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Getting from the Average to the Individual When Reading Reports of Research
Paula Derry
Dec. 10, 2012

We are unique individuals. Or, we are like everyone else. Which is it? For menstrual periods and the menopausal transition, as perhaps for most things, we're a little bit of both. For me, keeping in mind that both are somehow true, and understanding the ways in which each is true, is a crucial but tricky business. Scientific findings are often reported as though they are universal truths. "The normal menstrual cycle is regular and occurs every 28 days." "Depression is more likely during the transition to menopause." However, research most typically examines groups of people, and results are most often average findings. A discrepancy between the average and the range of real experience isn't surprising.

Take, for example, a study of the transition to menopause. This was longitudinal research—that is, the same group of women was studied for many years, and the patterns of change in their menstrual cycles over time could be documented. The authors conclude that there are three stages in the transition to menopause. At first women experience, perhaps beginning in their thirties, subtle changes in menstrual flow (like periods becoming heavier or lighter) without cycle length becoming irregular. Next, periods become irregular. Finally, women skip periods in the run-up to menopause. The stages are based on what, in the authors' words, occurs "most frequently"; the average or frequent result is the basis for understanding the underlying pattern. Yet there is also a lot of variation. As reported in the article, only 39% of the women progressed in a forward manner through the three stages. Almost half seesawed back and forth. In addition, it is known that a significant minority of women report that they have gone from regular cycle lengths straight to menopause without a time of menstrual irregularity. I remember that when I first read this study I felt a certain comfort that changes in my body, like lighter periods and other changes, were predictable and fit into a pattern that other women experience. Yet, on the other hand, the findings can't be used as a blueprint for what is supposed to happen. We share experiences with others, but we're also unique individuals.

The average menstrual cycle is said to be 28 days—well, I don't know many women with a 28-day cycle, and while some women describe themselves as "regular as clockwork" other women are bewildered that anyone could think that the cycle was regular. Rates of depression have been found in many studies to increase during the menopausal transition. However, the great majority of women do not become depressed (the "relative risk" has increased, but the "absolute risk" remains low). Knowing that the rate increases might suggest to a woman that she consider this possibility, but does not

answer the question of whether she will become depressed, or, if she does, whether or not her depression is related to perimenopause or something else.

In trying to use scientific facts to understand ourselves or the world around us, the difference between the particular and the general, the predictable and the unpredictable, is important. Our individual behavior and physiology aren't random or without form, but neither are they completely predictable.

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Menopause Tales
Paula S. Derry, Ph.D.
Feb. 6, 2012

The philosopher of science Mary Midgley (1995) doesn't mince words. She tells us: "The theory of evolution is not just an inert piece of theoretical science. It is, and cannot help being, also a powerful folk-tale about human origins." Along these lines, stories about reproductive physiology are important folk-tales about what's natural for women and what their life course should be.

What are the stories about menopause? One is that living beyond menopause is a biological puzzle. The argument goes like this: Most animals reproduce up until, or close to, the end of their natural life span. This makes sense, because theoretical biology tells us that animals reproduce as much as possible to leave as many offspring as they can. Why women live beyond menopause is therefore a puzzle. One answer is that we can expect to live thirty years past menopause because technological innovations have resulted in the conquest of infectious disease, the generation of great food stores, and other advances. As recently as the turn of the century, the average woman lived 47 years. Far longer, probably, than our prehistoric forebears: prehistoric hunter-gatherers were probably old at thirty. Living many years past menopause is therefore a recent historical development. Not surprisingly, if aging women are "outliving their ovaries," menopause is associated with a variety of unpleasant experiences and health problems.

What are some facts relevant to this story? First, is living past menopause a new historical development? Well, ….No. Old age is not an invention of the twentieth century. Betsy Ross died when she was eighty-four. Classic Greek and Roman medical writers (including Hippocrates himself) and traditional Eastern medical systems all discuss menopause. In the Old Testament, Sarah laughed when God said she would bear a child even though it had "ceased to be with her after the manner of women." Might the Bible have been referring to menopause?

What about the idea that prehistoric humans died before menopause? Studies by anthropologists suggest that modern hunter-gatherers do live to old age. Therefore, perhaps our prehistoric hunter-gatherer forebears did so as well. Richard Lee (1985), for example, studied the !Kung San in Botswana. About 10% of the population were over sixty years old, and it was not unusual to find !Kung aged 70 or 80. Lancaster and King (1985) found, when twenty-four hunter-gatherer and horticulturalist groups were examined, that 53% of the women who lived to age fifteen could expect to still be alive at age 45.

If a small number of older people are found in simpler societies, is this important? Is ten percent survival so small that for all intents and purposes fifty years is the real limit on lifespan? Older people, as described by anthropologists, are not viewed by the members of their own societies as oddities. That is, if living into middle-age and beyond were an anomaly, it is unlikely that people in a society would have expectations about what role an older person should play. Older people might be viewed as curiosities. However, older people more typically have important places in their societies. At least through their fifties and sixties, they are relied on to do important things. It is relatively common in nonindustrial societies for women to experience positive changes in status

when they become middle-aged (Brown, 1985). In cultures without written legal systems or CEOs, older people often have authority over younger people. They can be decision-makers about the distribution of property, allocation of jobs, and other social behaviors. Among the !Kung, for example, older women assign younger relatives what jobs they need to do, arrange marriages, decide on kinship classifications. In cultures that don't have books or the internet, older people may be sources of stored and accumulated knowledge, like the location of a watering hole that hasn't been needed since the last drought thirty years ago (Diamond, 1996), or social and technical skills (Kaplan, et al., 2010).

If it was important to have a number of older adults as members of social groups, then perhaps old age is a genetic given, not an anomaly resulting from modern technologies. That is, if many people didn't live to midlife because of accumulated accidents of living, perhaps natural selection favored everyone having the genetic potential to live to old age. If only a few people had the genetic potential to live to old age, and they got eaten, no one would be left.

What, then, does it mean that the average life expectancy for women was 47 years at the turn of the 20th century? It does not mean that 47 was the end of the life span. The definition of life expectancy is this: The age at which half an entire original population is still alive. Life expectancy is longer now basically because far fewer babies and children are dying. (In addition, fewer women are dying in childbirth.) This decrease in child mortality raises the entire average. In cultures as disparate as hunter-gatherer groups, tribal cultures, and turn-of-the-century Europe, if a person lived through adolescence, his or her expectation of living to old age was pretty good. According to Roger Gosden (1996), for example, in 1888 Scotland a newborn female had an average life expectancy of only 46.3 years. However, if she lived until age fifteen her life expectancy was 60.6 years; if she lived until 45, it was 69.6; if she lived until 65, it was 76.9 years. In 1988, life expectancy in Scotland varied much less at different ages. It was 76.7 years at birth and remained between 77 and 82 years throughout life. We always had the potential to live to old age, but before the twentieth century fewer of us made it.

If living beyond menopause were not a biological puzzle, then what might it be? A different evolutionary story begins with the observation that menopause is a human universal, yet an oddity in nature. Humans, unlike other animals including our closest relatives, monkeys and apes, universally shut down the reproductive system decades before other body systems show advanced signs of aging (Pavelka and Fedigan, 1991). Among monkeys and apes, some individuals become reproductively inactive while others don't, and those that do are more typically very old, close to the absolute end of the life span, at an age when many body systems have declined. This suggests that menopause may somehow be an intentional part of the human body plan. Perhaps it developed because of natural selection, or perhaps older age and not younger menopause was selected for. Regardless of cause, women have a life stage that precedes old age during which they are postreproductive and relatively healthy. It is unusual for an animal to have such a life stage, but there's nothing unusual about humans having unusual life stages compared to other animals. Perhaps this was adaptive because human groups distinctively benefit from older members with social and technical skills (Kaplan et al., 2010). Perhaps older "grandmothers" aided younger women with childrearing during the distinctively long human childhood (Hawkes, O'Connell, & Burton Jones, 1997).

