of what constitutes poor, good, and best evidence, but in the early 1990s, the term evidence-based medicine appeared for the first time,[156, 157] reflecting an increasing consensus that a more standardized approach to the use of medical evidence was on the way. Early efforts sought explicitly to reduce "...the emphasis on unsystematic clinical experience and pathophysiological rationale" while promoting "the examination of evidence from clinical research."[158]

A hierarchy of evidence reliability was proposed, with meta-analyses and systematic reviews at the top and personal communications at the bottom (see Figure 5). Over the years, this hierarchy has been revised and adapted many times for a number of reasons:

- It did not identify a mechanism for decreasing or increasing an assessment of value based upon, for example, study size, adequacy of blinding, bias, directness of the evidence, and other factors.[159]

» **Page 237:**
"Patients with chronic conditions, for which certain routine examinations and tests are crucial in order to prevent complications, do not all get the care they need."

Note: Citations included in the above quotations are available in the Institute of Medicine report, but are not provided here.

- It failed to accommodate many important criteria for translating evidence into clinical practice—for example, the degree to which outcomes being tested were important to patients, whether results were consistent with past studies, and whether confidence intervals were overly broad.[160]
- It inappropriately identified systematic reviews and meta-analyses as evidence (they are, rather, interpretations of the evidence and should be produced, at least in part, based on EBM principles).[161, 162]
- It did not differentiate between quality of evidence and strength of recommendations. "High quality evidence doesn't necessarily imply strong recommendations, and strong recommendations can arise from low quality evidence."[163]

One example of a subsequent adaptation is provided in Figure 6, where we can see that other useful criteria were added to the model, altering the earlier and more simplistic assessment of evidence usefulness.[164]

The basic concepts have continued to evolve. "In 2000, the Evidence-Based Medicine Working Group presented the second fundamental principle of EBM: the hierarchy of evidence being the first. Whatever the evidence, value and preference judgments are implicit in every clinical decision. A key implication of this second principle is that clinical decisions, recommendations, and practice guidelines must not only attend to the best available evidence, but also to the values and preferences of the informed patient."[165]

A major advance over the use of any hierarchy, however complex, has been the development of the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system. Figure 7 shows a partial representation of this system; in practice, it has other important elements as well. The GRADE system describes a very sophisticated, multi-level evaluation of evidence; its purpose is to strengthen recommendations for clinical practice and to increase confidence in those recommendations. Because of its complexity, however, it is not intended for use by individual clinicians, who generally have neither the time nor the expertise to implement it. It is aimed primarily at researchers and clinical guideline developers, who have not heretofore used a consistent and uniform methodology that is transparent to all potential users.[166] GRADE software is now available for free at the GRADE Working Group's Web site,[167] making it even more likely that its use will continue to expand.

1. A Systematic reviews; meta - analyses
   B RCTs
   C Experimental designs
2. A Cohort control studies
   B Case control studies
3. A Consensus conference
   B Expert opinion
   C Observational study
   D Other types of study (e.g., interview -based)
   E Quasi-experimental, qualitative design
4. Personal communication

Figure 5:
Heirarchy of evidence (Sackett)

	Effectiveness	Appropriateness	Feasibility
Excellent	Systematic reviews Multi-center studies	Systematic reviews Multi-center studies	Systematic reviews Multi-center studies
Good	RCTs Observational studies	RCTs Observational studies Interpretive studies	RCTs Observational studies Interpretive studies
Fair	Uncontrolled trials; dramatic results Before and after studies Non-randomized CTs	Descriptive studies Focus groups	Descriptive studies Action research Before and after studies Focus groups
Poor	Descriptive studies Case studies Expert opinion Studies with poor methodology	Expert opinion Case studies Studies with poor methodology	Expert opinion Case studies Studies with poor methodology

Figure 6:
Heirarchy of evidence (Evans)

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A. Criteria for Assigning Level of Evidence

Type of Evidence	
Randomized trial	High
Observational study	Low
Any other type of research evidence	Very Low
Increase level if:	
Strong association	(+1)
Very strong association	(+2)
Evidence of a dose-response gradient	(+1)
Plausible confounders reduce observed effect	(+1)
Decrease level if:	
Serious or very serious limitations in quality	(-1) or (-2)
Important inconsistency	(-1)
Some or major uncertainty about directness	(-1) or (-2)
Imprecise or sparse data*	(-1)
High probability or reporting bias	(-1)

B. Definitions for levels of evidence

High Further research is not likely to change our confidence in the effect estimate

Moderate Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate

Low Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate

Very Low Any estimate of effect is uncertain

*Few outcome events or observations or wide confident limits around an effect estimate

Figure 7:
Overview of the GRADE system for evaluating evidence (Bagshaw)

Over the years, a number of studies have verified that teaching EBM will, in fact, significantly increase the degree to which practitioners apply it.[160] Training is more successful if it is both experiential and didactic.[169, 170, 171] Unfortunately, there are very few studies available as yet that tell us whether EBM improves overall patient health over a period of years.

Strengths and weaknesses

There can be little doubt that a thoughtful evaluation of evidence is an indispensable factor in delivering high-quality health care. The emergence of formal assessment processes reflects a desire to establish greater clarity and confidence about the reliability of evidence. Even a

casual user of Medline or PubMed quickly becomes aware of the overwhelming quantity of published research available today; it is a daunting prospect to identify the best or most relevant papers among hundreds or thousands that may be available on a particular topic. For example, a PubMed search for the phrase *evidence-based medicine* in titles and abstracts returns nearly 5000 entries encompassing dozens of journals! There are, of course, tools for narrowing a search term or process, but it is still inordinately time consuming to obtain, read, evaluate, and then compare even a few individual research papers on a specific subject. Such a process, even if an EBM hierarchy is used, is also subject to a great deal of individual bias. Thus, any tool that provides significant and reliable assistance in such an endeavor is welcome, and that is one of the primary rationales for the development of clinical guidelines.[6]

As the use of EBM has become increasingly widespread, its limitations and weaknesses have also become more apparent. Paramount among the problems is that EBM reflects an acute-care model: it most often assumes that the goal of care is a single diagnosis followed by a hierarchy of (primarily) single-agent treatments. Although GRADE has made an admirable attempt to compensate for many EBM weaknesses, these fundamental goals remain the gold standard. Therefore, EBM fails at the same point where the research itself fails—in its inability to account for unique patient geno/phenotypes, multiple comorbidities, and personalized approaches to care that include multiple interventions for complex, chronic disease. Such multifaceted interventions may include dietary, nutraceutical, pharmaceutical and/or surgical recommendations, as well as many options from the natural medicine world (e.g., botanical medicine, acupuncture and oriental medicine, body/mind practices).

EBM and any guidelines derived from applying an EBM model to the evidence are, of course, only as good as the underlying research, which presents several problems:

- Not only is the research agenda disproportionately driven by the pharmaceutical industry, but it is tainted by the failure to publish negative or neutral results and by industry bias (see Chapter 2).
- Much of generally accepted medical practice has not been systematically evaluated. For example: "Of around 2500 treatments covered [in *BMJ Clinical Evidence*] 13% are rated as beneficial, 23% likely to be beneficial, 8% as trade off between benefits and harms, 6% unlikely to be beneficial, 4% likely to be ineffective or harmful, *and 46%, the largest proportion, as unknown effectiveness* [italics added]."[172]
- Individuals studied in RCTs do not reflect the patient population seen most often in primary care; confidence in the transferability of the data is thereby reduced.[173]
- "Randomized trials, especially if evaluating complex interventions or with strict inclusion/exclusion criteria, often only provide data in a clinical context that does not exist outside the trial itself and have limited power to detect harm.... Systematic reviews require vigilant interpretation and should not necessarily be considered as high level evidence due to issues related to ... incomplete reporting and the inclusion of evidence from trials of poor quality.... Meta-analyses are not primary evidence; they are statistically assisted interpretations of

[6] "Clinical guidelines are "systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances" —Institute of Medicine, 1990. They define the role of specific diagnostic and treatment modalities in the diagnosis and management of patients. The statements contain recommendations that are based on evidence from a rigorous systematic review and synthesis of the published medical literature"—http://www.nhlbi.nih.gov/guidelines/about.htm.

primary evidence. They have been shown to contradict confirmatory trials, especially when such meta-analyses are based upon small, low quality studies."[171]

- "Even the most promising findings of basic research take a long time to translate into clinical experimentation, and adoption in clinical practice is rare."[175] Evidence-based guidelines of genomic applications are even more rare, and thus are unavailable to practitioners who rely on EBM processes to update their clinical practices.[176]

Common ground with other emerging models

EBM is, to differing degrees, part of all the other models described in this paper. Since EBM focuses primarily on mechanisms for translating research findings into clinical applications, it is less useful for those aspects of personalized medicine and systems biology that concentrate on the basic research itself. Also, as noted above, integrating personalized assessment and treatment with EBM models is not yet feasible on a systematic basis. It will be extremely interesting to see whether this can be done.

Role in a synthesized, comprehensive model of 21st century medicine

In our opinion, the role of EBM is strongest in acute-care situations, where the physician or healthcare team must focus on short-term and fairly narrowly defined issues. When we consider its role in outpatient primary care for complex, chronic disease, however, it is more difficult to make an overall determination of usefulness. Certainly there are situations where EBM and the clinical guidelines that flow out of it are extremely useful. In general, however, it seems easier to see the problems (described above) than it is to detect the benefits. Nonetheless, there is great benefit to researchers, practitioners, and patients in improving our ability to objectively and systematically evaluate data and determine clinical usefulness. Overall, this is perhaps the most important role that EBM will play over time.

Systems Biology

What is it?

Although there is not yet a universally recognized definition of systems biology, the National Institute of General Medical Services (NIGMS) at NIH provides the following explanation: "A field that seeks to study the relationships and interactions between various parts of a biological system (metabolic pathways, organelles, cells, and organisms) and to integrate this information to understand how biological systems function."[177] The *Molecular Systems Biology Blog on Systems & Synthetic Biology* poses—and provides some possible answers to—the question of why it appears to be difficult to come up with a concise and generally applicable definition: "One of the reasons might be that every definition has to respect a delicate balance between 'the yin and the yang' of the discipline: the integration of experimental and computational approaches; the balance between genome-wide systematical approaches and smaller-scale quantitative studies; top-down versus bottom-up strategies to solve systems architecture and functional properties." The blog hypothesizes that, "despite the diversity in opinions and views, there might be two main aspects that are conserved across these definitions: a) a system-level approach attempts to consider *all*

the components of a system; b) the properties and interactions of the components are linked with functions performed by the intact system via a *computational model*."[178]

We would add to the NIGMS definition that it is also vital to understand how the human system interacts with the environment, as well as how all the components act and interact. We see systems biology as a broad term for the basic science underlying the personalized medicine revolution (described above). While the fields of personalized, prospective, and integrative medicine all recognize (to varying degrees) the importance of nutritional genomics, pharmacogenomics, metabolomics, and proteomics to the future of health care, most of the scientific research has been generated by systems biologists (whether or not they identify with that term or any of the many definitions proposed). Thus far, although systems biology *claims* virtually the same broad territory as personalized medicine, it actually *focuses* almost exclusively on pharmacogenomics—in the Willie Sutton idiom, "That's where the money is." Attention to the applicability of those findings to patient care (i.e., the gene-environment interaction that creates the phenotype) is what connects systems biology to personalized medicine.

Strengths and weaknesses

Identifying the nature and effects of the myriad interactions that occur where human biology is exposed to the environment is almost unimaginably complex. Yet that effort is critical to a better understanding of the multifactorial nature of disease development. We know that "the causes of most chronic diseases will require an understanding of both the genetic and environmental contribution to their etiology.... The most critical issue is how to relate exposure-disease association studies to pathways and mechanisms.... Scientists will need tools with the capacity to monitor the global expression of thousands of genes, proteins and metabolites simultaneously.... Even when all the highly relevant genes and their interactions with specific environmental components have been identified, it will still be difficult to relate the influence of an individual's genotype to their disease phenotype due to the added complexity of gene-gene interactions, post-translational processing, and protein-protein interactions."[179]

Because of the magnitude and complexity of the challenge, "Systems biology research should create an interactive inter-disciplinary scientific culture. For progress to occur, experts in engineering, physics, mathematics, and computer science must join biochemists, cell biologists, and physiologists in the effort to figure out how to obtain the required data and develop the sophisticated computational approaches that will be needed to make viable predictions."[180] This is a long-term prospect, of course, although early studies have shown some highly beneficial outcomes of genomic medicine[181] (a plausible term for applying the findings of systems biology to patient care).

