What Causes Rheumatoid Arthritis?

Can Early Life Events Affect Risk?

By Veronique Mead, MD, MA   February 3, 2017

Here’s the link for this post, which contains the citations and full references and updates to the main text.

What causes rheumatoid arthritis? Kelly Young, founder of an organization dedicated to improving the lives of people with rheumatoid disease, blogger at Rheumatoid Arthritis Warrior (RAW), and designator of February 2nd as Rheumatoid Awareness Day, ponders this question on a regular basis. She introduces evidence that environmental factors and epigenetics provide the missing link. She wonders which environmental trigger may affect risk that occurs long before diagnosis. This is because, as in type 1 diabetes, disease activity and antibodies can precede the onset of RA/RD for years.

Like so many other autoimmune diseases, genes affect risk for rheumatoid arthritis (RA) but are not actually the cause. It is increasingly understood that what causes rheumatoid arthritis is the interaction between genes and the environment.

If you have a chronic illness other than RA stay tuned because similar events contribute to risk for autoimmune diseases and other chronic illnesses as well (Meda p. 234).

If you have a different autoimmune disease or other chronic illness keep reading

Today I look at how life events alter genes and related research in rheumatoid arthritis as I continue my explorations: "Do chronic illnesses arise from an intelligent process gone awry rather than from random or genetic errors?"

Did These RAW Readers' Early Life Events Affect Risk for Rheumatoid Disease (RD)?

Readers on Kelly's blog have shared stories of how their rheumatoid diseases started. Some refer to events in their early lives as part of their onset stories. Kate had polio in her first year of life. Julie was so sick after she was born that her doctors didn't think she'd live through the night. Brenda was born with a birth defect that left her deaf and with neck and back problems. Another reader has a form of autoimmune arthritis called ankylosing spondylitis and was born 3 1/2 weeks premature.

Researchers are just beginning to look at events that happen during pregnancy, birth and infancy as possible risk factors for RD. No such studies existed when I first started looking into the research 10 to 15 years ago. Searching for articles in preparation for today's post has revealed a whole new world of information that has not yet made it into the trenches of everyday clinics and medical care.

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What we're learning is pretty big news.

I. Early Experiences Alter Genes

In part 2 of the series I describe research studies showing that a woman's experiences during pregnancy, birth and in the first few years of her child's life affect his or her risk of developing asthma. One way it does so is by interfering with her natural ability to bond with her child.

Michael Meaney, the behavioural epigeneticist and neurobiologist at McGill University I mentioned in part 3, found that a mother rats' behaviors alter her pup's genes in the first week of life. He showed that nurturing behaviors alter genes through the process of epigenetics. In other words, nurture (behavior) influences nature (genes). More on epigenetics in a moment.

Psychologist Tony Madrid's work with mothers of asthmatic kids found that a mother's nurturing behaviors are shaped by her experiences during pregnancy, birth and in her child's early life. He discovered that risk for asthma wasn't about will power or "choice." It was often about what had happened to mothers. Even more eye-opening was the fact that helping women heal from difficult experiences that had interrupted their abilities to bond also often enabled their kids' recover from asthma.

Could similar approaches be helpful in understanding, preventing, reducing or even curing symptoms rheumatoid arthritis?

Epigenetics 1.0

Epigenetics refers to small molecules that attach to the surface of genes and shape their activities without changing the genes themselves. This is part of a natural process in which genes are instructed on what to make and how to function according to the circumstances in their environments. Genes make enzymes for digestion when we eat, insulin to absorb the sugars afterwards, and cortisol when we are stressed, for example. These and other functions are guided by epigenetic marks on our genes that switch them on or off or somewhere in between.

Epigenetic processes also guide development in the womb. They instruct that first single cell to divide and grow into heart cells or brain cells, blood cells or bone cells. They influence which cells grow into livers, joints and lungs ((Here is a great 1992 article in Discover magazine about this process of early development, before the discovery that these changes were guided by epigenetics)).

Life experiences influence our genes through epigenetics. And we are particularly sensitive to events occurring during periods of intense growth and development, such as occurs during pregnancy, birth and in early life when we, along with our brains, nervous systems and other organ systems, are coming into being.

Epigenetics 2.0

Michael Meaney and colleagues have found that, just like rat pups', human genes are altered by prenatal events. Adverse experiences during pregnancy are associated with epigenetic changes in cord blood (Turecki).
Prenatal stress alters genes in babies and epigenetic changes are found in cord blood.