This latter metatheory, or story about human origins, leads to different basic assumptions and speculations. Aging is de-coupled from menopause. Midlife is a stage of productive, mature adulthood. Whether menopause causes health problems is an open question: for example, menopause would not be expected, a priori and in the absence of strong evidence, to cause cognitive decline if post-reproductive women were important, skilled members of their social groups (Kaplan et al., 2010). Perhaps this story is correct, perhaps not. I prefer it to the idea that I'm outliving my ovaries.

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My Aching Foot and the Menstrual Cycle
Sept. 17, 2012
Paula Derry, Ph.D.

About two weeks ago, I injured my foot. Like many accidents, it was stupid, quick, and avoidable. A heavy storm door was swinging shut, I somehow didn't get out of its way, and it sheared open the back of my left foot, behind the ankle. Luckily, I didn't cut an artery, the Achilles tendon, or any other tissue that would have caused a crisis or long-term problem. However, I did end up with eleven stitches and orders to stay off my feet for over a week.

If life gives you lemons, make lemonade. During my enforced inactivity, I surrounded myself with projects I had not had time for. The reverse appliqué hand sewing I had started in a class last summer but never finished. A creative writing project I had hoped to do. My long-neglected Native American flute. Yet, as the days wore on I found myself increasingly unable to do much more than stare into space, watch TV, or do a bit of sewing. It was hard to focus my attention and to concentrate, I felt an increasing paralysis of will to initiate and sustain activity. When I did walk around, using crutches to keep weight off my foot and to avoid flexing the ankle, I felt easily fatigued and vaguely ill.

I did also do some reading, and happened upon a recent re-evaluation of a book by Oliver Sacks called "Leg to Stand On." Sacks, a neurologist, had written the book in 1984 after he broke his leg in a traumatic accident. He found, to his surprise, that his injury resulted in important changes in his body image. In the early part of his recovery, his leg did not feel like part of him. Although he couldn't feel or voluntarily move the leg, and couldn't even remember moving it in the past, it could move in response to music. He later discovered that his experience was shared by other patients. In the re-evaluation, authors Stone, Perthen, and Carson suggest that Sacks' problem was functional (i.e., psychological not physical). Sacks, in response to their reevaluation, suggests that activity and sensation in the periphery—that is, arms and legs—is intrinsically involved in how the central nervous system organizes information, experience, and cognitive function. That is, the mind and entire body are interconnected.

There are many ways in which physical experiences other than injuries have broad systemic, mind/body interconnections. If we have a fever, we're not surprised if, in addition to our stomachs hurting or our heads throbbing, we feel wonky, unable to concentrate, distressed. Illness is a whole-body experience. Many years ago, I had an amniocentesis. The doctor told me I could go about my business after he finished the procedure, but a nurse said to me that many people felt they needed some rest. Indeed, after having a large needle penetrating my abdomen, which felt, irrationally but unmistakably, like an invasion of body boundary, I did feel shaken and like I needed to recupe. Even my husband, a physicist, a very nice but definitely not a touchy-feely kind of guy, felt invaded by a large needle penetrating his body to take a bone marrow sample.

So it is with uncomfortable experiences associated with the menstrual cycle. Menstrual cramps, hot flashes, menstrual migraines, are not isolated symptoms occurring in far-out or isolated body parts. If we have menstrual cramps we may be tensing our entire body, our abdomens may feel like invaded strangers rather than like parts of ourselves, the cramps may have specific meanings about who we are, our lives, or the

meaning of pain or discomfort. If I have menstrual migraines I may wonder why people don't show me more sympathy and help me, or I may want to keep my headaches secret. Not always, but often, menstrual cycle experiences, like many other experiences, are holistic, mind/body phenomena.

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Periods: A Human Oddity
Paula Derry
February 4, 2013

What does it mean to have menstrual periods? This is an intensely personal question, but it is also a scientific and a cultural one.

The menstrual cycle can of course be described in terms of a woman's personal experience of menstrual flow. It can also be described by the complex physiology of hormones climbing, pulsating, falling. However, what are some other things we know about periods?

We know that they are an oddity in nature. Most animals, aside from monkeys, apes, and us, thicken the wall inside the uterus only after an egg has been fertilized. We have periods because we routinely build a thicker wall inside the uterus, just in case it's needed, which must be eliminated if we don't become pregnant. According to Ann Voda, much of this wall is absorbed back into our bodies (the same way that if you smash your finger and get a clot under the skin, that blood is absorbed into the body then eliminated). Some of it is released to the outside world in an organized manner in what we call our period.

We know that the menstrual cycle is only one part of a larger whole. I've always liked the description of adolescent development in Barry Bogin's textbook *Patterns of Human Growth*.

To summarize the content of his book: A part of the brain called the hypothalamus changes. Then a growth spurt begins (we all remember growing taller quickly): this is unique to humans, nonhuman primates and other animals don't have a growth spurt. Then a girl begins developing secondary sexual characteristics, breast buds (the beginning of breasts) and the beginning of pubic hair. Then estrogen levels begin to rise, which leads to a particular female shape due to fat in the hips, buttocks, and thighs. The first menstrual cycle occurs some years after these other changes begin. We're not done yet. Menstrual cycles are at first irregular and girls rarely ovulate, it is a few years before girls ovulate as regularly as does an adult. In addition, the bones of the pelvis don't grow quickly during the growth spurt, and it is many years after menarche, when a girl is in her late teens, that the pelvis has finished growing.

To continue the summary: Reproductive maturity means biological, social, and psychological maturation. It means being an adult. In Bogin's words, "[b]ecoming pregnant is only a part of the business of reproduction. Maintaining the pregnancy to term and raising offspring to adulthood are equally important (p.212)." In cross-cultural research, behavioral and social events typically co-occur with adolescent physical changes. As girls visibly physically mature, and as they begin menstruating, they are invited into the world of adult women. They develop adult modes of thinking (for example with regard to Piagetian stage), interacting with men and women, sexuality. They refine practical skills needed for the tasks and occupations of a competent adult. Age of having a first child is often years after menarche, often around nineteen years of age among women from many diverse cultures. When compared with animals, this complex transitional stage of life from adolescence through adulthood is a human oddity.

Nobody knows biologically for sure why women menstruate, but cultures, including ours, typically assign meaning to menstruation. Personally, I'd say that getting

your period isn't a transition in the sense of flipping a switch on. However, in most cultures menstruation is an important marker or component with multi-layered meaning for a larger, rich life stage.

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The eternal feminine: Focused, goal-oriented, practical, and loving
Paula Derry, Ph.D.
April 30, 2012

Visiting colleges became part of our repertoire of family trips back when my daughter was a senior in high school. We visited many schools to get a sense of the range of possibilities that existed. As was typical, Vassar offered a tour of the campus for groups of prospective students and their parents, led by tour-guides who were undergraduate students. Vassar's tour had one unique feature. An original campus building, which dated to the post-civil war era, had an exceptionally wide hallway. This, we were told, was because the all-woman student body needed to be able to walk back and forth repeatedly in the halls in their wide skirts, as part of a college program in physical fitness. Vassar, founded on the idea that the education of women should equal that of men, had a program of physical culture to offset criticisms that the school was endangering women's health by educating them.