Many of the same obstacles discussed earlier in this chapter vis-à-vis personalized medicine and pharmacogenomics are inherently shared by systems biology. In addition to barriers of cost, complexity, equipment, ethics, and education, "the evidence and importance of most pharmacogenomics associations are not sufficient to overcome the barriers to clinical implementation.... It is likely that complementary technologies, such as metabonomics, will be able to compensate for some limitations of genotype-phenotype association."[182]

Common ground with other emerging models

Systems biology seeks to elucidate the biological underpinnings of disease risk and apply that knowledge within a personalized, predictive, prospective, and participatory model of patient care. The science of systems biology clearly underlines the congruent goals of personalized medicine, prospective medicine, and—to a lesser extent—integrative medicine. It is not entirely congruent with evidence-based medicine, because it has not yet generated a large number of clinical trials. In fact, systems biology somewhat reverses the direction of EBM described above, in that it takes us back to a more "pathophysiological rationale" of disease and treatment. Eventually, research models will be devised to test the effectiveness and reliability of patient care based on diagnostic tests and therapeutic recommendations derived from systems biology.

Role in a synthesized, comprehensive model of 21st century medicine

Systems biology illuminates the science that will support a new model of health care—one that is based on an intimate understanding of complex human systems interacting with complex environments and unique genetic inheritances. In order to achieve its greatest potential, it must broaden its scope far beyond pharmacogenomics, which represents a very small portion of what we need to know about preventing and treating complex, chronic disease.

Integrative Medicine

What is it?

"Integrative medicine can be defined as an approach to the practice of medicine that makes use of the best available evidence taking into account the whole person (body, mind, and spirit), including all aspects of lifestyle. It emphasizes the therapeutic relationship and makes use of both conventional and complementary/alternative approaches."[105] The field is now nearly 10 years old and it is the only one of the emerging models discussed in this paper to explicitly encompass the integration of therapeutics that, until recently, were the sole purview of complementary and alternative medicine[8] (CAM). A number of forces are responsible for the emergence of this new discipline:

- The initial driver was undoubtedly the burgeoning interest in and demand for CAM displayed by consumers over many years. As reported in the *Annals of Internal Medicine* in 2001, "Use of CAM therapies by a large proportion of the study sample is the result of a secular trend that began at least a half century ago. This trend suggests a continuing demand for CAM therapies that will affect health care delivery for the foreseeable future."[106]
- The establishment of the NIH National Center for Complementary and Alternative Medicine (NCCAM) provided research funding to investigate CAM therapies. As research into CAM therapies revealed many effective natural (nonpharmaceutical, nonsurgical) approaches to

[8] A widely used definition of CAM therapies from the Osher Institute at Harvard: "clinical services not routinely used within conventional care, such as chiropractic, acupuncture, massage therapy, homeopathy, meditation, music therapy, therapeutic touch, yoga, Reiki, and advice involving herbal products and other dietary supplements."

a wide variety of diseases and conditions, it was thought desirable for physicians to understand CAM in much greater depth[187] and to devise a pathway for validated approaches to be brought into the standard "medicine chest."[188]

- The philanthropic funding of centers and departments of integrative medicine within the academic medicine community (e.g., University of Arizona, Harvard, Vanderbilt, Duke; also see list in the Appendix of members of the Consortium of Academic Health Centers for Integrative Medicine) brought high-level attention to the educational element: "Integration of CAM with conventional health care requires educational venues that prepare conventionally trained caregivers with a sufficient knowledge base for assessing beneficial and detrimental interactions between CAM and conventional care approaches; development of criteria for making informed referrals to CAM practitioners; and enhanced research capacity."[189]
- Integrative medicine might also be characterized as a response to the increasing depersonalization of health care that came with the rise of HMOs, greater use of technology, decreasing time spent in the outpatient visit, and the insertion of third-party payers into the doctor-patient relationship.[190]

Integrative medicine curriculums now commonly describe a fairly comprehensive set of core competencies that include dietary interventions, nutraceuticals, botanical medicines, body-mind practices (see, for example, **Sidebar** on meditation), energy medicine (e.g., acupuncture), and manual medicine (e.g., massage, chiropractic).[191, 192] The balance of didactic knowledge (for the purpose of providing better-informed advice and referrals to patients) vs. practical skills (for actually integrating clinical applications) varies from program to program.

Strengths and weaknesses

Integrative medicine is an important step toward a functionally integrated healthcare system that includes all appropriately credentialed practitioners. Not only does it provide an avenue for validated CAM therapies

Meditation and Brain Science

Meditation may be one of the best studied body-mind modalities. The effects of meditation on the brain have been studied using sophisticated functional MRI (fMRI) and electroencephalographic (EEG) techniques. Not only have researchers detected significant differences in brain activity between experienced meditators and nonmeditators (or inexperienced meditators), but there also may be detectable differences resulting from the particular type of meditation studied.[193] Although more substantial differences can be found with long-term meditators, even a short training period of eight weeks "produces demonstrable effects on brain and immune function."[194] Some findings suggest that "the resting state of the brain may be altered by long-term meditative practice," and that "attention and affective processes…are flexible skills that can be trained."[195] The practical implications of such findings, if replicated on a large scale, could be considerable. One report concluded that "it is plausible from our results that meditation may strengthen the ability to inhibit cognitive and emotional mental processes such as rumination that can lead to or exacerbate stress, anxiety, or depression."[196] A subsequent study to test this hypothesis returned startling results[197]:

> MBCT [mindfulness-based cognitive therapy] was more effective than m-ADM [maintenance antidepressant medication] in reducing residual depressive symptoms and psychiatric comorbidity and in

to be more widely used, but it supports the interdisciplinary team concept in both educational and clinical settings. It allows patients greater freedom of choice in both therapies and providers, and it encourages dialogue among all health practitioners.

There is a danger that integrative medicine physicians will extend their practices beyond the scope of their education. Completing a program in integrative medicine does not turn an MD or a DO into a trained chiropractor, acupuncturist, naturopathic physician, or other such practitioner. It is important that those who wish to fully practice an alternative discipline seek comprehensive training from accredited institutions, just as those who wish to practice as medical doctors must do.

improving quality of life in the physical and psychological domains. There was no difference in average annual cost between the two groups. Rates of ADM usage in the MBCT group was [illegible] significantly reduced, and 46 patients (75%) completely discontinued their ADM. For patients treated with ADM, MBCT may provide an alternative approach for relapse prevention.

Common ground with other emerging models

Integrated medicine uses evidence-based medicine to select the practices to integrate. It is multidisciplinary and oriented toward whole-person health care. It is the only one of the models to explicitly integrate alternative practitioners and approaches, to emphasize the importance of the practitioner-patient relationship, and to bring body-mind issues to the fore. Other than EBM, it is the only one that already has a significant foothold within academic medicine.

Role in a synthesized, comprehensive model of 21st century medicine

Integrative medicine provides great leadership in demonstrating the importance of a more integrated healthcare system and in creating academic models to educate practitioners in this new approach. It could benefit from a greater emphasis on genomic medicine, perhaps by incorporating some of the principles or recommendations of personalized or prospective medicine.

Chapter 4

THE CLINICIAN'S DILEMMA

[W]hat we observe is not nature itself, but nature exposed to our method of questioning.
Natural science, does not simply describe and explain nature;
it is part of the interplay between nature and ourselves.

—WERNER HEISENBERG, PHYSICS AND PHILOSOPHY, 1958

We have spent, to this point, a great deal of time and effort exploring both the challenge of 21st century medicine—to first halt and then reverse the epidemic of chronic disease—and some of the most prominent among many proposed solutions. We hope we have achieved a shared recognition that our current tools and approaches are not sufficient to the task, and that changes in the practice of medicine are necessary and imminent. At the same time, we cannot ignore the challenge of making these conclusions relevant to the individual practice of medicine. For, ultimately, most health care is delivered one patient and one practitioner at a time. In this chapter, we explore the clinician's dilemma: how to practice in such a way that both the continuing advances of science and the essential art of medicine are integrated seamlessly into clinical practice, neither overshadowing the other. It won't matter how intelligent and persuasive the arguments for change may be if we cannot convert them into practical approaches that can be taught to and adopted by individual clinicians.

This paper is not intended as an exploration of the actual clinical interventions that comprise functional medicine nor of the extensive science that underlies them. For that purpose, we refer the reader to the books, monographs, and courses available through The Institute for Functional Medicine (IFM).* In these final two chapters, we address clinical practice at a different level, presenting the foundational concepts and principles that we believe should shape the coming changes in health care.

The Central Hub of 21st Century Medicine

The primary principle around which 21st century medicine—functional medicine—*will revolve is personalized, systems medicine*. Grouping people into categories based on organ system diseases, and then

*A complete list of IFM publications and courses can be found at www.functionalmedicine.org.

prescribing as though all people with a given diagnosis were inherently alike, is beginning to give way to a model that recognizes each patient's genetic and environmental uniqueness. Clinicians must develop the knowledge and skills to deliver individually tailored care. They must be able (and willing) to incorporate the science of systems biology, the emerging discipline of personalized care, and a much broader array of assessment, therapeutic, and preventive strategies into a new therapeutic relationship.

Each human emerges from a mold that has but one model.[xx] Uniqueness continues to develop throughout life as a result of myriad influences. Family, school, work, community, diet, exercise, stress, and environmental toxicity all communicate information from outside the organism to the epigenetic translational structures that are married to nuclear DNA and that create powerful downstream effects on the genome, proteome, and metabolome. This phenomenon of biochemical uniqueness was recognized, researched, and documented in the 20th century, and is the foundation from which many key constructs have evolved, including systems biology and systems medicine, prospective health care, patient-centered health care, nutrigenomics, pharmacogenomics, proteomics, and metabolomics/metabonomics (see Chapter 3).

Decision Making in the Face of Uncertainty

From this chaotic, nonlinear interplay of complex factors, involving the integration of both genetics and context of living, emerges the haunting reality that all care is provided in a context of uncertainty. This is the shadow side of modern clinical medicine and it poses a daunting conundrum—how do you structure and systematize the assessment and treatment of patients when each is the product of a multitude of unique genetic and environmental influences and interactions? Kathryn Montgomery in her scholarly book, *How Doctors Think*, directly addresses this challenging issue:

> Complexity and uncertainty are built into the physician's effort to understand the particular in light of general rules.... The obstacle they encounter is the radical uncertainty of clinical practice: not just the incompleteness of medical knowledge but, more important, the imprecision of the application of even the most solid-seeming fact to a particular patient.[199]

What elevates the importance (and the stress) of clinical care over the work of, for instance, engineers, lawyers, accountants, and other nonclinical professionals is its continuous involvement in matters of life and death. The cost of failure is so high—death, when life might have been possible; illness, when health might have been attainable. The daily unconscious concern of every clinician is the weight of this cumulative decision making—inherently uncertain and lacking full (or sometimes even adequate) information to inform the clinical picture. Dr. Jerome Groopman in his provocative book with the same title, *How Doctors Think*, addressed this issue from his clinical perspective:

> Uncertainty creeps into medical practice through every pore. Whether a physician is defining a disease, making a diagnosis, selecting a procedure, observing outcomes, assessing probabilities, assigning preferences, or putting it all together, he is walking on very slippery terrain. It is difficult for nonphysicians, and for many physicians, to appreciate how complex these tasks

[xx] The potential for human cloning might be considered the exception to this rule. However, exact replication from a clone donor cannot duplicate the pre and post epigenetic imprinting that skews the exactness of a clone

are, how poorly we understand them, and how easy it is for honest people to come to different conclusions.[19]

Personalized, systems medicine serves to inform us about the enormity of the uncertainty. The message is clear: there is no one-size-fits-all solution to resolve any specific diagnosis. The limitations of clinical algorithms and evidence-based medicine can now be more clearly discerned. We can no longer allow them to skew our understanding of the larger picture, however difficult it may be to look at unflinchingly. We are at a crossroads where only honesty about the limitations of strategies that seek to avoid or ignore uncertainty will suffice.

> For the great enemy of truth is very often not the lie — deliberate, contrived, and dishonest — but the myth — persistent, persuasive, and unrealistic. Too often we hold fast to the clichés of our forbears. We subject all facts to a prefabricated set of interpretations. We enjoy the comfort of opinion without the discomfort of thought.
>
> —John F. Kennedy, Yale Commencement, 1962

Medicine has attempted historically, through a number of shifts in perspective, to provide greater certainty to both practicing clinicians and patients, a patently valuable goal. Setting aside traditional methods of instilling confidence—oracles or shamans, for example—science has been a very important tool for reducing uncertainty.

Twentieth century medicine completed a great philosophical and practical transformation into the *organ system* model of disease and diagnosis. This provided an evolving and reassuring sense of control and certainty as a result of ever-increasing specialization (often described as knowing more and more about less and less) as well as myriad fascinating scientific breakthroughs in understanding the nature of life, health, and disease. From early x-rays through the sophisticated imaging processes in use today, through ever more complex and detailed biochemical pathways, we have explored the silos of mammalian organ systems taxonomy. Objective facts accreted in uncountable numbers during the 1900s, describing human anatomy, physiology, and mechanisms of dysfunction from the cellular level to the specific organs themselves. The medical specialties (e.g., cardiology, neurology, nephrology) emerged and grew strong from these historic breakthroughs.