The effects of prenatal stress can influence very specific cell and tissue types as well as the HPA based stress response (Turecki).

What this means is that life experiences can have a very refined impact on particular tissues or cells. This could be how one person who experiences difficult events early in life develops RA while another develops ankylosing spondylitis and a third gets type 1 diabetes or multiple sclerosis. Or, in my case, chronic fatigue and asthma.

They've also found that epigenetic changes add up. They are influenced by the amount of exposures to adverse events that happen over time, including in childhood.

Michael Meaney set out to find out whether maternal bonding in humans had an impact on genes through epigenetics as it did in rat pups.

I set out to find out whether events in early life were associated with risk for rheumatoid disease as they are in type 1 diabetes and asthma.

II. A Few Facts About Rheumatoid Arthritis

Rheumatoid arthritis as an autoimmune disease most well-known for causing pain, inflammation and deformity in joints. It is now understood to be a system-wide disease that affects many organ systems including the lungs, heart, eyes and other tissues. Joints are not always involved and are just one of many potential systems affected. As such, RA is increasingly referred to as rheumatoid disease. Because RA is the more familiar name I use both terms interchangeably.

Very loosely, there are two general types of autoimmune rheumatoid arthritis.

Juvenile Idiopathic Arthritis (JIA)

Juvenile idiopathic arthritis (JIA) (formerly referred to as juvenile rheumatoid arthritis (JRA) in the U.S. and juvenile chronic arthritis (JCA) in Europe) begins in childhood, often in the first 1 to 3 years of life although age of onset varies depending on the kind. JIA is diagnosed before the age of 16. It has many symptoms in common with adult onset RA/RD but comes in multiple different forms instead of one, can affect growth and development, and may remit with time (Huang, 2012). Antibodies are less common in JIA than in RA/RD.

Rheumatoid Disease

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Onset of RA/RD begins around puberty although highest rates of onset are in the 40s ad 50s in women and slightly later in men (wiki). There may be a family history of RA and it is much more common than JIA. Women are affected more than men in RA and in most types of JIA as well. Not everyone with RD tests positive for the antibodies we are currently aware of.

**Cause Unknown**

As with other autoimmune diseases including type 1 diabetes, what causes rheumatoid arthritis remains unknown. Smoking is the one well recognized risk factor in whites (wiki) but appears to require 20 years or more of accumulated exposure to influence onset of the disease (Klareskog, 2004, full text).

### III. Looking From Another Angle

**Risk for Rheumatoid Arthritis is < 50% Genetic**

- Risk for RA/RD is less than 50% genetic. If one identical twin develops RA/RD, for example, the co-twin will develop the disease 15%-20% of the time (wiki). In some studies none of the co-twins developed RA/RD, suggesting that genes actually play a very minor role in risk (SVENDSON 2002.)
- Risk is 3 to 5 times higher when a first degree relative (parent or sibling) has RA/RD (Holers, 2014).

The fact that genes are responsible for less than half of the "cause" of rheumatoid arthritis means that other risk factors exist. These other factors are not genetic. They are environmental.

Non-genetic factors may be preventable.

It also means that even when there is a family history or genetic risk for the development of RA/RD it is far from predetermined that you will ever develop the disease.

Typical environmental factors include elements such as diet, exercise and other lifestyle habits such as smoking; infections, vaccines, vitamins and hormones, medications and life experiences, among others.

**Antibody Patterns in RA/RD Suggest Risk in Early Life**

Not everyone who develops rheumatoid disease tests positive for antibodies but we are still in the early stages of knowledge about what to look for antibody patterns in RA/RD.

- antibodies typically precede onset of symptoms by 3 to 5 years (Holers, 2014) and sometimes by 10 years or more (Edwards, 2006). This is sometimes referred to as a latency period.
- antibody levels fluctuate in the early stages and can increase, decrease and resolve completely
- almost 50% of first degree relatives in one study were found to have one RA related antibody; the only family member to develop RA/RD had 4 different types of antibodies
- greater risk for RA/RD is associated with more types of antibodies (5 types of antibodies on average in contrast to 1 in family members without RA/RD) (Barra, 2013 abstract relatives)
Because RA/RD is influenced by nongenetic factors and because numbers and types of antibodies fluctuate and can appear so long before the onset of symptoms, researchers have begun to search for risk factors earlier in life (Colebatch, 2011; Edwards, 2010; Carlens, 2009; Huang?).