Sheila Rothman describes Vassar's history in her book "Woman's Proper Place," published by Basic Books in 1978. The common wisdom in the second half of the 19th century was that people have a limited amount of biological "vital energy." Rothman (p.24) quotes a contemporary physician: "Woman has a sum total of nervous force equivalent to a man's" but the force is "distributed over a greater multiplicity of organs…The nervous force is therefore weakened in each organ…it is more sensitive, more liable to derangement." Menstruation and pregnancy were times of special danger, when the demands on her system were greater and the possibility of physical and mental disorder increased. Menstruation was a time when women were irrational, even insane. Caution, however, was always called for, as when intellectual activity or other exertion used up nervous energy. Thus, when Vassar was founded, a program was put in place to overcome women's predisposition to illness through a structured environment and programs of physical exercise. Later, the Association of Collegiate Alumnae conducted a survey to provide research evidence as to whether female college graduates were normal.

Back in the Vassar of the present, our student tour guide wondered: "How could anyone believe anything so silly?" It's true that we no longer talk about a "vital force." Yet, broad generalizations about the nature of women and reproductive physiology continue to exist that have an air of plausibility, based today on a different scientific language, one of hormones, neurotransmitters, and other players. Not very long ago, menopause was defined as an "estrogen deficiency disease" that had a uniquely powerful effect on health. Heart disease was a disease of civilization for men and a disease of the ovaries for women. The idea that the menstrual cycle destabilizes women's minds, creating mood and intellectual changes, continues to exist.

One of my favorites is the idea that women are somehow receptive, loving, and self-denying because of their maternal role, which is somehow mediated by estrogen. Thus menopause may be said to be a time that women regain the ability to focus more on themselves, liberated from a physiological preparedness for reproduction and its needs. Pregnancy is a dreamy time when women are moody and unable to think clearly.

Sure, mothers are receptive, loving, self-denying, but they are also many other things. I love being a mother. My relationship with my daughter has been powerful, unique, and wonderful. However, I know that a mother who is lost in a dreamy

connectedness to her child or reflexively puts her child before herself can't do everything she needs to do. A mother is emotionally connected to her child but also must be an individual who perceives the child accurately, as a separate person, in terms of the child's motivation and perspective, in order to provide both a sense of connection and the mirroring needed for a child's emotional development. Further, children misbehave, make mistakes, and must be taught all kinds of things; mothers must have clear-headed, pragmatic, problem-solving skills.

Sometimes we read works by evolutionary theorists and others that presuppose prehistoric women were sort-of-like housewives, dependent upon men for food and safety. This overlooks the fact that women were the gatherers in hunter/gatherer societies, providing a significant amount of the family's food. Over the course of history, women were potters, weavers, cooks, doing all kinds of necessary work. Women with leisure to devote themselves primarily to childrearing must have historically always been a minority. Would women have survived, or would their children have survived, if they were muddle-headed when pregnant or menstruating, or ruled by their hormones rather than tasks that needed to be done?

Even rat mothers must continue to feed themselves, retrieve pups if they wander off, and engage in other instrumental tasks or their young won't survive. Being a human mother involves love, receptivity, psychological maturity, thinking skills, and practical competence, neurons as well as hormones.

Hot Flashes Are Weird
Paula Derry
Nov. 12, 2012

I have two pretty contradictory sets of opinions about hot flashes. In a previous blog (May 28, 2012) I emphasized one of them. Namely, that flashes are a mind/body phenomenon in which a woman's interpretation of her physical experiences are central to her being distressed or not, of being able to cope or not, of what an experience is and means. A woman can identify her "real" self with her thoughts or her body, or she can experience her embodied self as a totality. In my first set of attitudes, the diversity of physical experiences is part of the mix: The same term, "hot flash," is used for a wide family of experiences that range from mild to unbearable, from heat to heart palpitations, from empowerment to anxiety. However, in my second set of opinions, physical experience is front and central, and my thoughts can be summarized as follows: Hot flashes are weird.

In a conventional view, flashes are simply something that happens because of the hormonal changes surrounding menopause. They are often defined as a transient feeling of heat, sometimes accompanied by sweating or the skin turning red, that typically lasts a few minutes but can persist up to an hour. Flashes are most common in the years surrounding menopause, but can begin many years before or occur many years after the final menstrual period. One theory is that fluctuating levels of estrogen affect a part of the brain that controls heat regulation. As a result, small changes in temperature are interpreted by the brain as meaning that the body's temperature is outside the normal range; the hot flash is the body's attempt to cool the body down. Alternatively, perhaps the hormonal imbalance affects the brain or other endocrine glands in other ways, or perhaps some women are simply more sensitive to these changes.

However, the experience of flashes is complex. A woman who is overheated for other reasons may not feel like a woman having a hot flash. A flashing woman might feel like she is on fire. Or she may feel hot only in an isolated body part, like her back or earlobes. Or the feeling of heat may start in one part of the body (like her head or upper back) and travel. Some women may not realize their feeling of gentle warmth is caused by a flash until later. Further, there are experiences in addition to that of warmth. The experience might feel like anxiety rather than heat. There may be a sharp physical shock or jolt. Some women, for example, may wake up in the middle of the night with a shock of anxiety and wonder what has threatened them. Some women report other associated sensations such as a racing heart, nausea, and breathlessness. Some feel dizzy, anxious, and unable to concentrate. Others experience cognitions and feelings such as empowerment, anxiety and catastrophic thoughts.

Flashes are basically not understood. Beneath the scientific generalities, there is no specific understanding of what underlies flashes. They do clearly have something to do with estrogen: they increase in frequency in the years surrounding menopause and treatment with a hormone medication is helpful. However, while fluctuating estrogen levels are assumed to be causal, clear

evidence of this has been notably lacking. Further, flashes are found during the menopausal transition and postmenopausally, two very different hormonal situations, but are not a widespread phenomenon during premenstrual hormone fluctuations. For the minority of women with severe symptoms, there is no understanding that would lead to correction of underlying problems beyond symptomatic treatment with medications like estrogen. Why would a brain center regulating body heat be affected in some women but not others or in the same woman only sometimes? There are speculations that estrogen is needed for brain general health and proper neurotransmitter balance, or that some women are "more sensitive" to normal changes in hormone levels. It seems that additional factors must also be at play. The large cross-cultural differences in flash frequency and the large placebo effects of medications are not understood; neither is the role of stress or other psychological or situational factors.

So, I think it's weird. I think it's weird to have odd physical experiences like a sudden experience of intense heat or a sharp jolt, even though for most women the experience seems to cause no significant or permanent harm. For women who find these experiences unsettling: why wouldn't they? it's almost sensible. The idea that we're told "it's just menopause" is weird. Personally, I wish more basic research was being done about what hot flashes are. I wish that more basic research was being done to understand women who have serious problems. As an analogy to the idea that there is "normal pregnancy and childbirth" and there are "complications of pregnancy and childbirth," which discomforts are "just menopause" and which are "complications of menopause"?

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Make Friends With Hot Flashes
Paula S. Derry, Ph.D.
May 28, 2012

One important idea in a holistic approach to health is that symptoms or uncomfortable physical experiences don't exist separate and apart from the whole person. For this reason, it is important to know how a unique individual experiences that symptom or experience. Another important idea is that the whole person consists of a physical body, but also thoughts, feelings, even spirit, and she lives in a social and physical world that affects her. Holistic practitioners say "I am a body," not "I have a body."