Near the end of the 20th century, however, the reality of the web-like, chaotic, nonlinear and complex nature of life (and health)—exposed by advances in the systems-oriented life sciences—began to erode this reassuring sense of certainty. Twenty-first century medicine has now come face-to-face with the practical implications of uncertainty—a problem that flummoxed many mid-20th century physicists (including the great Albert Einstein, who ultimately rejected what is now an accepted principle) when they first confronted Heisenberg's articulation of the principle of uncertainty in physics. Fortunately, since the seriousness of this issue is consciously acknowledged, management strategies can be developed. First, however, we have to stop denying the presence and power of uncertainty in medicine. Research by brain scientists using advanced imaging and electronic technologies and analytic techniques equips the clinician with important knowledge for facing squarely the daunting task of assessing and treating each patient as a unique individual, shaped by innumerable complex interactions between genetics and the cumulative influences of daily life.

The rest of this chapter will discuss these findings and will describe why the context of uncertainty in medicine requires a change in our view of evidence and the therapeutic relationship, and a considerable expansion in the clinical tool kit of the practitioner. The increasingly technical (and increasingly brief) clinical encounter that has characterized the last few decades in medicine can be transformed into a *healing partnership* through the appropriate integration of relevant evidence from clinical trials, the knowledge gained from breakthroughs in brain science and systems biology, and an expanded clinical armamentarium. Within this complex relational system can be found effective strategies for individualized assessment and treatment, taking into account the uncertainty generated by the complex genetic and environmental uniqueness of each patient—we can, in fact, begin the practice of *personalized, systems medicine* today.[200, 201]

Evidence-based Medicine in the Clinical Setting: Uses and Limitations

The scientific method disciplines the creative process of human inquiry. In the applied biological sciences (e.g., clinical medicine) prior to World War II, evaluation of emerging therapeutics was mainly the purview of recognized leaders in the medical profession, based primarily on their clinical experience and reputations, and without the rigor of systematic controls or external standards.[202] To improve the quality of evidence and render a more accurate judgment with less personal bias, postwar researchers developed the randomized controlled trial (RCT) protocol. The major characteristics of this method include blinded assessment (of subjects, investigators, or both), often in the presence of a placebo control; random assignment to comparable groups; and inferential statistics as a surrogate for establishing causation.[203]

The reliance on the expert gave way to reliance on results from RCTs. Clinicians could no longer reduce uncertainty by following the lead of a confident expert, but they increasingly appreciated the power of the double-blind, randomized, placebo-controlled clinical trial—a step up in certitude.[204, 205] Putting aside, for the moment, the many problems inherent in the RCT model, not the least of which is the bias introduced by the influence of big Pharma,[206, 207, 208, 209] let's briefly explore EBM—the offspring of the RCT model—as understood and used by clinicians to reduce uncertainty.

Proponents of the RCT as the gold standard for unbiased research results have fostered its preeminence in the applied medical fields, both in primary and specialty care. They have argued for and developed algorithms for grading recommendations based on a research quality scale that ranks methodologies in descending order of accepted best evidence:[210, 211]

- Systematic reviews and meta-analyses of RCT studies
- RCTs
- Nonrandomized intervention studies
- Nonexperimental studies
- Expert opinion

Amid the early excitement generated by this new schema, certain assumptions were posited as foundational:

> A new paradigm for medical practice is emerging. *Evidence-based medicine de-emphasizes intuition, unsystematic clinical experience, and pathophysiologic rationale as sufficient grounds for clinical decision making* and stresses the examination of evidence from clinical research. Evidence-based medicine requires new skills of the physician, including efficient literature searching and the application of formal rules of evidence evaluating the clinical literature.[212] [Italics added.]
>
> —Evidence-based Medicine Working Group, JAMA, 1992

The application of EBM in the clinical setting is described as following this general scenario:[213, 214]

- Select specific clinical questions from the patient's problem(s)
- Search the literature or databases for relevant clinical information
- Appraise the evidence for:
  - validity against the hierarchy of evidence as described above, and
  - usefulness to the patient and practice
- Implement useful findings in everyday practice

Arguments in favor of EBM infusion into both medical education and clinical practice are based on the following facts and inferences:[215, 216]

- Available new evidence can and should lead to major changes in patient care
- Practicing physicians often fail to obtain available newer relevant evidence
- Medical knowledge and clinical performance deteriorate over time without the leavening of newer evidence influencing clinical decisions
- Traditional continuing medical education (CME) alone is deficient and generally does not improve clinical performance without significant follow-up and evaluation measures
- The discipline of using evidence-based medicine can keep clinicians up-to-date

In a cogent paper in *The Lancet* in 1999, van Weel and Knottnerus responded to the proddings of many eminent medical thought leaders to move ahead quickly and comprehensively with the integration of EBM into the clinical setting by pointing out the many difficulties of using this schema to manage the care of individual patients with complex, chronic illness:[217]

- EBM tends to concentrate on research methodology and reduces clinical practice to the technical implementation of research findings. In a more colloquial view, it is the tail wagging the dog. Rather than using clinical judgment to guide the choice of relevant evidence, EBM is structured with a hierarchy of evidence as the driver of clinical judgment.

- The structure of RCT methodology assumes the consequences of individual variability in response to treatment will "wash out" if the subject pool is large enough and the statistical analyses sophisticated enough. *While this may be true for populations, it seriously limits the applicability of the research in primary care, where therapy is delivered one unique patient at a time.*
- Co-morbid conditions are the usual justified reason for the exclusion of many patients from RCTs, *so the very patients most in need of usable evidence (e.g., those with complex, chronic conditions) are often not in the cohorts of patients being studied,* making the findings from the research trials very limited in their applicability.
- In primary care, treatment usually involves several interventions, sometimes delivered concurrently and sometimes sequentially. Unfortunately, combinations of evidence-based interventions do not sum to a treatment plan that is evidence-based. Interactions between single interventions may increase or decrease their efficacy (even under ideal trial conditions), when blended into a comprehensive plan. Adverse interactions among treatments may, and often do, occur.
- Clinical research does not focus on the overall outcome of composite interventions because of the complexity of such studies and the absence of well-developed tools for studying such whole systems approaches.
- Drug interventions have been studied more extensively than nonpharmacological interventions, in part due to the technical and methodological difficulties in the design of RCTs for nondrug interventions (and, in part, because of the nonpatentable nature of most lifestyle interventions). This situation creates a significant problem in primary care, where the use of educational, dietary, and lifestyle interventions is attractive because of their resonance with the principle of "maximum effect using minimum resources."

In marked contrast to the assertions of the EBM Working Group cited earlier, van Weel and Knottnerus suggest that the driving force behind EBM should be a coherent system of fundamental research in *pathophysiology and the humanities,* combined with careful clinical observations, on which systematic (RCT-based) evidence of effectiveness is superimposed. Existing clinical practice should be supported or, if erroneous, corrected on the basis of this coherent system. They go on to propose that "two complementary approaches are needed to strengthen the evidence base of nonpharmacological interventions and complex multifaceted strategies. First, the generic characteristics of complex interventions must be acknowledged as essential for its evaluation. Second, a methodology to allow the assessment of complex effects should be further developed."

Dr. David Mant in his seminal 1999 paper, "Can randomized trials inform clinical decisions about individual patients?" takes a slightly different tack in exploring the irony that the RCT combines strength of concept for the population being studied with weakness of specific application to the individual patient:[2(p)]

> The paradox of the clinical trial is that it is the best way to assess whether an intervention works, but is arguably the worst way to assess who will benefit from it... However, the nub of the argument for me is that randomized controlled trials are primarily about medical interventions and not patients. In clinical trials, patients are randomized to allow a comparison of intervention efficacy unbiased by the individuality of patient. This methodological approach provides society with powerful protection against witch-doctoring, and helps us eliminate the inefficiencies in the provision of medical care described by Cochrane. *But the methodological minimization of information on effectiveness in relation to the individual patient leaves an evidence gap for clinicians.* [Italics added.]

Dr. Alan Feinstein, from the Department of Medicine at Yale University, echoes similar reservations in his article, "Problems in the evidence of evidence-based medicine."[219] Larry Culpepper and Thomas Gilbert, in their Lancet commentary, "Evidence and ethics," focus on this same difficulty in the primary care arena.[220] Although the debate has continued over the past decade, these reasoned arguments have been heard less frequently as the push toward EBM has gained momentum. However, the problems described above have not been solved. Rather, with the advent of personalized medicine and systems biology, it is even more clear that the reductionist simplicity of the RCT frequently does not work to address the significant questions now facing 21st century practitioners in their struggle to cope with the epidemic of complex, chronic disease.[221,222,223,224,225]

We can now begin to understand why the effect of research findings on clinical practice has been weaker than the early proponents of EBM postulated. The first problem that has impeded the successful application of EBM to patient care is the complex nature of the translation of research studies to the individual patient's unique clinical problem(s)—what Larry Weed called knowledge coupling.[226,227] John Hampton, Professor of Cardiology, University Hospital, Nottingham, England, in a review titled "Evidence-based medicine, opinion-based medicine, and real-world medicine," reasons: *"Clinical trials will tell us what treatments are effective, but not necessarily which patients should receive them... Treatment must always be tailored to the individual patient."*[228] (We would add to that statement that RCTs can only tell us what treatments are effective *from among those studied*. The decision about what to investigate introduces so much bias into the evidence base that it would be difficult to overstate its impact.)

Added to this methodological conundrum are the real-world exigencies of daily clinical practice that make it virtually impossible to acquire, collate, and filter all relevant evidence prior to direct application to the unique needs of the patient. Imagine a clinic where, after each therapeutic encounter—involving both appropriate history taking and physical examination procedures—a problem list is developed and then carefully subjected to a medical literature search and analysis. The pace of clinical practice will not tolerate the inertia of such a process, even to improve the care of patients who may be in desperate need of new interventions based on emerging evidence.

A second major issue is even more complex. If medical care were as simple as making a diagnosis and then prescribing an appropriate pharmacologic agent (or agents), then the EBM system, as presently configured and applied, might work—but only if appropriate *Problem Oriented Evidence that Matters* (POEMs)[xiii,230] were available for each medical problem (and disregarding, for the moment, that most

[xiii] To assist the practicing physician's effective inclusion of new evidence into daily practice, both government-sponsored and commercially affiliated organizations have moved EBM forward with a collation of filtered studies called: *Problem Oriented Evidence that Matters* (POEMs). Most POEMs and most studies in the Cochrane Collection are research trials of pharmacologic therapeutic interventions. It is now possible to search these specific databases or self-developed relevant databases that retrieve groups of studies that directly link research findings with specific clinical problems.

chronic disease is complicated by multiple comorbidities that are rarely addressed by POEMs). Unfortunately, the "better living through chemistry" dream that fueled half a century of research has not, in fact, created a healthier population (see Chapter 2).[231] Although many acute medical problems do appear to respond consistently as envisioned by the EBM model, more than 70% of health problems presenting to clinicians today are both chronic and complex[232] (Chapter 2), and they require a different approach. "Treating only known biological components of disease minimizes the ability of the practitioner to tailor therapeutic interventions to individual patients."[233]

Despite these sobering facts, physician education, training, and reimbursement, as well as research designs for clinical studies that physicians depend upon for effective decision making, continue to be focused primarily on an acute-care model that emphasizes pharmacologic solutions for complex, chronic problems, leaving the discerning clinician without the evidence and tools needed for addressing their patients' complex needs.

It's not enough, of course, for us to understand what's wrong. We must also seek better solutions for these urgent problems, regardless of the difficulty of the task and the elusiveness of the answers. The RCT tool was developed during a specific period in our medical history and worked well to differentiate the traditionalists, who claimed that clinical experience trumped bench science, from the scientists, who perceived the value in systematic inquiry. Major strides in treatment have occurred in the intervening 50 to 60 years as a result of the shift toward the use of RCT methodology. But we are now at another nodal decision point, unique to our cultural and medical evolution. We need more sophisticated tools to shed light on the nature of the web-like interweaving of mechanisms at work in complex, chronic illness.[234, 235, 236] While alternate study designs and statistical methodologies are being developed for analyzing complex data sets,[237, 238, 239] we must return the practice of EBM to its original mission of using evidence to inform clinical experience and to expand the understanding of basic mechanisms of health and disease.[240, 241] This will help to reverse the decade-long plunge toward "... reducing clinical practice to the technical implementation of research findings."[242, 243]

In sum, we are now facing another major transition in how we perceive and utilize evidence in clinical medicine. Thomas Kuhn offers this insightful analysis:

> When defects in an existing paradigm accumulate to the extent that the paradigm is no longer tenable, the paradigm is challenged and replaced by a new way of looking at the world. Medical practice is changing, and the change, which involves using the medical literature more effectively in guiding medical practice, is profound enough that it can appropriately be called a paradigm shift.

A Science-Using Profession

Given the serious limitations of applying the EBM model in clinical practice, we must ask two questions central to the future of medicine:

- How do we develop an effective therapeutic relationship based upon (1) efficacious, reproducible, and personalized clinical applications that are solidly anchored in science, (2) emerging knowledge about the multifactorial causes of chronic disease, and (3) an expanded awareness of the nature of clinical/critical thinking?

- How do we transition from an EBM-based, guideline-driven, prescriptive clinical practice to an individualized, patient-centered approach that captures both the science and the art of medicine?