It has become clear that immunological and inflammatory changes begin many years before the onset of joint pain and swelling. The autoantibodies rheumatoid factor (RF) and anti-cyclic citrullinated peptides (anti-CCP) and a raised C-reactive protein (CRP) are all detectable in serum years before symptoms begin.

There is now a large body of evidence suggesting that early life events can lead to disease in later life (Edwards, 2010, p1).

The HPA Axis is Influenced in Early Life - is RA too?

RA//RD researchers are also interested in the fact that the nervous system, including the hypothalamic-pituitary-adrenal axis (HPA) which affects the symptoms of RA, is also influenced during early development in the womb.

Like type 1 diabetes researcher Dr. Gisela Dahlquist, Dr. Lisa Mandl and others are increasingly referencing the long-term studies showing that prenatal stress (such as occurred during the Dutch Hunger Winter in WWII) affects birth size and adult health.

Mandl and her colleagues are among those now looking at what causes rheumatoid arthritis in early life.

The “fetal origins of adult disease” hypothesis posits that an increased risk of adult onset chronic disease can be a function of fetal environment. ... Changes in fetal nutrition or gene-environment interactions could be responsible for determining a fetus’ susceptibility to disease later in life (Mandl).

IV. What Causes Rheumatoid Arthritis?

Risk for RA/RD in Pregnancy, Birth & Infancy

A number of studies have begun looking at early risk factors for rheumatoid disease (see reviews of RA by Edwards 2010 and of JIA by Huang). Most have looked at risk factors such as birth weight, breast feeding and premature birth. As in type 1 diabetes and other chronic illness research I've seen, many studies have similar findings but there isn't 100% agreement.

**Larger at Birth.** Many studies have found that people who develop rheumatoid arthritis were larger babies than their counterparts at birth. Higher birth weights are also linked to risk in type 1 diabetes and lupus, and Sjogren's (Mandl, Jacobsson 2003; Colebatch, Edwards). Others studies have not found such an association with risk (Carlens).

**Breast Feeding.** Some studies have found people with RA/RD were breastfed less often. Risk was even lower with having been breastfed for longer periods of time (Jacobsson 2003, Colebatch). Mason also found breastfeeding to be protective in kids with JIA (1995). Other research found no link to RA or JIA (Carlens, Sweden 16yo to 29yo; Simard, 2010 Nurses study). One possible clue for the different findings was suggested by Young et al. Their study noted that breastfeeding reduces risk in children with JIA who were antibody positive for rheumatoid factor AND also had a particular genetic risk.
Timing of Birth (premature vs late). Premature birth has not been found to be a risk factor to date Colebatch; SIMARD, 2010 Nurses. Being born 2 weeks after one's due date, however, may affect risk Carlen.

Cesarean Birth. Very few studies have looked at the role of birth complications and events. One study found a statistically borderline increase in risk for RA with cesarean birth. This study compared a group of individuals with RA with controls and ranged in age from 16 to 29. Both had birth data in a Swedish registry that tracks events and other information during pregnancy and birth. Given that RA most commonly begins at later ages their data are only just beginning to identify associations and stronger links may emerge with time (Carlens).

Hospitalization for Infection in First Year of Life. The single factor most clearly identified with increased risk for JIA as well as RA in Carlen's study in Sweden is that of "infections leading to hospitalization during the first year of life." Carlens

How to Interpret Early Risk Factors in RA?

So what does one do on learning that early life events may contribute to what causes rheumatoid arthritis?

What if you have RA but were born small or preterm? How do you make sense of "borderline" risk for anything, such as being born cesarean? What about the fact that some studies show risk while others do not?

Ultimately, what can we do about something that happened so many years or decades in the past?

What we are seeing with these first research findings is the tip of the iceberg. When scientists explore whether early life events affect risk for rheumatoid disease, they get hints that it does. But it's not a linear, black and white, all-or-none relationship.

We're discovering that risk factors for chronic illnesses like rheumatoid arthritis, type 1 diabetes, and other autoimmune and chronic diseases such as asthma are not purely mechanical, biological or genetic.

Our health is influenced by interactions with our environments. And this includes what we and our mothers experienced during conception and pregnancy, birth and infancy.

What we're seeing is that there are complex interactions between risk factors. Some of these are understood. Few are recognized in medical practice.

Risk Factors Reflect Events and Interactions

Here are ways for making sense of what causes rheumatoid arthritis. And here's what it might mean for you.

This is based on research I've been presenting in this series of blog posts about the role of early life events [Part 1 (insights from type 1 diabetes); Part 2 (insights from asthma); Part 3 (insights from epigenetics)].