What does this mean to a woman bothered by hot flashes? First, one good starting place for a woman is to look inside herself at her individual experience. Hot flashes are often said to be the bane of a woman's existence, creating intense discomfort, mood swings, embarrassment. However, in reality women differ. Some women are greatly bothered by flashes. Others are not. Some say flashes are power surges. For some, the flash is purely a feeling of heat; for others, it feels more like anxiety. Very distressed women may have experiences like insomnia, depression, fatigue, fogginess. It turns out that the frequency of flashes is distinct from how distressing they are. For some women but not others simple remedies like dressing in layers works. In a scientific sense, we know more than we did not long ago, but there is still no fundamental understanding of what a hot flash is, or why some women but not others experience them.

Cultivating an inner observer can be useful to identify personal experience. Mindfulness is one approach to this. For many women, thoughts are an integral part of the hot flash experience, and these thoughts might contribute to how distressing flashes are. Expecting the worst might amplify distress, as it does for other experiences like pain. One example of an expectation is: "I'm going to have hot flashes for the rest of my life." The meaning of flashes—natural, an indication of aging, a worrisome sign that something puzzling is going on in your body--might be important. Embarrassment and self-doubt in social settings are known to sometimes contribute to experiencing flashes as problems. Coping self-talk—for example, "this is a hot flash, it will pass" –might be helpful. Relaxing the body and observing a flash rather than tensing the body to resist it might make flashes less distressing. Paradoxically, distancing ourselves from bodily experience—for example, tensing the body until a flash passes, may be less effective than accepting bodily experience as our own with an attitude of observing it. Other active problem-solving might also be useful, like finding solutions to social problems. Women who talk with other women about flashes tend to find them less distressing.

Of course, other women just want to be rid of flashes. They might have very distressing, debilitating symptoms. They may simply just not want to put up with them. For some, focusing their attention on flashes might not make things better or even make things worse. Active problem-solving can work here, also. For example, flashes are often associated with triggers (stress, foods like chocolate, caffeine, etc.) that vary from woman to woman. Triggers, once identified, can be avoided. A woman can make time to take care of herself, doing something pleasurable or rejuvenating, find ways to reduce stress, or otherwise alter her lifestyle. A variety of remedies have been suggested, ranging from herbal remedies, to alternative practices and practitioners, to hormone therapies. Actively deciding that a hormone therapy is needed given her own situation might be a way a woman actively takes charge of her experience.

Hot flashes are not invaders. They are sometimes welcome, often not, but always one's own bodily experience. Through gathering information, self-observation, talking with others, or finding helpful practices and practitioners, they can be dealt with.

Medicating the Postmenopausal Vagina
Paula Derry
March 4, 2013

On February 26, 2013, the Food and Drug Administration issued a news release saying that it had approved a medication called Osphena to treat a problem called postmenopausal dyspareunia (pain during sexual intercourse associated with changes in the vagina after menopause). The medical website Medscape reported that the news release had been issued. How to read these announcements? It seems as though FDA approval should be enough to know that a medication is safe and effective. However, what are some guidelines in reading and evaluating this announcement?

First, some background: After menopause, when estrogen levels decline, tissues (cells) of the vaginal lining can become thinner, drier (thus providing less lubrication during intercourse), and less elastic or flexible. This can result in pain during intercourse, feelings of burning or soreness, inflammation and irritation.

There are a variety of solutions for dealing with this situation. Regular sexual stimulation (intercourse, masturbation) is recommended to keep vaginal tissues healthy. Water-based lubricants can help reduce discomfort during intercourse. Expanded views of sexual pleasure connected to entire phrase "expanded views of sexual pleasure"] that don't include intercourse might work around the problem. Leaving enough time to become aroused during intercourse (extended foreplay), communication between partners about when sex is painful and when not, can also help. Herbs like dong quai and black cohosh are recommended, especially by complementary/alternative practitioners, although the herbs lack a research base. A low-dose estrogen applied to the vaginal area (as a cream, tablet, etc.), is effective. A local medication minimizes the effects of estrogen being absorbed into the bloodstream and traveling through the body: there is, however, controversy about some estrogen being absorbed.

Now, to the FDA announcement: The FDA requires proof of a medication's safety and effectiveness before it is approved. According to the news release: "Osphena's safety and effectiveness were established in three clinical studies of 1,889 postmenopausal women with symptoms of vulvar and vaginal atrophy. Women were randomly assigned to receive Osphena or a placebo. After 12 weeks of treatment, results from the first two trials showed a statistically significant improvement of dyspareunia in Osphena-treated women compared with women receiving placebo. Results from the third study support Osphena's long-term safety in treating dyspareunia."

Notice, first, that the drug's effectiveness was tested for 12 weeks. This is not an unusual amount of time for such a study, but it is not very much time. Notice also that women treated with Osphena had a "statistically significant" improvement. As I discuss in a previous blog, "statistically significant" means "unlikely to have occurred by chance." In other words, there was evidence that Osphena really did have an effect, but we don't know how big an effect—it might be very large or very small.

Safety was established by studying the experiences of women for one year: however, one year is not a long time for side effects to develop. Osphena is a systemic medication. That means it is not applied locally in the vaginal area, it is ingested as a pill so that it travels to all parts of the body in the bloodstream. It is a selective estrogen-receptor modulator, or SERM. SERMs act like estrogen in some places in the body

while not in others. The idea is that a SERM like Osphena would act like estrogen in keeping vaginal cells healthy while not acting like estrogen to increase health risks like certain cancers. However, more time than a year might be needed for health problems to show up. Indeed, the FDA news release stated that "Osphena is being approved with a boxed warning alerting women and health care professionals that the drug, which acts like estrogen on vaginal tissues, has shown it can stimulate the lining of the uterus (endometrium) and cause it to thicken…. Women should see their health care professional if they experience any unusual bleeding as it may be a sign of endometrial cancer or a condition that can lead to it." The FDA announcement also stated that "Common side effects reported during clinical trials included hot flush/flashes, vaginal discharge, muscle spasms, genital discharge and excessive sweating" and that Osphena should be prescribed for the "shortest duration consistent with treatment goals and risks for the individual woman."

In conclusion: It's always a good idea to approach information with an alert and critical mind, to have some information about background and context, and it's always great when you have a resource you trust to help interpret information.

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Musings on Menopause and Heart Disease
August 27, 2012
Paula Derry

A recent article by Swift et al. looked at the effects of aerobic exercise on heart health. Midlife women with high blood pressure were assigned to one of three exercise groups—a program of exercise that met National Institutes of Health (NIH) guidelines, one that was half the amount of exercise recommended by the NIH, or one that was 150% of the NIH recommendations. The study did not examine who actually got heart disease. Instead, the researchers looked at the ability of arteries to function normally, which is a precursor to disease. Specifically, the researchers measured one component of artery health called "flow mediated dilation" (FMD)—the ability of arteries to respond normally to changes in blood flow by dilating (getting larger), which is one indicator of "endothelial (the inner lining of the artery) function." The authors found that aerobic exercise improved flow mediated dilation. The amount of exercise was not important—the authors suggest that once some minimum amount of exercise exists, improvements will occur. They also found that women with problems benefited from exercise, but not those with normal FMD.

Well, I have to admit this isn't an area of my expertise. I'm not going to evaluate how solid the methodology was, how close to normal the improvements brought the women, compare these results with the entire body of knowledge, all of which are important to really understanding the import of a study. However, I'd like to share some musings that the article triggered.