First, we must recognize that most clinicians, by professional training and inclination, are not scientists. ***Clinical medicine is a science-using profession.*** It is true that diagnosis and treatment have become intensely science-using activities, but these activities have a distinctly different process and endpoint than those of the professional scientist.[245] "Physicians start from the demands of the patient's condition and not from the demand for generalizable knowledge, and their goal is just as particular: to treat the patient's illness, not to test the therapy."[246] The evidence needs of clinical medicine are also distinctly different. The focus on application and usefulness centers on how the evidence informs the assessment and treatment process for each individual patient, given that patient's unique genetic propensities and unique environmental influences.

At a number of points in this paper, we have documented how most clinical evidence based on RCTs informs about cohorts of patients with similar signs and symptoms (the basis of diagnosis and diagnostic groups), but not does not necessarily provide decision support for an individual patient. The primary responsibility of the attending clinician is to ferret out meaningful evidence for each patient, knowing that unique genomic specificities may predispose that patient to unanticipated results. From this perspective, evidence often serves to qualify *insight*, but when applied in a simplistic or statistically linear way, can create unintended mischief.[247] From this perspective, every maneuver, either further assessment or therapeutic intervention, becomes a clinical probe that must be assessed in partnership with the client as the shared journey of investigation and healing proceeds.

Dr. Sackett, founder and advocate for EBM, was quite clear about this in the early development of EBM: "Evidence based medicine is the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients. The practice of evidence based medicine means integrating individual clinical expertise with the best available external clinical evidence from systematic research.... *Good doctors use both individual clinical expertise and the best available external evidence and neither alone is enough.*"[248] [Italics added.]

The combining of these elements can be viewed as a Venn diagram, where the best outcomes occur when all three elements are represented (Figure 8).

Figure 8: Optimal Outcomes: Applying evidence-based medicine to the real world

David Deutsch, in *The Fabric of Reality*, describes the need for a next step in using the science of underlying pathophysiological mechanisms of disease in the clinical setting of medicine:

> The science of medicine is perhaps the most frequently cited case of increasing specialization seeming to follow inevitably from increasing knowledge, as new cures and better treatments for more diseases are discovered. But as medical and biochemical research comes up with deeper explanations of disease processes (and healthy processes) in the body, understanding is also on the increase. More general concepts are replacing more specific ones as common, underlying molecular mechanisms are found for dissimilar diseases in different parts of the body. Once a disease can be understood as fitting into a general framework, the role of the specialist diminishes.... Physicians... can look up such facts as are known. But [more importantly] they may be able to apply a general theory to work out the required treatment, and expect it to be effective even if it has never been used before.[216]

The real question now facing every discerning, informed clinician[257] is how to bring relevant, graded, emerging scientific evidence to the complex list of problems made unique by the patient's genetic susceptibilities and potentialities that, in turn, communicate constantly with the ever-changing environment within which the patient lives. No RCT can inform, *in a specific way*, the appropriate clinical roadmap for assessment and planning for therapeutic interventions in this complex environment.[258] Clinicians must use science; it is a powerful tool. But they should be in charge of how and when to use it, not dominated and intimidated by it.

The Heuristics that Guide Doctors' Thinking

We believe it is fair to say that the fear of uncertainty has led us to narrow our field of vision far too soon. "Science has not one method, but many. These include observation in the natural world, experimentation in the laboratory, mathematical proof, computer simulation with real data, analysis of surveys and demographical statistics, and thought experiments for the great geniuses, such as Galileo and Einstein.

Another Perspective on the Biomedical Model

The complexity of the developing explanatory models has been serially addressed in the *Annals of Family Medicine*, a peer-reviewed medical journal "dedicated to advancing knowledge essential to understanding and improving health and primary care," including the development of methodology and theory for addressing this conundrum. In the article, "The biopsychosocial model 25 years later: Principles, practice, and scientific inquiry,"[249] the authors critique the limitations of the conventional biomedical model and the research methodologies that evolve from this model and preview the evolving model of complexity and causality and the nested model of structural causality":

> Few morbid conditions could be interpreted as being of the nature "one microbe, one illness"; rather, there are usually multiple interacting causes and contributing factors. Thus, obesity leads to both diabetes and arthritis; both obesity and arthritis limit exercise capacity, adversely affecting blood pressure and cholesterol levels; and all of the above, except perhaps arthritis, contribute to both stroke and coronary artery disease. Some effects (depression after a heart attack or stroke) can then become causal (greater likelihood of a second similar event).... These observations set the stage for models of circular causality that describe how a series of feedback loops sustain a specific pattern of behavior over time.[230,231,232] Complexity science is an attempt to understand these complex recursive and emergent properties of systems[233,234] and to find interrelated proximal causes that might be changed with the right set of interventions.[235]

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Has broad-based and open-minded scientific inquiry been skewed by EBM and its hierarchy of evidence codification and ranking?[260, 261, 262, 263, 264, 265] Is the hegemony of EBM in contemporary medicine, as exemplified by Drs. Montori and Guyatt,[266] closing the door on the reintegration of the science and art of medicine?[m] We need to ask what we have surrendered by de-emphasizing "unsystematic clinical experience and pathophysiologic rationale." What is the irreplaceable loss in patient outcomes with the dismissing of experience, intuition, and wisdom? What must we do to develop skills and methodologies appropriate to clinical decision making in a context of uncertainty?

[m] In their 2008 review of the progress in EBM, VM Montori and GH Guyatt reiterate a basic principle of EBM cited earlier in this chapter: "Evidence-based medicine *de-emphasizes intuition, unsystematic clinical experience, and pathophysiologic rationale* (italics added) as sufficient grounds for clinical decision making and stresses the examination of evidence from clinical research. Ignoring the significant push back from the international scientific and clinical community regarding the troubling effects of EBM on both research and translational medicine

There is a robust literature that explores the actual methodologies used by clinicians who must make decisions when time and information are limited and the outcome is uncertain. It is clear from brain research that there is an important difference between the human brain and other features of the universe. The brain is a complicated, nonlinear, living system capable of self-organization. The brain does not respond to incoming stimuli in a direct, reflex-like action but continuously changes, constructing its own neural activity patterns in order to adapt to and synchronize with external stimuli. Genetic makeup and continuous stimuli from the environment are the only factors that create individual differences; the twin magnets of chaos and self-organization shape the constant interplay of those factors. The human mind is highly capable of dual processing; in fact, the continuous and virtually seamless integration of reason to test intuition and of intuition to generate the creative thinking that fuels rational inquiry is what advances insight and knowledge.

We usually represent problems in a linear fashion despite the convincing evidence that this type of modeling is not appropriate or adequate for studying the nervous system or human behavior.[267, 268] This naturally leads to some interesting conclusions about the interrelationship of brain and mind when faced with decision making in a sea of uncertainty.[269, 270, 271, 272, 273] The mind is an adaptive toolbox with genetically, culturally, and individually created and transmitted rules of thumb. These rules of thumb are called heuristics and are foundational to daily function, intuition, or inspiration.[274] *The study of judgment under uncertainty is the study of heuristics.* The human species' response to uncertainty is to rely upon experience, coupled with knowledge, data, and applied wisdom through processes such as heuristics and insight.

Heuristics and "rules of thumb" are synonyms terms. It is important to distinguish between heuristic and analytic thinking. For instance, heuristic thinking is indispensable for discovering a mathematical proof, whereas analytic thinking is necessary for checking the steps of the proof.[275] A limited number of simplifying heuristics rather than more formal and extensive algorithmic processing is the rule.[276] The classic example of a heuristic that most people have experienced is the "rule of thumb" (gaze heuristic) used for catching a ball, as illustrated in Figure 9.

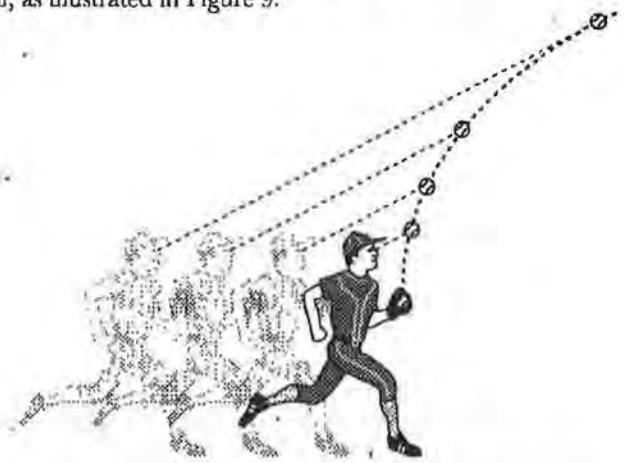

Figure 9:
How to catch a fly ball. Players rely on unconscious rules of thumb. When a ball comes in high, a player fixates his gaze on the ball, starts running, and adjusts his speed so that the angle of the gaze remains constant.

The angle of gaze is the angle between the eye and the ball, relative to the ground. For years, brain scientists assumed that a complex process of computations was required for tasks like catching a ball. The artificial intelligence (AI) groups attempted to duplicate these tasks with robotic technologies. However, research by the 'heuristics' groups showed a very different process at work.[277] It turns out that a player who uses the *gaze* rule does not need to measure wind, air resistance, spin, or the other complex, causal variables. "All the relevant facts are contained in one variable: the angle of gaze. Note that a player using the *gaze heuristic* is not able to compute the point at which the ball will land. Yet the heuristic leads the player to the landing point....most fielders are blissfully unaware of the gaze heuristic, despite its simplicity. Once the rationale underlying an intuitive feeling is made conscious, however, it can be taught."[278]

Elwyn et al., in their well reasoned paper, "Decision analysis in patient care,"[279] demonstrate the efficacy and comprehensiveness of this methodology. Naylor summarizes in his editorial comments on their paper (published in the *Lancet*):

> The process of individualized decision analysis might best be viewed as a way of enhancing communication with patients, rather than as a "black box" from which directives emerge. But if that is the ultimate aim, it seems more useful to develop simple decision aids aimed at helping patients and doctors share information and work through tough choices in the clinical setting. To that end, Elwyn and colleagues call on clinicians and patients to communicate better while embracing fast and frugal rules of thumb [heuristics]. In so doing they have arguably drawn their readers full circle *from clinical art to bedside science and back again*. It is ironic, moreover, that the best lessons in *fast and frugal rules of thumb* may well come from understanding the cognitive processes of those master clinicians who consistently make superb decisions without obvious recourse to the canon of evidence-based medicine.[280] [Italics added.]

If we are to develop both a clinical methodology and a curriculum that will approximate the best characteristics of successful clinicians, we must compare what is usually done with what could be done. A very pertinent example of how we might transform medical care affects the primary heuristic of contemporary medicine—the patient history and physical exam reporting structure (the H&P heuristic)—that dominates all communication among healthcare practitioners today. We will then compare it to the new heuristic developed by IFM to achieve a more comprehensive communication tool.

Every healthcare provider recognizes this formal construct for medical information and communication. It both describes and dictates the process of the patient visit. The story that emerges from a clinical encounter is typically organized around the following elements:

From Patient Encounter to the Diagnosis:
The Conventional Medical Heuristic

- **Chief Complaint (CC)***
- **History of Present Illness (HPI)***
- **Past Medical History (PMH)***
- **Review of Organ Systems (ROS)***
- **Medication and Supplement History***
- **Dietary History***
- **Social, Lifestyle, Exercise History****
- **Physical Examination (PE)***
- **Laboratory and Imaging Evaluations***
- **Assessment and Diagnosis***
- **Treatment Interventions *usually pharmaceutical and/or procedure -based)***

* = STANDARD PRACTICE
** = EXPANDED MODEL

It is not always recognized that this construct facilitates the "fast and frugal processing" needed to efficiently collect, collate, and use patient information. The conventional H&P heuristic propels all information headlong toward the diagnosis, with the intention of identifying and prescribing the pharmaceutical or procedural therapy associated with that diagnosis. Each individual diagnosis is viewed as a distinct entity unto itself—often investigated during separate office calls and/or by different practitioners. There is no place in the conventional H&P heuristic to tie together multiple diagnoses into a consistent and coherent patient narrative. There is no identification of the antecedent conditions that may predispose the patient to the triggering of dysfunctional adaptive responses, nor of the mediators that may perpetuate the dysfunction. Thus, patients filtered through this conventional heuristic never have a chance to be fully heard and understood in the context of their whole life experience. Instead, their stories are reduced to a series of diagnoses, treated by different specialists, often in isolation from one another.

The H&P heuristic was shaped by, and thus reinforces, the organ-system model of disease, with its distinct and separate information silos, rather than a systems-medicine perspective that encourages the search for common underlying mechanisms of, and pathways to, disease.