Birth Size and Prenatal Stress. Stress during pregnancy can affect the size of a baby at birth. Many women who experience prenatal stress during the middle and later parts of their pregnancies have smaller

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babies. There is some thought that larger size at birth may reflect stress in the first three months of pregnancy although it's nowhere near as clear (foadh study).

This is an example of what you find when you delve further and learn about interactions. Studies of women exposed to famine and war have shown that a baby's size at birth is not the risk factor for health problems in and of itself. *Birth size is a reflection of what a woman and her baby experience during pregnancy.* And the timing affects whether small babies are at risk for chronic illness or for just being smaller human beings throughout their lives. Birth size is also affected by events that happened during our grandmother's pregnancies with our mothers (more on all this (more on wiki about fetal programming), Hurley's Discover).

The research is showing us that our experiences affect our health. And that of future generations.

It's quite staggering when we start to put it all together. But it can also validate what we've experienced and start to give us a new way of understanding our symptoms and diseases. As I'll mention in a few paragraphs, it also offers us options for working with our symptoms.

**Stress & Bonding.** Stressful events influence the degree to which mothers are able to bond with their babies. This includes emotional as well as physical stressors. Most of these are never measured in research studies but affect a mother’s behaviors nonetheless. And maternal behaviors alter our genes.

**Bonding & Breastfeeding.** Whether a mother is able to bond with her baby influences her behaviors towards her baby and the ease with which she is able to breastfeed. It also affects how long she breastfeeds (KK). Additionally, rates of breastfeeding tend to be lower after cesareans (isik).

**Breastfeeding & Cesareans.** Cesarean sections are done for reasons ranging from life-saving and highly stressful, to avoidance of risk due to past events such as previous emergency c-sections and other issues. They are also done for convenience. A cesarean can be an intensely stressful or scary procedure for women (c/s ptsd article) as well as for their babies (think life-threatening situations). They may also be low stress. They, do however, also influence a baby's gut flora and microbiome and increase risk for respiratory infections. As mentioned above, cesareans are also linked to decreased rates and durations of breastfeeding (Isik).

**Hospitalization & Separation.** One of the influences on bonding, nurturing behaviors, and breastfeeding is a mother's experience of physical or emotional separation from her baby. She may be physically separated from her baby after birth if she or the baby is sick and needing treatment for example. She may be unable to connect emotionally if she is experiencing feelings that are too overwhelming or scary (such as from the recent loss of a parent, spouse or other child, for example). Separation may occur if her baby is hospitalized. And separation interferes with bonding.

**Infections and Separation.** Infections may be important risk factors for chronic illness such as RA. It's important to note, however, that separation associated with treatment - and the effects of separation on bonding, safety, perceptions of threat, epigenetics and the HPA axis - may be the more important risk factor RD just as it appears to be for asthma and type 1 diabetes.

**V. Explaining RAW Reader's Onset Stories**

Understanding the role of early risk factors may help explain events that happened to readers of Kelly's rheumatoid arthritis blog.
Kate's polio would have been associated with long periods of treatment, separation and stress for both her and her parents.

Julie's life-threatening illness at birth could have contributed to bonding interruptions (then and later) through multiple kinds of emotional and physical separation. It may have been associated with other risk factors such as a complicated birth, inability to breastfeed, hospitalization(s) etc.

The reader who was born prematurely ((she goes by the name "URandomnessK")) and has ankylosing spondylitis describes multiple challenging events related to her birth:

I was born ... three and a half weeks premature. I was the first child to be carried “to term” and born to my parents. My mother had experienced ten years of fertility challenges including more miscarriages than she could ever count. She begged and pleaded with G-d for ten years before being blessed with a child. I was born with no complications but soon after ... was diagnosed with asthma.

As discussed in a recent blog post (Part 2), kids develop asthma more frequently when their mothers have experienced bonding disruptions. Bonding disruptions, in turn, are linked to difficulties before and during pregnancy, birth, and in the first years of a child's life. They include the emotional distress that can follow a miscarriage, let alone so many challenges of coping with 10 years of infertility. These types of events are not usually included in research studies. The details offer a hugely relevant context for understanding the complex yet increasingly recognizable links between risk factors.

Brenda's birth defect(s) may reflect a prenatal exposure during one or more sensitive period of development. This type of "critical period" could also have been a time period associated with risk for RA/RD. I'll be writing more about these "sensitive periods," which occur when organs undergoing various stages of development are more malleable and easily shaped by their environments. I introduced the concept in The Bonding Effect.