First, the article assumes that menopause and the menopausal transition increase a woman's chances of getting heart disease by modifying her precursors and risk factors. The title of the article is: "The Effect of Different Doses of Aerobic Exercise Training on Endothelial Function in Postmenopausal Women With Elevated Blood Pressure." The introduction states that their research is important because menopause is associated with worsening of heart disease risk factors. However, they are not studying postmenopausal women. They are studying overweight, sedentary women with high blood pressure who are old enough to be postmenopausal. It used to be more commonly stated, as though it is a fact, that menopause increases a woman's chances of getting actual heart disease. However, this assertion does not appear to be supported by the facts. A recent paper in the British Medical Journal concluded that aging rather than menopause was key: "Heart disease mortality in women increased exponentially throughout all ages, with no special step increase at menopausal ages." In 2011, the American Heart Association issued the Effectiveness-based Guidelines for the Prevention of Cardiovascular Disease in Women—2011 Update. These guidelines include a long list of risk factors and suggestions for how to prevent disease such as modifying lifestyle factors like cholesterol and inactivity. Menopause is not included as a risk factor and is mentioned in just one sentence in the document. The line of research that has now arisen which states with equal certainty that risk factors and precursors to heart disease increase with the menopausal transition thus must be looked at critically. Do these changes in precursors really co-vary with menopause? Do they lead to actual disease? How important are they relative to other factors leading to heart disease, like aging or lifestyle?

The article does not, however, suggest that these menopause-related precursors and risk factors doom women to increased heart disease risk. Indeed, the point of the article is that they can be modified through lifestyle changes, here, aerobic exercise. A lifestyle change that can increase health seems like a good thing. However, what also did strike me was something about the meaning of a healthy lifestyle. Sometimes healthy lifestyle is presented as though it is something that is "added on" to normal daily life. Sometimes it's almost analogous to a medical prescription—take 20 minutes of exercise daily. However, in the article the women who benefited, in terms of improved endothelial function, were the women who had abnormal function. The authors found that a small amount of exercise did the trick, with no additional benefit from increased exercise. So is it that supplementary exercise cured the problem, or was the problem an abnormal lifestyle deficient in exercise? As an analogy, if I don't have enough vitamin C I might get a disease called scurvy, because my body needs vitamin C. Once I meet my body's need, I won't get the disease, I don't need twice the requirement. The 2008 federal guidelines recommend that adults up to age 65 will get substantial health benefits from two and a half hours a week of moderate aerobic physical activity. Examples of moderate activity are gardening, walking briskly, ballroom dancing, shoveling snow, and stair walking. Maybe the idea is that our bodies need to move, and if we deny them a minimum amount of movement we have an unhealthy lifestyle. Maybe physical movement and activity are bodily needs, along with other components of a healthy diet and lifestyle.

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On Menopause Definitions
December 28, 2011
Paula S. Derry, Ph.D.

In a recent blog (November 10), Heather Dillaway commented on the uncertainty, confusion, and frustration she felt as a menopause researcher given the lack of consensus about the most basic aspects of the menopause transition. Researchers don't agree about their definitions, and can't even agree on what needs to be defined. She asked for reactions to her entry; I've found that my reaction has grown into this separate blog.

I, unlike Heather, am not a sociologist. I'm a health psychologist. My training and current work include analyzing, critiquing, and making sense of experimental research and theories. I have also developed workshops for community women and for professionals whose aim is to provide health-promoting information and decision-making heuristics. I have given a lot of thought to the issues that Heather raises, and this is as far as I've gotten with them.

To me, there are many layers of issues involved. The first is the fact that the science, about the physiology of menopause and the processes leading up to it, is limited and incomplete. Part of the reason that professionals disagree about whether the life course of menstruation has five stages or seven, or why women have hot flashes, or even why women have a menopause, is that we don't actually know. We simply do not have the scientific facts. We don't understand what the underlying process is or how it works.

Given this uncertainty, professionals must make judgments about how to define terms and what their hypotheses (or best guesses) are about underlying processes. A second fact, along with our limited real knowledge, is the tenacity with which professionals assert their judgments and argue against competing views. People disagree and they hold strongly to their positions—about language and the facts. To me, it makes sense to have definitions of stages of menstrual life that are objective and easily measurable (like the STRAW staging system) for researchers who need to compare results with each other. It doesn't make sense to assert that this system, based on expert opinion and not on experimental facts, actually defines when a particular stage really "begins." It makes sense to say that experimental research supports the idea that changes in the thermoregulatory center of the hypothalamus are important processes if you're trying to understand hot flashes. It does not make sense to conclude that these brain changes in themselves explain hot flashes; other factors must also be involved.

I think another source of confusion is that menopause is not one thing, but many. It is a circumscribed biological change (lack of periods and what leads up to them physiologically) and also a psychosociocultural matter. We have a term for when girls begin to menstruate (menarche), a separate term for the larger biological changes of which menarche is a part (puberty), and another term for the biopsychosociocultural changes of which puberty is a part (adolescence). I think these kinds of distinctions are confused with regard to understanding menopause in part because there is cultural confusion about midlife (or mature adulthood or whatever term you use) as a life stage. There is no cultural consensus about this stage of life. And, indeed, this isn't surprising. Some women are planning retirement while others are training for a new job or career. Some are grandmothers while others are raising a young child. My opinion, also, is that

we as a culture have a paucity of concepts of mature, responsible adulthood and what it means.

Finally, I think another source of confusion has been relying on biomedical information to understand menopause. Biomedical information is important. A woman who is experiencing odd changes in her periods, clots or frequent bleeding or whatever, should be able to get information about whether this is a health problem. And so on. However, research has shown that the kinds of questions that interest women are often not the questions that interest physicians. What does this stage of life mean to me? What are good ways of coping with uncomfortable or distressing experiences? All too often, biomedical information has encouraged a negative view that menopause is the gateway to old age or a body that is vulnerable to illness, a view that goes far beyond the facts. The biomedical perspective has thus often encouraged a view that menopause is extremely important, a watershed experience that must be vigilantly attended to and worried about, while not providing information about how to effectively deal with the changes ascribed to menopause. Biomedical perspectives have even encouraged a passivity in the face of physiological changes, a pessimism that anything other than medical care can be effective in alleviating problems.

Of course, there are also many things that we do know. We know that every woman will naturally experience menopause at some time during midlife, and we know more about the underlying physiology than was the case 30 years ago. We know that certain changes statistically are associated with menopause, which an individual woman may or may not experience. For example, in the years preceding menopause periods will likely become irregular and odd, and the likelihood of hot flashes increases. We know that the trajectory of changes varies from woman to woman. Etc.

To me, one important question is: Why is uncertainty discomforting? There are a lot of things in life that are uncertain. Anyone who has raised a child knows how to take action in situations rife with ambiguity and uncertainty. Why does uncertainty become a problem? Again, I think there are many layers of answers. Researchers have one set of issues; for example, they need to be able to communicate with each other. In my opinion there need to be multiple research definitions. Definitions need to be multi-layered and specific to contexts, not "either/or" but "also/and." A researcher studying physiology needs a different definition from one who is studying the perceptions of women. For midlife women, uncertainty may be discomforting if they are experiencing physical changes or distress that they don't understand, or if they are told that menopause puts their health at risk and that they need to be vigilant to avoid this.

Uncertainty can also be discomforting if there is an expectation that it should not exist. Many cultures do define life stages. Wanting to understand what menopause means seems to me to be natural and a fundamental process. But creating meaning is a psychological/social/cultural process which includes physiological facts but goes beyond them. I go back to the idea in cognitive/behavioral and narrative therapies that experiences are the complex outcome of physiology and appraisal processes. Appraisal—assigning or creating personal meaning—requires individual psychological processes and social meanings and constraints.