IFM's functional medicine heuristic (FM heuristic) expands upon the same basic structure we are all familiar with, but organizes the information to integrate the patient's genetic and developmental susceptibilities (*antecedents*), historical *triggers*, and ongoing *mediators* of disease. Thus, the patient's story emerges with greater detail, a broader context, and a different focus and ultimate goal:

HA 09/01/2015

The Functional Medicine Heuristic

- **Chief Complaint (CC)**
- **History of Present Illness (HPI)**
- **Past Medical History (PMH)**
  - —Explore antecedents, triggers, and mediators of CC, HPI, and PMH
- **Review of Organ Systems (ROS)**
  - —Genetic predispositions?
- **Medication and Supplement History**
- **Dietary History**
- **Social, Lifestyle, Exercise History**
- **Physical Examination (PE)**
- **Laboratory and Imaging Evaluations:**
  - —Immune/inflammatory imbalance
  - —Energy imbalance/mitochondrial dysfunction
  - —Digestive/absorptive and microbiological imbalance
  - —Detoxification/biotransformation/excretory imbalance
  - —Imbalance in structural, boundary, and membrane integrity
  - —Hormonal and neurostransmitter imbalances
  - —Imbalance in mind - body - spirit integration
- **Initial Assessment:**
  - —Enter data on Matrix form; look for common themes
  - —Review underlying mechanisms of disease
  - —Recapitulate patient's story
  - —Organ system-based diagnosis
  - —Functional medicine assessment: underlying mechanisms of disease; genetic and environmental influences
- **Treatment Plan:**
  - —Individualized
  - —Dietary, lifestyle, environmental
  - —Nutritional, botanical, psychosocial, energetic, spiritual
  - —May include pharmaceuticals and/or procedures

As can be seen in the FM heuristic, the diagnosis is one factor among many that help the clinician and patient explore why and how a condition was triggered and why and how the dysfunction is being mediated. From a disciplined filtering of the patient information through the Functional Medicine Matrix Model™, patterns emerge that illuminate both the underlying causes of dysfunction as well as plausible (and multiple) points of leverage where individualized treatment can create improved function. The potential interventions reflect a broader array of health vectors than just pharmaceutical and procedural interventions because the FM heuristic elicits a pattern that helps the clinician and patient identify where lifestyle and environmental interventions can be applied.

Because clinical reasoning is very often grounded in heuristics (simplified models that guide evaluation and treatment at an unconscious level of awareness), we argue that to change the outcome, we must change the model. The ability to utilize heuristics when time and information are limited and outcomes are uncertain is a very special cognitive trait—an evolutionary breakthrough in adaptive cognition. To understand and refine clinical reasoning and clinical practice—to ultimately improve outcome—a deeper understanding of these adaptive skills must be understood and consciously applied.

Insight

If we are to develop an effective model for the healing partnership, we must also explore the research that illuminates the emergence of insight as a reproducible phenomenon.[a] Brain research has illuminated very different functions of the left and right brain that explicate the objective neural correlates of a brain that produces insight. Among the most important features of this emerging view of brain function are the following:

- Solving computational questions is primarily a left-brain function. Asking a computational question triggers left-brain activity at the expense of right-brain function. (This has tremendous relevance to the interactions between doctor and patient. When a patient is interrupted with a computational question in the midst of an attempt to describe a pattern of dysfunction, the patient's own opportunity for insight may be lost.)
- If the left hemisphere excels at denotation—storing the primary meaning of a word—the right hemisphere deals with connotation, everything that gets left out of a dictionary definition, such as the emotional charge in a sentence or a metaphor. Language is so complex that the brain has to process it in two different ways at the same time. As humans, we need to see both the forest and the trees. The right hemisphere is what helps you see the forest.[201, 202]
- Much of the research into the adaptive unconscious (aka unconscious cognition) suggests that pattern recognition capacity resides in the right brain, but is not specifically localized.[203, 204] Solving questions requiring insight generates activity that starts in the prefrontal cortex and eventually extends throughout the cortex and deeper structures, searching for possible experiential information that contributes to the emergence of a pattern. It is the appearance of that pattern that sparks the "aha" or "Eureka!" experience in the connotative language centers of the right brain.

In brief, left-brain function helps us with the denotative, computational, linear functions of life and thought, whereas the right brain provides the connotative shadings that give depth and character and color to meaning. Right-brain function is the source of pattern recognition and moments of insight.

The researchers in this field have produced a robust and credible body of research about pattern recognition from experiments that delineate and substantiate the functions of unconscious cognition (the

[a] "What is insight? The term 'insight' is used to designate the clear and sudden understanding of how to solve a problem. Insight is thought to arise when a solver breaks free of unwarranted assumptions, or forms novel, task-related connections between existing concepts or skills." (Bowden EM. New approaches to demystifying insight. TRENDS in Cognitive Sciences. 2005;9(7):322-28.)

adaptive unconscious) that shape moments and expressions of insight.[285, 286, 287] Reproducible patterns of brain activity correlate with the experience of insight.[288] The prefrontal cortex does not simply function as an aggregator of information. Instead, like the conductor of an orchestra, brain wave activity and energy expenditure are coordinated as if instructed by the prefrontal cortex maestro, waving its baton and directing the players.

This is known as top-down processing, since the prefrontal cortex (the top of the brain) is directly modulating the activity of other areas. Studies show that cells in the right hemisphere are more broadly tuned than cells in the left hemisphere, with longer branches and more dendritic spines. As a consequence, neurons in the right hemisphere are collecting information from a larger area of cortical space. They are less precise but better connected. When the brain is searching for an insight, these are the cells that are most likely to produce it. A small fold of tissue on the surface of the right hemisphere, the anterior superior temporal gyrus (aSTG), becomes unusually active in the second before the insight. The activation is described as sudden and intense, a surge of electricity leading to a rush of blood.[289, 290]

One of the unusual aspects of insight is not the revelation itself but what happens afterward. The adult brain is an infinite library of associations, a cacophony of competing ideas, and yet, as soon as the right association appears, we *know*. The new thought, which is represented by that rush of gamma waves in the right hemisphere, immediately grabs our attention. As soon as the insight happens, it seems so obvious. People can't believe they didn't see it before.[291, 292, 293]

Insight researches call the "aha" experience the *moment of categorical insight*. This moment of epiphany registers as a new pattern of neural activity in the prefrontal cortex. The brain cells have been altered by the breakthrough. An insight is a restructuring of information—it's seeing the same old thing in a completely new way. Once that restructuring occurs, you never go back.[294]

Insight and the Healing Partnership

"While it's commonly assumed that the best way to solve a difficult problem is to focus, minimize distractions, and pay attention only to the relevant details, this clenched state of mind may inhibit the sort of creative connections that lead to sudden breakthroughs. We suppress the very type of brain activity that we should be encouraging. Jonathan Schooler has recently demonstrated that making people focus on the details of a visual scene, as opposed to the big picture, can significantly disrupt the insight process. 'It doesn't take much to shift the brain into left-hemisphere mode, he said.'"[295] We can extrapolate that, as clinicians, although we don't ignore evidence, when we want insight about a patient's condition, we are clearly better off not turning to left-brain analysis of the most recent RCTs. And, when we want the patient's insight, we must learn to elicit the patient's story (pattern) and really listen to it.

Research focused on the typical, clinical therapeutic encounter has noted that clinicians interrupt the patient's flow of conversation within the first 12 to 18 seconds or less of the patient's response to a question.[296, 297] This reproducible phenomenon in the conventional clinical setting makes sense if you compare the heuristic for contemporary medicine to the functional medicine heuristic. The heuristic of conventional medicine (rule of thumb) achieves the stated goal in an expeditious manner: clinicians use it to identify the primary organ system domain of the presenting problem and then focus on the differential diagnosis within that domain, narrowing relatively to the final diagnosis. This is

a computational process, without need for a partnership that can produce insight into the underlying causes and mechanisms of the medical problem.

The functional medicine heuristic, on the other hand, requires a carefully nurtured and protected partnership between the clinician and the patient to illuminate the underlying mechanisms of the patient's illness(es). The FM heuristic requires an iterative, cooperative process that yields a more complete narrative story. From a thorough investigation of the antecedents, triggers and mediators of the patient's condition, emerge information and insights that can help to shape a deeper and more comprehensive therapeutic response.

Summary

We have devoted this chapter to achieving a better understanding of an urgent problem facing clinicians today: how to combine both science and art, evidence and insight, into an individualized, patient-centered approach to complex, chronic disease. We do not claim to have *the* (sole or definitive) answer. But we do offer a new focus for both education and practice that can be described and substantiated, taught and practiced. We have presented findings that suggest that the management of uncertainty—the inherent context of clinical medicine—requires a change in the therapeutic relationship on the part of both clinician and patient and a change in how we view and use evidence. The technical therapeutic encounter that has characterized a great deal of patient care for last few decades must be transformed into a healing partnership through appropriate applications of scientific understanding, evidence from clinical trials, and a new understanding of brain function.

The Institute for Functional Medicine's model of comprehensive care and primary prevention for complex, chronic illnesses (described further in Chapter 5) is grounded in both science (the Functional Medicine Matrix Model; evidence about common underlying mechanisms and pathways of disease; evidence about effective approaches to the environmental and lifestyle sources of disease) and art (the healing partnership and the search for insight in the therapeutic encounter). These two cornerstones of clinical medicine must be integrated into our teaching and practice in order to achieve what we owe to our patients and ourselves—a more effective response to the epidemic of chronic disease. We assert that this can be done.

Chapter 5

FUNCTIONAL MEDICINE: A 21ST CENTURY MODEL OF PATIENT CARE AND MEDICAL EDUCATION

It is much more important to know what sort of a patient has a disease than what sort of a disease a patient has. The good physician treats the disease; the great physician treats the patient who has the disease.

—WILLIAM OSLER

Treat the patient, not the diagnosis.

—THE INSTITUTE FOR FUNCTIONAL MEDICINE

In this chapter, we will review the basic principles, constructs, and methodology of functional medicine. It is not the purpose of this paper to recapitulate the range and depth and science of functional medicine; books and monographs covering that material in great detail are already available for the interested clinician and for use in health professions schools. Our purpose in the first part of this chapter is to describe how functional medicine is organized to deliver personalized, systems medicine and, as such, is equipped to respond to the challenge of treating complex, chronic disease more effectively. In the second part of the chapter, we will discuss how clinicians can be helped to re-integrate the art and science of medicine to create a healing partnership.

Part I: What is Functional Medicine?

Functional medicine conceptualizes health and illness as part of a continuum in which all components of the human biological system interact dynamically with the environment. These interactions produce patterns that change over time in individuals. To manage the complexity inherent in this approach, functional medicine has adopted practical models for obtaining and evaluating clinical information that leads to individualized, patient-centered therapies.

Functional medicine encompasses a dynamic approach to assessing, preventing, and treating complex, chronic disease. It helps clinicians identify and ameliorate dysfunctions in the physiology and biochemistry of the human body as a primary method of improving patient health. In this model of practice, we emphasize that chronic disease is almost always preceded by a period of declining function in one or more of the body's systems. Returning patients to health requires reversing (or substantially improving) the specific dysfunctions that have contributed to the disease state.

Those dysfunctions are, for each of us, the result of lifelong interactions among our environment, our lifestyle, and our genetic predispositions. Each patient, therefore, represents a unique, complex, and interwoven set of influences on intrinsic functionality that have set the stage for the development of disease or the maintenance of health.

Historically, the word "functional" has been used somewhat pejoratively in medicine. It has implied a disability associated with either a geriatric or psychiatric problem. We suggest, however, that this is a very limited definition of an extremely useful word. Medicine has not really produced an efficient method for identifying and assessing changes in basic physiological processes that produce symptoms of increasing duration, intensity, and frequency, even though we know that such alterations in function often represent the first signs of conditions that, at a later stage, become pathophysiologically definable diseases. If we broaden the use of functional to encompass this view, *functional medicine* becomes the science and art of detecting and reversing alterations in function that clearly move a patient toward chronic disease over the course of a lifetime. Thus, with functional medicine, we begin to define a model of patient care that seeks to identify underlying chronic dysfunctions associated with altered physiological processes and to maximize functionality at all levels of body, mind, and spirit.

One way to conceptualize where functional medicine falls in the continuum of health and health care is to examine the functional medicine "tree." In its approach to complex, chronic disease, functional medicine encompasses the whole domain represented by the graphic shown in Figure 10, but *first* addresses the patient's core clinical imbalances, fundamental physiological processes, environmental inputs, and genetic predispositions. Diagnosis, of course, is part of the functional medicine model, but the emphasis is on understanding and improving the functional core of the human being as the starting point for intervention.