VI. There IS Good News!

Amidst all this potentially disturbing news, remember that early life events are filled with many positives. These experiences interact with one another in positive ways to naturally heal the effects of difficult experiences. In other words, interactions work both ways.

Giving birth and having children is one of the highlights of many people's lives. Newborns elicit feelings of elation, profound love, and joy. Parents are designed to fall in love with their babies and to bond with them. When something happens that is stressful or interrupts that bond, we are designed to recover. It can be repaired and its effects healed, even months and years after birth. One example of this has been demonstrated with the use of therapy in working with mothers to heal their asthmatic kids.

Here's a list of therapies for working with difficult events in early life - whether you are an adult with RA, the parent of a child with JIA or planning a pregnancy.

It is possible to heal at least some - and perhaps many - of the effects of early life events. Even as adults.

Another example of the potential for reversibility is how RA/RD sometimes resolves in childhood or regresses when caught early (Holers). And some adults have recovered and healed their symptoms of RA/RD (see last year's blog post).
The possibilities for improving and healing are among the most important reasons I am so impassioned with this kind of research. It's also why I want to share the information.

Our chronic illnesses may not be as solid or irreversible as we think they are or have experienced so far. And many of us have a sense that certain life events have affected our risk. As a result, it can also be a huge help to better understand our chronic illnesses, our symptoms and the contexts that contributed to them. In this sense, knowing about the studies can be hugely validating. And reassuring that our illnesses are not "all in our heads."

The critical overarching theme here is that life experiences interact with genes to influence long-term health.

The epigenetic mechanisms that make them happen are now being recognized.

**Do we see epigenetic changes in rheumatoid disease?**

Yes, we do.

### VII. Epigenetics, Autoimmune Disease & RA

Epigenetic changes have been identified in a number of autoimmune diseases, including rheumatoid arthritis. These changes are specific to each disease and studies have begun to find large numbers of changes in other diseases as well including type 1 diabetes, lupus, inflammatory bowel disease, and others (Meda, Wang).

**To restate two important points:**

1. Key risk factors for autoimmune diseases such as RA/RD come from environmental factors that interact with genes.

2. Epigenetics is the means by which environmental events interact with genes to trigger the immune system and risk for autoimmune diseases

**Epigenetic Changes in RA**

In rheumatoid arthritis, one example of epigenetic changes is seen in cells called "fibroblast-like synoviocytes (FLS). These FLS cells interact with the immune cells in RA and can be distinguished from FLS cells in people who have osteoarthritis (a common joint-specific form of arthritis symptoms associated with "wear and tear" rather than an autoimmune process) and from people who are healthy.
A 2013 study found that as many as 1,859 loci that were relevant to cell movement and other cell functions ("adhesion and trafficking"), were epigenetically altered in RA compared with osteoarthritis (Viatte, p. 149).

This speaks to a large number of changes influencing gene function in RA.

For the purpose of today's post this little glimpse tells us is that there is indeed evidence of effects of environmental risk factors in RA (Holers, p6) and it will have many implications for treatment.

**VIII. A Summary of What Causes Rheumatoid Arthritis**

Here's a summary of the research findings and the major points made in today's post:

**Autoimmune Diseases**

- Autoimmune diseases require environmental events to trigger autoimmunity
- Environmental events interact with genes through the process of epigenetic changes
- Epigenetic changes have been found in many autoimmune diseases
- Environmental events capable of altering genes include life experiences.
- A common risk factors affect epigenetics and risk for autoimmune diseases

**Rheumatoid Disease**

1. Antibodies for RA/RD arise years before onset, suggesting risk in early life
2. Early risk factors for RA/RD include birth size, breastfeeding rates, hospitalization in first year
3. Risk factors for RA/RD may reflect interactions from bonding interruptions and prenatal stress
4. Bonding interruptions and prenatal stress alter epigenetics in babies
5. Epigenetic changes have been found in RA/RD and other autoimmune diseases

In the next posts of this series I will talk about the role of timing as a factor in determining risk for particular chronic illnesses. I will also be introducing surveys to learn more about the role of life events in shaping our lives and chronic illnesses. What this all is heading towards is support for new ways of working with our symptoms and gaining ground.

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REFERENCES

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2. ↑ Here is a great 1992 article in Discover magazine about this process of early development, before the discovery that these changes were guided by epigenetics


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38. ↑ she goes by the name “URandomnessK”