In the workshops I developed for community women and for professionals, I present information about menopause and the processes leading up to it—what we know and what we do not know. I also present uncertainty, ambiguity, and diversity as facts

characterizing the process. A woman doesn't even know she's stopped menstruating until she's been there for a year (since menopause is typically defined retroactively after 12 months without a period). Regardless of how the transition is defined, the experiences of one woman will differ from those of another. What I emphasize is the usefulness of each woman arriving at a personal definition of what menopause means. This individualized appraisal also refers to problems. The question, for example, in an individualized appraisal is not whether the likelihood of a sleep disorder increases during perimenopause but rather "Is my sleep disorder related to perimenopause," or, even better "How can I cope with, eliminate my sleep disorder?" (since whether the cause is perimenopause-related or not may not be crucial to getting rid of it).

I see in re-reading this blog that my own language style is definitive and authoritative-sounding, even as my content is arguing for modesty in one's claims. A didactic call for modesty. It may be difficult to get around my language style, but I hope the content of the blog will be useful.

Thanks to Heather for raising the issues.

What is a hormone?
Paula Derry, Ph.D.
March 5, 2012

What is a hormone? All too often, hormones are portrayed in the media, and even in professional articles, as strangers inside our bodies that control us. Sometimes hormones are personified as bosses that order our bodies around. Sometimes they are portrayed as akin in function to gasoline or motor oil, needed to keep the machinery of our body moving or smoothly gliding. Hormone levels that oscillate rather than maintaining a reassuring stability might be especially suspicious or even uncanny. Take oxytocin. According to the website ScienceDaily.com, which summarizes recent scientific studies, the hormone oxytocin (Aug. 1, 2011) is the "cuddle chemical," promoting positive feelings, especially between mothers and infants, but it also has a "dark side," promoting envy and gloating. An oxytocin nasal spray (Dec. 9, 2011) might help shy people behave in a less introverted manner, and (Jan. 5, 2012) can make "surly monkeys treat each other a little more kindly." Or, take estrogen. Teenagers are at the mercy of their "raging hormones." Premenstrual syndromes, perimenopausal mood changes, menstrual migraines, and hot flashes have all been attributed to hormones that oscillate (i.e., go up and down), dip, or are present in the wrong amount; thus, the orders barked out by the hormones go awry. Perimenopausal estrogen changes are feared to destabilize the brain, creating preconditions for cognitive decline, or to increase risks for bone or heart disease. A recent article (2010, vol. 1204) published by the *Annals of the N Y Academy of Sciences* was titled "Estrogen and the aging brain: an elixir for the weary cortical network?" A Science Daily report on estrogen and menopause (Oct. 4, 2011) was entitled "This is your brain on estrogen." Of course, not all hormones have this mythic status. Important as diabetes is as a public health problem, I don't recall seeing an article entitled "This is your liver on insulin."

Here's another view of hormones: Most introductory science textbooks define them as chemical messengers, typically released from special tissues called glands, into the bloodstream. In order for a hormone to affect a cell, the cell must have a receptor for the hormone. If there is no receptor, the hormone does not affect the cell. If there is a receptor, the hormone changes the rate at which cells work, it does not make cells do things they would not otherwise do. Hormones are chemical messengers that are involved in coordinating physiology, behavior, and development.

Consider a simple case, a person who is sitting in a chair and wants to stand up. The muscles in a variety of parts of her body have to work together. She can't, for example, lift her buttocks before her feet push down on the ground, or lean so far forward that she falls. Other parts of the body have to get into the act, also. For example, her blood pressure must go up before she starts to stand; otherwise she would become dizzy since as she rises less blood reaches her head. Mind and body work together; blood pressure rises in response to her mere intention to get up. In a similar manner, purposiveness is typically coordinated by hormones, the nervous system, and other players.

The way I think about it is that hormones are team players in complex, multi-determined systems that have a purpose. Hormones help to coordinate what happens in

the body, but in normal functioning they do not act alone; they are part of a larger whole. They are kind-of more like telephone wires than like the content of the conversation.

For example, what are some natural effects of oxytocin? As summarized in the textbook "Introduction to Behavioral Endocrinology" (Randy Nelson), oxytocin does indeed have strong effects on the behavior of female rats. Rats who have never been pregnant avoid pups, but begin taking care of their own pups as soon as they give birth. Do their hormones make them do it? Apparently. When the blood of a new mother (which will contain her hormones) was given to a rat who had never been pregnant, the never-pregnant rat began acting like a mother within 24 hours. However, when never-pregnant rats were housed with pups for an hour or two a day, after about 5 or 6 days they also began to behave maternally. That is, being around baby pups also resulted in behaving like a mother. The hormone speeded things up, but didn't change the animal's essential nature. Rat mothers retrieve their young if they wander off, but injecting a human with rat hormones does not make the human build nests.

Or take adolescence. Is it estrogen that makes a girl a girl? As summarized in the textbook "Patterns of Human Growth" (Barry Bogin), reproductive maturity (human adulthood) occurs years after menarche and is due to a combination of changes in the brain, hormones, and social and psychological experiences. Puberty involves lawful changes in a girl's body and experience that estrogens help to orchestrate but are only one part of. The process begins with changes in the central nervous system. Secondary sexual characteristics begin to develop before estrogen levels rise, with estrogen fat is deposited, an adolescent growth spurt comes next, secondary sexual characteristics continue to develop, then a girl begins to menstruate. The rise in estrogen can begin years before menstruation starts. Socially, girls do not reach reproductive maturity (adulthood) until years after menarche, since in most cultures they do not marry right when they begin menstruating.

Or consider that the powerful effects of hormones vary from situation to situation. For example (Bogin), humans have a growth spurt in adolescence. In girls, the bones of the pelvis march to a different timetable, continuing to grow after the spurt has ended in most other bones. Human males have a growth spurt but chimpanzees, who have similar changes in hormone levels, do not. Or consider that hormones do not act alone. Female rats, for example, who have had their ovaries removed and thus have no estrogen, absolutely will not copulate. However, they also will not copulate if the male does not engage in certain courtship behaviors (Nelson, Pfaff—"Drive").

Hormones are important. In disease, they can, indeed, be present in the wrong amount or otherwise create dysfunction. However, understanding the larger system of which they are part is important to understanding both normal function and what is happening when things go awry. Further, part of their normal function of helping to coordinate changing physiological states, behaviors, and development, presupposes that levels will vary. As the psychologist Joan Chrisler has said: "Hormone don't rage, they cycle. They just cycle."

Anyway, that's what I think.

Understanding Research: Media Reports of Research
Paula Derry

The Huffington Post posted a story on March 26 titled "Last Menstrual Cycle Could Be Predicted With New Model." The Huffington story stated that a research study had just been published about a new method for predicting the end of menstruation, in which researchers developed a formula for using the levels of two hormones, estradiol and follicle stimulating hormone (abbreviated FSH), to make this estimate. This "new method for predicting a woman's last menstrual cycle could have broader implications for menopausal women's health." Since "in the year leading up to the final menstrual period, women are met with faster bone loss and a greater risk of heart disease," if the end of menstruation could be predicted, medical monitoring and interventions would become possibilities. The research was also reported as news on the medical website Medscape.

Research results are often reported as news stories, as though these results are facts. However, "dog bites man" and "man bites dog" are facts, but research results are not facts in the same way. They are "evidence" that most often must be evaluated, understood, and put into the context of many other studies. There could very well be disagreement about whether a study's methods really did accurately make a point, or whether the conclusions the researchers drew from their work were justified. Sadly, it happens all too often that research does not make the point that the headlines claim.