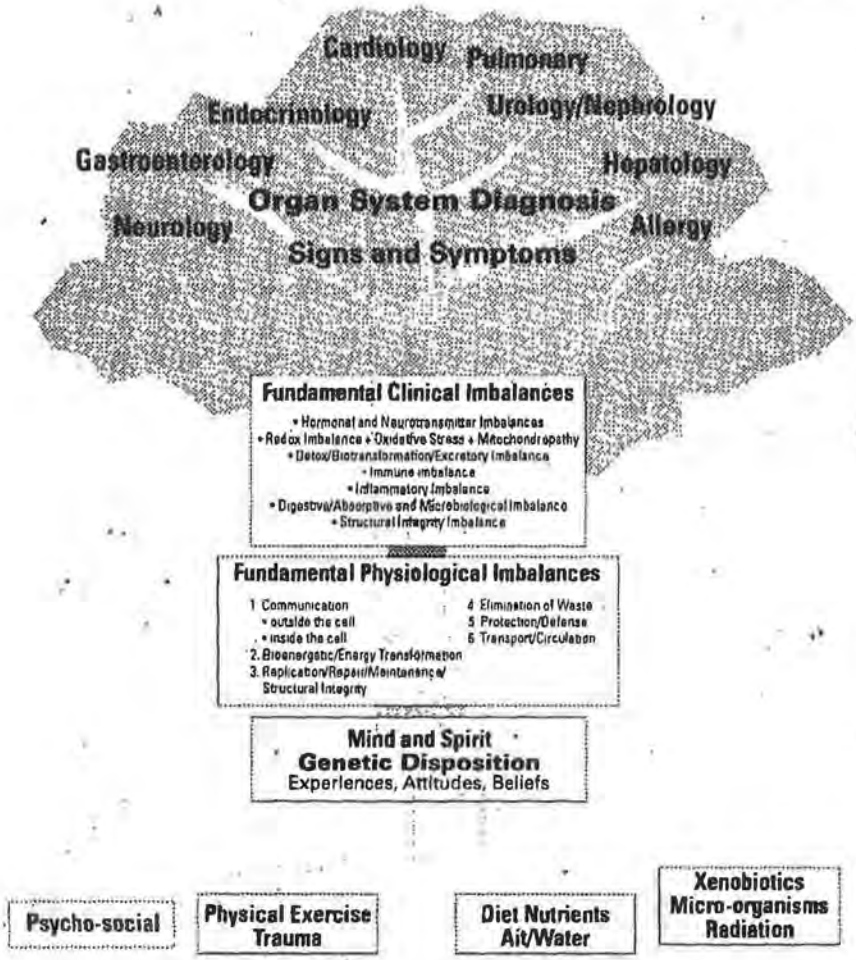

Figure 10:
The Continuum of Health and Health Care

Functional medicine clinicians focus on restoring balance to the dysfunctional systems by strengthening the fundamental physiological processes that underlie them, and by adjusting the environmental and lifestyle inputs that nurture or impair them. This approach leads to therapies that focus on restoring health and function, rather than simply controlling signs and symptoms.

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Principles

Seven basic principles characterize the functional medicine paradigm:

- Acknowledging the **biochemical individuality** of each human being, based on the concepts of genetic and environmental uniqueness
- Incorporating a **patient-centered** rather than a disease-centered approach to treatment
- Seeking a dynamic balance among the internal and external factors in a patient's body, mind, and spirit
- Addressing the **web-like interconnections** of internal physiological factors
- Identifying **health as a positive vitality**—not merely the absence of disease—and emphasizing those factors that encourage a vigorous physiology
- **Promoting organ reserve** as a means of enhancing the health span, not just the life span, of each patient
- Functional medicine is a **science-using profession**

Environmental Inputs

At the base of the medicine tree graphic are found the building blocks of life, as well as the primary influences on them. When we talk about influencing gene expression, we are interested in the interaction between environment in the broadest sense and any genetic predispositions with which a person may have been born—including the epi genome[m]. Many environmental factors that affect genetic expression are (or appear to be) a matter of choice (such as diet and exercise); others are very difficult for the individual patient to alter or escape (air and water quality, toxic exposures); and still others may be the result of unavoidable accidents (trauma, exposure to harmful microorganisms in the food supply). Some factors that may appear modifiable are heavily influenced by the patient's economic status—if you are poor, for example, it may be impossible to choose more healthful food, decrease stress in the workplace and at home, or take the time to exercise and rest properly. Existing health status is also a powerful influence on the patient's ability to alter environmental input. If you have chronic pain, exercise may be extremely difficult; if you are depressed, self-activation is a huge challenge.

[m]Epigenetics—the study of how environmental factors can affect gene expression without altering the actual DNA sequence, and how these changes can be inherited through generations.

The influence of these inputs on the human organism is indisputable and they are often powerful agents in the battle for health. Ignoring them in favor of the quick fix of writing a prescription means the cause of the underlying dysfunction may be obscured, but is usually not eliminated. In general terms, the environmental inputs listed below should be considered when working to reverse dysfunction or disease and restore health:

- Diet (type and quantity of food, food preparation, calories, fats, proteins, carbohydrates)
- Nutrients (both dietary and supplemental)
- Air
- Water
- Microorganisms (and the general condition of the soil in which food is grown)
- Physical exercise
- Trauma
- Psychosocial and spiritual factors (including family, work, community, economic status, stress, and belief systems)
- Xenobiotics
- Radiation

Fundamental Physiological Processes

There are certain physiological processes that are necessary to life. These are the "upstream" processes that can go awry and create "downstream" dysfunctions that eventually become disease entities. Functional medicine requires that clinicians consider these in evaluating patients, so that intervention can occur at the most fundamental level possible. They are:

1. Communication
   - outside the cell
   - inside the cell
2. Bioenergetics/Energy Transformation
3. Replication/Repair/Maintenance/Structural Integrity
4. Elimination of Waste
5. Protection/Defense
6. Transport/Circulation

Although these fundamental physiological processes are usually taught in the first two years of medical training, where they are appropriately presented as the foundation of modern, scientific patient care, subsequent training in the clinical sciences often fails to fully integrate knowledge of the functional mechanisms of disease with therapeutics and prevention, emphasizing instead teaching/

learning based on organ system diagnosis.[298] Focusing predominantly on organ system diagnosis without examining the underlying physiology that produced the patient's signs, symptoms, and disease often leads to managing patient care by matching diagnosis to pharmacology. The job of the healthcare provider then becomes a technical exercise in finding the drug or procedure that best hits the diagnosis (not necessarily the patient), leading to a significant curtailment of critical thinking pathways: "Medicine, it seems, has little regard for a complete description of how a myriad of pathways result in any clinical state."[299]

Even more important, pharmacologic treatments are often prescribed without careful consideration of their physiological effects across all organ systems and physiological processes (and genetic variations).[300] Pharmaceutical companies have exploited this weakness. Did you ever see a drug ad that urged the practitioner to carefully consider the impact of all other drugs being taken by the patient before prescribing a new one? The marketing of drugs to specific specialty niches, and the use of sound bite sales pitches that suggest discrete effects, skews healthcare thinking toward this narrow, linear logic, as notably exemplified by the COX-2 inhibitor drugs that were so wildly successful on their introduction, only to be subsequently withdrawn or substantially narrowed in use due to collateral damage.[301, 302]

Core Clinical Imbalances

The functional medicine approach to assessment, both before and after diagnosis, charts a course using different navigational assumptions. Every health condition instigates a quest for information centered on understanding when and how the specific biological system(s) under examination spun out of control to begin manifesting dysfunction and/or disease. Analyzing all the elements of the patient's story, the signs and symptoms, and the laboratory assessment through a matrix focused on functionality requires analytic thinking and a willingness on the part of the clinician to reflect deeply on underlying biochemistry and physiology. The foundational principles of how the human organism functions—and how its systems communicate and interact—are essential to the process of linking ideas about multifactorial causation with the perceptible effects we call disease or dysfunction.

To assist clinicians in this process, functional medicine has adapted and organized a set of *core clinical imbalances* that function as the intellectual bridge between the rich basic science literature concerning physiological mechanisms of disease (first two years of medical training) and the clinical studies, clinical experience, and clinical diagnoses of the second two years of medical training. The core clinical imbalances serve to marry the mechanisms of disease with the manifestations and diagnoses of disease. Many common underlying pathways of disease are reflected in a few basic clinical imbalances:

- Immune/inflammatory imbalance
- Energy imbalance/mitochondrial dysfunction
- Digestive/absorptive and microbiological imbalance
- Detoxification/biotransformation/excretory imbalance
- Imbalance in structural, boundary, and membrane integrity

- Hormonal and neurotransmitter imbalances
- Imbalance in mind-body-spirit integration

Using this construct, it becomes much clearer that one disease/condition may have multiple causes (i.e., multiple clinical imbalances), just as one fundamental imbalance may be at the root of many seemingly disparate conditions (see Figure 11).

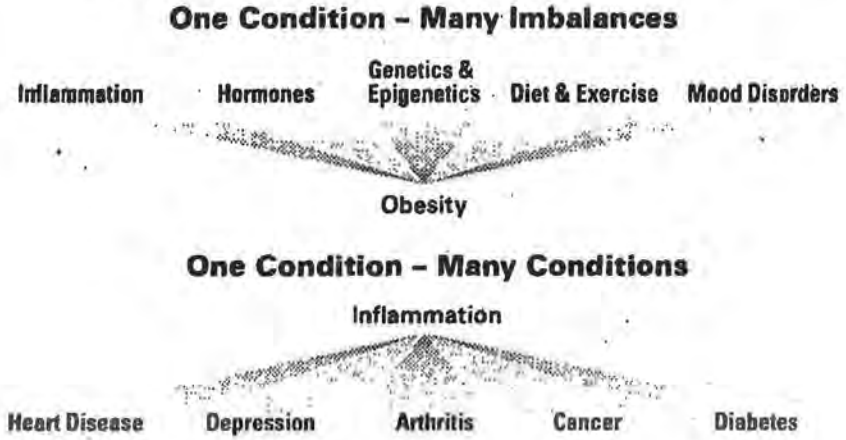


Figure 11:
Core Clinical Imbalances—Multiple Influences

The most important precept to remember about functional medicine is that restoring balance—in the patient's environmental inputs and in the body's fundamental physiological processes—is the key to restoring health.

Constructing the Model

Combining the principles, environmental inputs, fundamental physiological processes, and core clinical imbalances creates a new information-gathering-and-sorting architecture for clinical practice. This new model includes an explicit emphasis on principles and mechanisms that weld meaning and mechanistic explanations to the diagnosis and deepen the clinician's understanding of the often overlapping ways things go wrong. Any methodology for constructing a coherent story and an effective therapeutic plan in the context of complex, chronic illness must be flexible and adaptive. Like an accordion file that can compress and expand upon demand, the amount and kind of data needed will necessarily change in accordance with the patient's situation and the clinician's time and ability to piece together the underlying threads of dysfunction. There are many pathways to illness; therefore, the accordion file must expand to incorporate a much larger database of relevant information. For example, the Chief Complaint, History of Present Illness, and Past Medical History sections must expand to include a thorough investigation of antecedents, triggers, and mediators. Personalized medical care without this expanded investigation will fall short.

Distilling the data from the expanded history, physical exam, and laboratory into a narrative story line that includes antecedents, triggers, and mediators can be challenging. Key to developing a thorough narrative is organizing the story according to the seven common underlying mechanisms that influence health (the core clinical imbalances), as shown on the Functional Medicine Matrix Model™ form (see Figure 12).

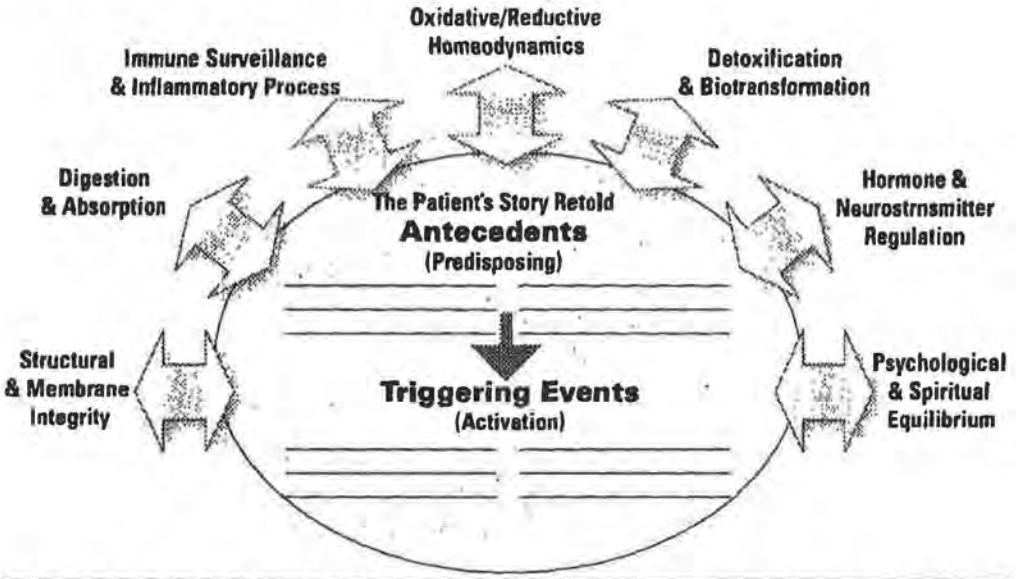


Figure 12:
The Functional Medicine Matrix Model™ form

The Matrix form helps organize and prioritize information, and also clarifies the level of present understanding, thus illuminating where further investigation is needed. For example, indicators of inflammation on the matrix might lead the clinician to request tests for specific inflammatory markers (such as hsCRP, interleukin levels, and/or homocysteine). Essential fatty acid levels, methylation pathway abnormalities, and organic acid metabolites help determine adequacy of dietary and nutrient intakes. Markers of detoxification (glucuronidation and sulfation, cytochrome P450 enzyme heterogeneity) can determine functional capacity for molecular biotransformation. Neurotransmitters and their metabolites (vanilmandelate, homo vanillate, 5-hydroxyindoleacetate, quinolinate) and hormone cascades (gonadal and adrenal) have obvious utility in exploring messenger molecule balance. CT scans, MRIs, or plain x-rays extend our view of the patient's structural dysfunctions. The use of

bone scans, DEXA scans, or bone resorption markers[303, 304] can be useful in further exploring the web-like interactions of the matrix. Newer, useful technologies such as functional MRIs, SPECT or PET scans offer more comprehensive assessment of metabolic function within organ systems. It is the process of completing a comprehensive history and physical and then charting these findings on the matrix that best directs the choice of laboratory work and successful treatment.