Here, we have a study by a respected researcher at a major institution, UCLA, with a grant from the National Institutes of Health and other prestigious grantors. However, we do not have the information with which to understand what it was the researchers actually did. UCLA issued a press release which states that the study "suggests" a way to predict the final period. The Medscape article states that "A new model MAY [my emphasis] help physicians determine how far a woman is from her final menstrual period." suggests? may? I have no idea what this means. As a researcher, I want to look at the published article to see what was actually done. However, the publisher does not make a free copy of the article available. Anyone who wants to look at the published article—a researcher or an informed consumer—would need to pay the publisher $37.00 to access this 20-page article for one day. Predicting the last menstrual period from hormone levels, which is what is claimed, is something other researchers have tried but failed to do, so how these researchers worked with the difficult problems is an important question.

Assume for a moment that the model was a big success, and it did predict the last menstrual period. The idea that this has important implications for women's health is stated as though it were another fact. However, this is not a fact, this is a complicated and controversial area. Bone density does decrease in the years surrounding menopause, but professionals disagree about how big an effect this has on bone disease. For example, current guidelines recommend testing bone density beginning at age 65, 15 years after the average age of menopause, because this is when the fracture rate has significantly increased. Heart disease risk factors may increase on average in the years surrounding menopause, but professionals disagree about whether menopause is important compared with other factors associated with aging.

Assume for a moment that bone disease really is an important negative health consequence of menopause. Whether interventions would be found that must be started in the year or two before menopause is another speculation. Such interventions might be found, or might not. Predicting the last menstrual period, even if the claim is valid that a method to do so has been found, is a long way from preventing disease.

The medical satirist Andrew Vickers wrote an article called "News On Cancer Drug Fails to Raise False Hopes," which begins: "A recent article on a novel cancer therapy has rocked the newspaper industry by giving a balanced and cautious review of an early-phase trial." Satirists make extreme statements to make a point. Media reports are often written to sound definite and to portray a study as really important. A cautious approach to medical news is to withhold judgment unless the methodology of the study is clear and the context of the study is understood.

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Understanding Research: Buyer Beware
April 2, 2012
Paula Derry

I certainly believe that scientific research is important. Research uncovers new knowledge and prunes away facts that are not accurate. However, in our society research is also a coinage to justify views of reality. A Biblical scholar might invoke a sentence from the Bible before holding forth on his own interpretation or opinions. In a similar manner, a scientific study might be cited or a scientist quoted to justify that something is real before jumping off into one's own thoughts, opinions, theories, or justifications. If a scientific result can be invoked, we can believe that something is true. Is there an unconscious? Freud said so, but he's out of date. Are we intrinsically social beings? Evolutionary theorists argue. Does meditation really result in an altered state of consciousness? If I present results from research, preferably using a high tech measurement like a brain scan, or if I can come up with a theory that uses words like "neural nets" or "neurotransmitters," then I can believe all of these things.

What's wrong with this? Isn't this science doing its job of uncovering truth? There are two kinds of things wrong with this. One is that not all knowledge is scientific knowledge. The second is that scientific results are often portrayed inaccurately in our society.

With regard to the first point, I'll just give a few examples. von Bertalanffy, a systems theory scientist, wrote that even a physicist will chase his (sic) hat when the wind blows it without knowing the mathematics determining which way the hat will blow. Einstein famously said that not everything that was important could be measured, and not everything that could be measured was important.

But what I really want to talk about here is the second point. We are inundated with scientific results in newspapers, websites, and other places. Most often, a brief summary of research is followed by broad generalizations about what the research means. However, the outcome of research is not simple facts. Experiments are complicated things that must be evaluated by readers and understood in context. When I was a graduate student in psychology, every class included practice in critiquing research.

To understand research, certain mathematical ideas are important. "Statistical significance" is important to both accurate interpretation of research and to inaccurate or misleading reports. If you'll bear with me, I'll run through what I mean. Suppose you have a coin. If you toss the coin 100 times, it will come up heads about 50 times, not exactly 50 but close. Why? That's just the way the world we live in works, there are laws of probability. Since there are two possible outcomes—heads or tails—each will come up about half the time. If I toss my coin 100 times and it always comes up heads, I'll probably conclude the coin is biased. Why? Because it just doesn't happen, it's extremely improbable, in the world we live in that an honest coin would do this.

What if the coin came up heads 60 times? Is the coin honest or not? The question is this: When is an outcome still "what you would expect by chance even though the numbers are not exactly alike (since we expect approximately 50 heads, not exactly 50)"? On the other hand, when is the difference big enough that you would conclude that the coin is probably biased? Sometimes it's hard to tell. In research, very often results are in the "hard to tell" category. For example, if 55 percent of the women in my research

prefer chocolate ice cream, while 65 percent of the men prefer chocolate, is there a real sex difference (it's so improbable there's a real difference) or is there not (the numbers seem different, but I'm not sure whether this is just because there is a range due to chance and not a real difference). Sometimes numbers that seem very different are actually what you could commonly get by chance, and sometimes numbers that don't seem very different are very improbable. In addition, what I'm studying may produce a weak rather than a larger, obvious effect because among us humans, for all kinds of psychological, social, and biological research, what is being studied is only one factor contributing to a situation and not the only thing going on. In the example, even if men and women do have different likelihoods of preferring chocolate, there are many possible reasons for a person's choices—diabetes, city you grew up in, getting rejected by a date while you were eating chocolate ice cream, etc.

Enter tests of statistical significance. These are mathematical procedures which assess how likely an outcome is to have occurred by chance if there was no real underlying difference. If my statistical test revealed that the difference in the percentages of men and women who prefer chocolate ice cream could have occurred purely by chance only one time out of a thousand, I would conclude that my results were in the "there probably is a sex difference" category. Researchers have an arbitrary convention: If results could have happened by chance 5% of the time or less, then the results are considered evidence of a real difference and are said to be "statistically significant."

When media reports state that results are "significant," very often they mean "statistically significant." However, statistically significant only means "unlikely to have occurred by chance." How important a result is is a completely different question. For example, suppose that I was studying a medication that worked about 70% of the time; a sugar pill didn't work. Suppose this was extremely unlikely to have occurred by chance; that is, the results were statistically significant and I therefore had evidence that the pill was having an effect. If we're talking about a cancer medication given to people who would otherwise die, but now 70% didn't, this would be a powerful effect. I would be happy and excited. Suppose instead that the medication was a weight loss pill, and 70% of the people using it lost 5 pounds after 18 months while people given a placebo sugar pill (or perhaps a sugar substitute) didn't. Even though this result was also statistically significant—I have evidence that those folks wouldn't have lost the 5 pounds without the pill—the amount of weight lost was so small that I wouldn't be happy and excited that I had found a new, important weight loss pill.

The research that Chris Hitchcock discusses in her March 13 ReCycling blog is a good example. Women were best at picking out a picture with a snake during the days immediately before their menstrual period. The results were extremely statistically significant—many of the results would have occurred by chance less than one time in ten thousand--and were reported in the media. However, what these results mean and how important they are in affecting behavior are separate questions. Chris discusses the results-- the response was faster by 1/5 of a second. She also discusses the theoretical implications the authors choose to draw—that women are responding to anxiety and fear, and that this has something to do with human evolution and PMS. However, does a tiny change in reaction time indicate a meaningful change in anxiety level or the ability to detect danger? Are the changes in reaction time necessarily due to anxiety? For example,

the subjects were assigned to experimental groups based on phase of their cycle. Does this mean that they knew the research was about menstruation? If so, this could have influenced their behavior.