A completed Matrix form facilitates the review of common pathways, mechanisms, and mediators of disease, and helps clinicians select points of leverage for treatment strategies. However, even with the matrix as an aid to synthesizing and prioritizing information, it can be very useful to consider the impact of each variable at five different levels:

1. Whole body (the "macro" level)
2. Organ system
3. Metabolic or cellular
4. Subcellular/mitochondrial
5. Subcellular/gene expression

Therapies should be chosen for their potential impact on the most central imbalances of the particular patient. Evaluating interventions that are available at each of the five levels can help to identify a reasonably comprehensive set of options from which to choose. The following lists incorporate only a few examples of various types of interventions within these five different levels.

1. **Whole body interventions:** Because the human organism is a complex adaptive system, with countless points of access, interventions at one level will affect points of activity in other areas as well. For example, improving the patient's sleep will beneficially influence the immune response, melatonin levels, T cell lymphocyte levels, and will help to decrease oxidative stress. Exercise reduces stress, improves insulin sensitivity, and improves detoxification. Reducing stress (and/or improving stress management) can reduce cortisol levels, improve sleep, improve emotional well being, and reduce the risk of heart disease. Changing the diet can have myriad effects on health, from reducing inflammation to reversing coronary artery disease.
2. **Organ system interventions:** These interventions are used more frequently in the acute presentation of illness. Examples include splinting; draining lesions; repairing lacerations; reducing fractures, pneumothoraxes, hernias or obstructions; or removing a stone to re-establish whole organ function. There are many interventions that improve organ function. For example, bronchodilators improve air exchange, thereby decreasing hypoxia, reducing oxidative stress, and improving metabolic function and oxygenation in a patient with reactive airway disease.

3. **Metabolic or cellular interventions:** Cellular health can be addressed by insuring the adequacy of macronutrients, essential amino acids, vitamins, and cofactor minerals in the diet (or, if necessary, from supplementation). An individual's metabolic enzyme polymorphisms can profoundly affect his or her nutrient requirements. For example, adding conjugated linoleic acid (CLA) to the diet can alter the PPAR system, affect body weight, and modulate the inflammatory response.[305, 306, 307] However, in a person who is diabetic or insulin resistant, adding CLA may induce hyperproinsulinemia, which is detrimental.[308, 309] Altering the types and proportions of carbohydrates in the diet may increase insulin sensitivity, reduce insulin secretion, and fundamentally alter metabolism in the insulin-resistant patient. Supporting liver detoxification pathways with supplemental glycine and N-acetylcysteine improves the endogenous production of adequate glutathione, an essential antioxidant in the central nervous system and GI tract.

4. **Subcellular/mitochondrial interventions:** There are many examples of mitochondrial nutrient support interventions.[310, 311] Inadequate iron intake causes oxidants to leak from mitochondria, damaging mitochondrial function and mitochondrial DNA. Making sure there is sufficient iron helps alleviate this problem. Inadequate zinc intake (found in >10% of the U.S. population) causes oxidation and DNA damage in human cells.[312] Insuring the adequacy of antioxidants and cofactors for the at-risk individual must be considered in each part of the matrix. Carnitine, for example, is required as a carrier for the transport of fatty acids from the cytosol into the mitochondria, improving the efficiency of beta oxidation of fatty acids and resultant ATP production. In patients who have had significant weight, carnitine undernutrition can result in fatty acids undergoing omega oxidation, a far less efficient form of metabolism.[313] Patients with low carnitine may also respond to riboflavin supplementation.[314]

5. **Subcellular/gene expression interventions:** Many compounds interact at the gene level to alter cellular response, thereby affecting health and healing. Any intervention that alters NFκB entering the nucleus, binding to DNA, and activating genes that encode inflammatory modulators such as IL-6 (and thus CRP), cyclooxygenase 2, IL-1, lipoxygenase, inducible nitric oxide synthase, TNF-α, or a number of adhesion molecules will impact many disease conditions.[315, 316] There are many ways to alter the environmental triggers for NFκB, including lowering oxidative stress, altering emotional stress, and consuming adequate phytonutrients, antioxidants, alpha-lipoic acid, EPA, DHA, and GLA.[317] Adequate vitamin A allows the appropriate interaction of vitamin A-retinoic acid with over 370 genes.[318] Vitamin D in its most active form intercalates with a retinol protein and the DNA exon and modulates many aspects of metabolism including cell division in both healthy and cancerous breast, colon, prostate, and skin tissue.[319] Vitamin D has key roles in controlling inflammation, calcium homeostasis, bone metabolism, cardiovascular and endocrine physiology, and healing.[320]

Experience using this model, along with improved pattern-recognition skills, will often lessen the need for extensive laboratory assessments. There will always be, however, certain clinical conundrums that simply cannot be assessed without objective data and, for most patients, there may be an irreducible minimum of laboratory assessments required to accumulate information. For example, in the clinical workup of attention spectrum disorders in children, heavy metal exposure and toxicity may play an important role. Heavy metal body burden cannot be sensibly assessed without

laboratory studies. Another example is in the context of the progressive, ongoing workup. When clinical acumen and educated steps in both assessments and therapeutic trials do not yield expected improvement, lab testing often provides rewarding information when focused on the unexpected outcomes in the progressive workup. This is frequently the context for focused genomic testing. In most initial workups, lab and imaging technologies can be reserved for those complex cases where the initial interventions prove insufficient to the task of functional explanation.

Even using the functional medicine model that has been reviewed here, no single practitioner—and no single discipline—can cover all the viable therapeutic options. Interventions will differ by training, licensure, specialty focus, and even by beliefs and ethnic heritage. However, all healthcare disciplines (and all medical specialties) can—to the degree allowed by their training and licensure—use a functional medicine approach, including integrating the matrix as a basic template for organizing and coupling knowledge and data. So, functional medicine can provide a common language and a unified model to facilitate integrated care. Regardless of what discipline the primary care provider has been trained in, developing a network of capable, collaborative clinicians with whom to co-manage challenging patients and to whom referrals can be made for therapies outside the primary clinician's own expertise will enrich patient care and strengthen the clinician-patient relationship.

Part II: The Healing Partnership— A Synthesis of the Art and Science of Medical Practice

We form partnerships to achieve an objective. For example, a business partnership forms to engage in commercial transactions for financial gain; a marriage partnership forms to build a caring, supportive home-centered environment. A *healing partnership* forms to heal the patient through the integrated application of both the art of medicine (insight driven) and the science of medicine (evidence driven). An effective partnership requires that trust and rapport be established. Patients must feel comfortable telling their stories and revealing intimate information and significant events.

The characteristics of a *therapeutic encounter* are fundamentally different from a *healing partnership*, and each emerges from specific emphases in training. In the therapeutic encounter, the relationship forms to assess and treat a medical problem using (usually) an organ system structure, a differential diagnosis process, and a treatment toolbox focused on pharmacology and medical procedures. The therapeutic encounter pares down the information flow between physician and patient to the minimum needed to identify the organ system domain of most probable dysfunction, followed by a sorting system search (the *differential diagnosis heuristic*). The purpose of this relationship is to arrive at the most probable diagnosis as quickly as possible and select an intervention based on probable efficacy. The relationship is a left brain-guided conversation controlled by the clinician, steeped in Bayesian statistics (EBM), and characterized by algorithmic processing and statistical thinking.[321, 322]

The functional medicine *healing partnership* forms with a related but broader purpose: to help the patient heal by identifying the underlying mechanisms and influences that initiated and continue to mediate the patient's illness(es). This type of relationship emphasizes a shared responsibility for both identifying the causes of the patient's condition and achieving insight about enduring solutions. The healing partnership is critical to the delivery of *personalized, systems medicine*, and to manage the uncertainty (choices

under risk, inherent in clinical practice. Here, in the healing partnership, we find the appropriate utilization and integration of left-brain and right-brain functions.

Germane to this discussion, Dr. Jerome Groopman—quoted previously in Chapter 4—states:

> So a thinking doctor returns to language: "Tell me the story again as if I'd never heard it—what you felt, how it happened, when it happened."[323]

In language, we have the fullest expression of the integration of left- and right-brain function. Language is so complex that the brain has to process it in different ways simultaneously—both denotatively and connotatively. For complexity and nuance to emerge in language, we need the left brain to see the trees, the right brain to help us see and understand the forest.[324, 325]

To grasp the profound importance of the *healing partnership* to the creation of a system of medicine adequate to the demands of the 21st century, we need to briefly address the nature of healing and its role in the therapeutic relationship. We have noted an emerging body of research in this area.[326, 327, 328] As Louise Acheson, MD, MS, Associate Editor for the *Annals of Family Practice*, articulated recently in that journal :

> It is challenging to research this ineffable process called healing.... Hsu and colleagues asked focus groups of nurses, physicians, medical assistants, and randomly selected patients to define healing and describe what facilitates or impedes it.[329] The groups arrived at surprisingly convergent definitions: "Healing is a dynamic process of recovering from a trauma or illness by working toward realistic goals, restoring function, and regaining a personal sense of balance and peace." They heard from diverse participants that "healing is a journey" and "relationships are essential to healing."

In the 20th century, contemporary medicine, traditionally considered a healing profession, evolved away from the role of *healer of the sick* to that of *curing disease through modern science.* Research into this transition reveals that healing was/is associated with themes of wholeness, narrative, and spirituality. Professionals and patients alike report healing as an intensely personal, subjective experience involving a reconciliation of meaning for an individual and a perception of wholeness. The biomedical model as currently configured no longer encompasses these traditional characteristics for practitioners. Healing in a holistic sense has faded from medical attention and is rarely discussed in biomedical research reports. Contemporary medicine considers the wholeness of healing to be beyond its orthodoxy—the domain of the nonscientific and nonmedical.[331]

Research into the role of healing in the medical environment has recently generated some thoughtful and robust investigations. John Scott and his co-investigators' research into the healing relationship found very similar descriptions to those of Hsu's group, mentioned above. The participants in the study[332] articulated aspects of the healing partnership as:

1. Valuing and creating a nonjudgmental emotional bond
2. Appreciating power and consciously managing clinician power in ways that would most benefit the patient
3. Abiding and displaying a commitment to caring for patients over time

Three relational outcomes result from these processes: trust, hope, and a sense of being known. Clinician competencies that facilitate these processes are self-confidence, emotional self-management, mindfulness, and knowledge.[313] In this rich soil, the healing partnership flourishes.

The starting point for creating a healing partnership is the patient's experience: *People, not diseases, can heal.* The integration of brain science research discussed in Chapter 4—to frame and apply right- and left-brain functions to create a *mindful, insightful* context—enhances the healing partnership during the therapeutic encounter. Mindful integration of brain function is at the heart of a healing partnership. Some of the basic steps for establishing a healing partnership include:

1. Allow patients to express, without interruption,[xm] their story about why they have come to see you. (This is an elaboration of the Chief Complaint and Present Illness.) The manner in which the patient frames the initial complaints often presages later insight into the root causes. Any interruption in this early stage of narrative moves the patient back into left-brain processing and away from insight.[314]
2. After focusing on the main complaint, encourage the patient's narrative regarding their present illness(es). Clarifications can be elicited by further open-ended questioning (e.g., "tell me more about that"; "what else do you think might be going on?"). During this portion of the interview, there is a switching back and forth between right- and left-brain functions.
   - During this conversation, signs and symptoms of the present illness are distributed by the practitioner into the Functional Medicine Matrix Model form, according to the functional medicine heuristic sorting system described in Chapter 4.
   - The parsing is determined by an assessment of probable underlying causes—based on the robust research evidence base about common underlying mechanisms of disease—and ongoing mediators of the disease.
3. Next, convey to the patient in the simplest terms possible that to achieve lasting solutions to the problem(s) for which he/she has come seeking help, a few fundamental questions must be asked and answered in order to understand the problem in the context of the patient's personal life. This framing of the interview process moves the endeavor from a left-brain compilation to a narrative that encourages insight—based on complex pattern recognition—about the root causes of the problem.
4. Explaining the structure of the next step helps the patient participate in a journey of exploration about their illness—and their search for health. At this stage, partial control is handed over to the patient with the statement: *"Without your help, we cannot understand your medical problem in the depth and breadth you deserve."* Leo Galland, MD originally articulated the structure for the patient's part of the investigation in his antecedents/triggers/mediators schema (ATM model).[315] (An excerpt from his outstanding chapter on this topic in the *Textbook of Functional Medicine* is included in the Appendix.)

[xm] Research focused on the therapeutic encounter has repeatedly found that clinicians interrupt the patient's flow of conversation within the first 18 seconds or less, often denying the patient an opportunity to finish. (Beckman DB, et al. The effect of physician behavior on the collection of data. Ann Intern Med. 1984;101:692-96.)

a) For determining **antecedent conditions**, the following questions are very useful:

- When was the present problem not a problem? When were you free of this problem?
- What were the circumstances surrounding the appearance of the problem?
- Have similar problems appeared in family members?

b) For **triggers**, the following question is critical:

- What conditions, activities, or events seemed to initiate the problem? (Microbes and stressful personal events are examples, but illustrate quite different categories of triggers. Triggers by themselves are usually insufficient for disease formation, so triggers must be viewed within the context of the antecedent conditions.)

c) **Mediators** of the problem are influences that help perpetuate it.

- There can be specific mediators of disease in the patient's activities, lifestyle, and environment. Many diverse factors can affect the host's response to stressors.
- Any of the core clinical imbalances discussed above and shown on the Functional Medicine Matrix Model, can transform what might have been a temporary change in homeostasis into a chronic allostatic condition.

It helps at this juncture to emphasize again that the following issues are elemental in forming a healing partnership:

- Only the patient can inform the partnership about the conditions that provided the soil from which the problem(s) under examination emerge(s). The patient literally owns the keys to the joint deliberation that can provide insight about the process of achieving a healing outcome.
- The professional brings experience, wisdom, tools, and techniques that can be applied to the journey of healing. The professional also works to create the context for a healing insight to emerge.
- The patient's information, input, mindful pursuit of insight, and engagement become "the horse before the cart." The cart carries the clinician—the person who guides the journey using evidence, experience, and judgment, and who contributes the potential for expert insight.

The crux of the healing partnership is an equal investment of focus by both clinician and patient. They work together to identify the right places to apply leverage for change. Patients must commit to engage both their left-brain skills and their right-brain function to inform and guide the exploration to the next steps in assessment, therapy, understanding, and insight. Clinicians must also engage both the left-brain computational skills and the right-brain pattern-recognition functions that, when used together, can generate insight about the patient's story.

Two patient case studies (presented below) provide a glimpse into a functional medicine practice and the healing partnership that is necessary for success. The Appendix contains a form developed by IFM faculty for enhancing the pattern-recognition process in ulcerative colitis.

Patient #1: Kikuchi syndrome in an 18 year old female—insight from the healing partnership

Lila was an 18-year-old female transitioning from high school to college, who during the intervening summer experienced rapid onset of unexplained fever, profound fatigue, and lymphadenitis, especially pronounced in the cervical region. Her extended family included physicians, one who lived locally and led the initial investigation. The differential included lymphoma; because of the seriousness of this possible diagnosis, a biopsy of the enlarged cervical lymph nodes was completed expeditiously. Fortunately, the biopsy was more consistent with Kikuchi syndrome than lymphoma. The pathology of Kikuchi is a histocytic necrotizing lymphadenitis. Her ANA was positive at 1:320, speckled. Kikuchi syndrome is presumed to be an immune response of T cells and histiocytes to an infectious agent, probably viral. At this point, I was asked to consult with the patient and her parents.

The patient was articulate, intelligent (she had been accepted to Harvard), and appeared recovered from the acute phase of her illness. Her father and mother were both present during the consultation. Lila was asked to narrate her story. During the telling of her story, I sorted her symptoms and signs using the FM Heuristic (Chapter 4) and the Functional Medicine Matrix Model (discussed above). At the end of recounting of her story, I explained to her and her parents the functional medicine sorting system, postulating that what we now knew from the history, lab results, and the biopsy was that Lila's immune system had probably been activated by a triggering agent (e.g., microbe, toxicant). I explained that our job now required forming a partnership, using Lila's and her parents' experiences through this episode of illness and my experience with immune-mediated illnesses to build a hypothetical story together.

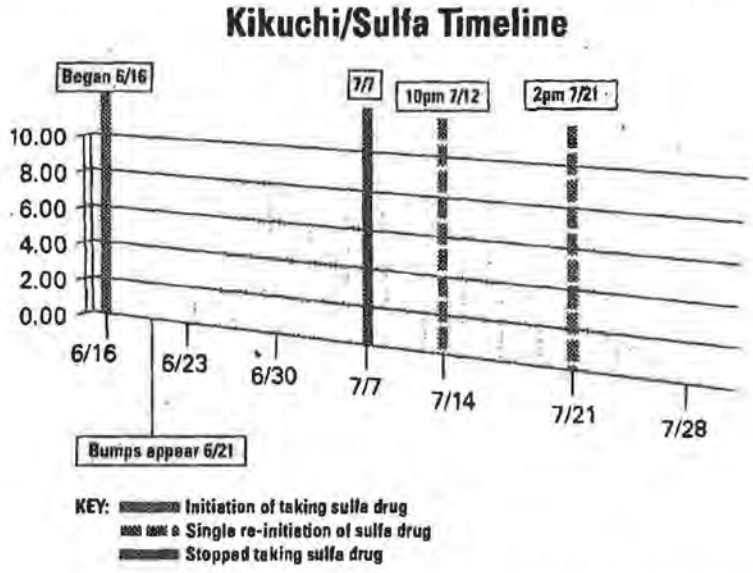
I further explained that we would need to consider the conditions in Lila's family and "habits of living" history that could be antecedent to her illness. I explained that we would then move to the possible triggers in her recent past that might be causal or correlative in the acute expression of her illness. I explained that once an acceptable model emerged from our joint inquiry into the antecedents and triggers of her present illness, we would evaluate the possible probes that might elicit further information or generate treatment plans. They agreed to work together with me using this partnering model.

They were not aware of any exceptional family history of autoimmune or other immune dys-regulatory illnesses. The family's lifestyle, including eating and exercise habits, was laudable. We next addressed the issues of triggers. We knew from reading research sources on Kikuchi syndrome that the most common cause of the lymphadenitis associated with the syndrome was a microbe trigger. The parents were hopeful that we could perform lab analyses for a host of potential viral agents. Lila interrupted her parents at this point to advocate for quite a different possible cause.

Lila recounted that she had been seen in the regional dermatologic referral center for her worsening *acne vulgaris*. The treatment recommended by the consulting dermatologist was a sulfa-containing antibiotic. Before coming for consultation in my clinic, Lila had posited to her dermatologist and her primary care physician that her lymphadenitis was an adverse drug reaction. She and her parents had been told that the severity of her illness, if caused by a drug reaction, would necessarily be accompanied by a rash; she, however, was absent a rash. She had been advised to continue her antibiotic. Her parents retreated from this inquiry in the face of the authoritative disclaimer by both the specialist and the family doctor.

However, Lila did not retreat from her insight. We discussed her intuition (insight) and her reasoning. On the basis of her hypothesis, we jointly finalized a plan that included abstinence from her antibiotic. I advised against a planned back-packing trip to Mexico because of possible toxicant exposures in that environment that might confound her clinical story. We chose to call this a therapeutic probe with my added advice regarding follow-up. (We planned a low allergy diet and detoxification program IF the simple step of removing the triggering agent proved to be an insufficient intervention.)

That evening, I received an email from Lila with the following graph of her illness:



Outcome: Lila has been asymptomatic following continued abstinence from the sulfa-containing antibiotic. She has started her first semester at Harvard. The student health center physician became very interested in her story and has provided regular follow up, including lab. Her ANA titer has slowly returned to normal. No further interventions have been required. She has sought non-pharmacologic treatment interventions for her acne.

Patient #2: Ulcerative Colitis in a 45 year old female—providing a context for insight

The next case illustrates the use of this same model: the pursuit of an antecedent and/or initial trigger for illness (these categories often overlap considerably)—that is, we looked for causes underneath the surface explanations for her condition. This 45-year-old female presented at my office for IBS and diverticulitis with a recent history of hemicolectomy for infectious colitis. The patient's primary residual postsurgical complaints were diffuse abdominal pain and loose stooling alternating with constipation. The review of her present illness revealed a history since her mid-twenties of "gut problems" (her words), including intermittent loose stools with alternating constipation. She had also over the years become intolerant of a plethora of foods. As a result, she had received thorough work-ups for food allergies and intolerances and was trying to follow a rather patchwork diet plan in response to these previous lab evaluations. She had received imaging and endoscopic procedures. However, she had not had follow-up colonoscopy since her surgery. We discussed the need to do follow-up endoscopy to evaluate her present symptoms (to rule out possible post-surgical adhesions complicating stool passage).

The conversation soon shifted into the ATM (antecedents, triggers, and mediators) portion of the investigation. After describing the joint responsibilities for a deeper understanding (insight) regarding her GI maladies, we moved to the questions regarding antecedents for her condition. She denied any family history of similar GI illnesses in her siblings. I then asked the question: *"When was the present problem not a problem? That is, when were you free of the problem and what were the circumstances of the problem's first appearance?"*

At this point, our conversation stopped. She looked a bit flummoxed and asked to consider the question further and more fully answer it when she next returned. At her next appointment, she returned to the question, stating that she wanted to share an experience that preceded her first episode of GI irritability. She said that she had not shared this story with any physician before in the context of the clinical workups for her GI problems. She then told the following story:

> I left home at an early age to escape my father. He sexually abused me and my sisters. There did not seem to be any way to stop him; my mother seemed powerless, even when she walked into an abusive episode. In desperation, I left my sisters and my family, married and moved away.
>
> My mother called me one afternoon, years after my leaving home. By that time I was a mother myself, having married and started my own family. My mother was quite upset and related that one of my sisters had arrived at her door, confronting her with the accusation of my father's sexual abuse of her in childhood and the lack of protection by our mother. My mother was adamant in her denial of knowledge of such wrongdoing by my father (my father had died in the intervening years since my leaving home).
>
> I was silent for a moment on the phone with my mother. I then made a choice to placate my mother; I responded to her distress with a lie: "Mother, you know how my sister is; she is so hysterical."

> My response seemed to settle my mother down. However, now that you have asked, this was the beginning of my gut problems. I stuffed that lie about our childhood with our father deep down into my gut and my gut has not been normal since.

Outcome: My patient's therapy for her GI problems has been guided by both this insight regarding the origins of her illness as well as by my professional expertise in the area of both mind-body connections and GI physiology. Her therapeutic interventions focused on the 4R functional medicine approach to GI dysfunctions[116] and EMDR psychotherapeutic modalities developed for PTSD[117] (an approach that has emerged from work with returning GIs from the Gulf War and the Afghanistan and Iran conflicts). She now reports no further problems referable to her GI tract.

Our healing partnership helped elicit the insights that focused our attention on a fundamental issue that was critical to her healing. Without the supportive, mindful context that encouraged her insight to emerge, we would not have had the comprehensive patient story that was necessary for resolution of her problems. In this journey together, both left-brain computation (clinical and scientific evidence about the importance of the 4R GI dysfunction program and EMDR therapy in the context of PTSD) and right-brain functionality (a context for insight) were necessary.

As described in Chapter 4, insight researchers call this "aha" experience the *moment of categorical insight.* The epiphany registers as a new pattern of neural activity in the prefrontal cortex. The brain cells have been altered by the breakthrough. An insight is a restructuring of information—it's seeing something in a completely new way. Once that restructuring occurs, you never go back."[118]

Summary

At The Institute for Functional Medicine (IFM) we believe that functional medicine exemplifies a systems-oriented, personalized medicine that recognizes the common underlying mechanisms of complex and chronic diseases that cut across multiple organ systems to shape a patient's trajectory toward health or disease. IFM's model of comprehensive care and primary prevention for complex, chronic illnesses is grounded in both science (the Functional Medicine Matrix Model™; evidence about common underlying mechanisms and pathways of disease; evidence about effective approaches to the environmental and lifestyle sources of disease) and art (the *healing partnership* and the search for insight in the therapeutic encounter). We have shown how this approach offers both a conceptual model and pragmatic tools that help to integrate the best of emerging models in both conventional and integrative medicine. When practiced with an explicit emphasis on the importance of pattern-recognition and heuristic competencies inherent to right-brain function, a healing partnership can flourish, insight can be achieved, and a broad array of assessment and therapeutic tools can be utilized. We can produce a *mindful* medical practice paradigm shift that can encompass the uniqueness of each person, deriving probabilities that are clinically meaningful.

As articulated in Gerd Gigerenzer's thoughtful book, *Rationality for Mortals: How People Cope with Uncertainty,* heuristic processing (right brain) and statistical thinking (left brain) are "complementary mental tools, not mutually exclusive strategies; our minds need both."[10] Through this uniting of competencies, we can incorporate the strengths of both science and art to craft an effective, personalized, and integrative approach to patient care. Without both elements steadily at work, we will find it exceptionally difficult to address successfully the epidemic of chronic disease that is the challenge of 21st century medicine.

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