There are other important points to being a canny consumer of research reports. As when buying a used car, or even a new car, you can get a really good vehicle, but it's a good idea to be knowledgable before making a purchase. Let the buyer beware.

Understanding Research: (Meta)Theoretical Frameworks
Paula Derry
August 19, 2013

Research results are often reported by the media as stand-alone statements and as though they are facts. "Slim women have a greater risk of developing endometriosis than obese women." "Respiratory symptoms vary according to stage of menstrual cycle." In previous blogs I have said that a reader needs to understand research methods and basic concepts found in statistics in order to make sense of what results really mean. This blog is about another ingredient that goes into making sense of research. Metatheoretical frameworks, basic ideas of how the world works, are important influences on how researchers choose what problem to study, choose the methods with which to study it, and choose how to interpret the results.

The context of research is always stated in research articles. Articles always include a write-up of previous work, discussing what has been done and what unanswered questions remain. This sets the stage for why the research being reported is interesting and important. However, what I want to discuss are more general, often implicit, basic assumptions. Even what seem to be brute facts are understandable as such only within a given set of basic assumptions or paradigms. Paradigms guide thinking, but change over time.

Thus, as discussed by Sheila Rothman, a nineteenth century metatheory was that assertiveness and activity are dangerous for women. As stated in a more specific scientific theory: All people have a limited amount of nervous energy; this nervous energy is distributed over a greater number of organs in women than in men (because of their reproductive organs); therefore, all of women's organs are more "sensitive and liable to derangement (p. 24)." It was concluded from these ideas that exercise and exertion are dangerous for women; further, mental exertion, such as going to college, should be avoided. Rothman describes case studies written up by physicians of women harmed by exertion and cured by rest. In this context, designing research to evaluate whether college harms women appeared to be a sensible, even important undertaking. So did structuring a college curriculum to avoid precipitating debility or insanity.

What are some of our current basic paradigms? One example: Menopause is senescence and reproductive physiology is central to women's health. It follows from these premises that menopause or the transition to menopause are key factors in the development of chronic illness; research addresses what harm is created or, alternatively, whether these premises are correct. Another example: Cyclic changes in mood, intellect, and energy during different stages of the menstrual cycle are very important, especially to understand distress. Alternatively, a healthy menstrual cycle suggests that a woman is physically healthy.

Research I am conducting with Greg Derry addresses another metatheory about the menstrual cycle. Periods are most often described as cyclic, recurring in a regular repetitive manner ("every 28 days"). However, modern systems theorists know that there is a different kind of system (a "nonlinear dynamical system") that by its nature generates a little bit of unpredictability and by its nature interacts with other systems ("is an open rather than a closed system"). Our research has provided evidence that the menstrual

cycle is a nonlinear dynamical system. This means, among other things, that menstrual periods would be expected to be a little bit irregular with an occasional extreme cycle length.

The psychologist Robert Abelson reminds us that research is an ongoing process of discussion. Understanding research means joining the conversation.

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Working Mothers
Paula Derry
March 29, 2013

Research is often reported as though it is news, as though the most recent article is the best and research that was not published this year is somehow not as interesting or is out-of-date. I recently dug out some articles I wrote about the psychology of working mothers that were based on a study I did in the mid-1980s. I interviewed psychotherapists about how being a mother had affected their professional lives. This study was what is called "qualitative research." I offer the results as interesting ideas, not as definitive conclusions. Some points I think are still interesting:

1. Overall, about 64% of the 25 mothers I interviewed opted for part-time work; when children were preschoolers, this was about 78%. Psychotherapists, unlike many other women, have the option of working part-time: part-time jobs, especially for therapists who see clients in private practice, are the same jobs that a full-time worker would have.
2. I compared the mothers with another group of 19 therapists who did not have children. The non-mothers tended to work full time (about 90%). However, both groups of women were deeply and apparently equally committed to their jobs.
3. Many of the mothers (about 60%) felt that work was not as important to them as it would be if they were childless. However, this did not mean that work was unimportant. For most women, it only meant that they now had two strong priorities instead of one.
4. Almost all of the mothers (88%) felt that having children affected their work as psychotherapists by deepening their empathy, understanding, or emotional knowledge about parents and parenting. This was not simply intellectual, that they knew more facts, although this was also true. It was experiential understanding, a different experience of what facts mean. This was so even though their profession involves helping clients understand their parents or their parenting, and was reported whether they had a child while in graduate school or after they had worked for many years.
5. One aspect of this increased knowledge was an experience of how passionate an experience mothering is. Another aspect was a less idealized view of both parents and children, and greater tendency to see the experiences of parents and children from their own perspectives. For example, in addition to seeing parents in terms of how their children felt (e.g., that the parent was mean or rejecting), the therapists might perceive more clearly where parents were coming from or that children might misunderstand or be unreasonable.
6. This greater ability to see the position of both parents and children more clearly is what a psychologist might call psychological individuation. That is, the stereotype is that mothers are or should be all-giving, selfless, thinking only about their children. However, these mothers seemed to grow more realistic, clear about and accepting of who children as well as parents are. As I said in one paper: "Interconnectedness, or intimacy, requires a sense of oneself and the other as separate but

related. (If children really do lack a sense of this separation, that is no reason why their parents, who are adults, should identify with their perspective.)"

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The biology of reproduction isn't just about you
Paula Derry
July 23, 2012

A scientific paper was recently published ("Environmental perturbation of the circadian clock disrupts pregnancy in the mouse" Summa, Vitaterna, & Turek) which looked at how shifting patterns of daily light and darkness affect pregnancy in mice. The authors were interested in this question because studies have suggested that humans who experience such patterns, such as shift workers or women who travel repeatedly across time zones, have reduced fertility. In their study, pregnant mice were divided into three groups. All groups had 12 hours of light followed by 12 hours of darkness. The "control group" had the same pattern throughout the 21 days of pregnancy. The other two groups had shifting patterns. In one, the 12 hours of light started 6 hours earlier every 5 days ("phase advanced group); in the other, 6 hours later ("phase delayed group"). In the control group, 90% of the mice had successful pregnancies and deliveries; in the phase advanced group, 22%; in the phase delayed group, 50%.

"Circadian rhythms" is the general term for biological activities that have a 24-hour cycle, like sleeping and waking, or like hormones whose amounts vary during the course of a day. There are many circadian rhythms in humans, animals, and plants. They are internal, determined by the physiology of the animal or plant. However, they are also "entrained" (synchronized with) environmental events like the amount of light at night vs. during the day. This "entrainment" means the rhythms match what is going on in the environment and also can adjust to environmental change. In the pregnant mouse experiment, the light shifts were so large they disrupted the internal circadian timekeeper, which had cascading effects on mouse physiology and success in maintaining a pregnancy.

There are also many physiological rhythms that mesh with environmental patterns on longer or shorter time scales, for reproduction as well as many other aspects of biology. Zucker (1988), for example, found an annual rhythm to whether the amounts of a hormone called luteinizing hormone (LH) had a feedback relationship (that is, interaction) with the amounts of estrogen in ground squirrels. Typically in a mammal, LH increases estrogen production, and then when estrogen levels reach a high point the LH surges which initiates ovulation. For ground squirrels, who only become pregnant during January to March instead of having a regularly repeating cycle throughout the year, this relationship between hormones only exists during the breeding season. If the ovaries of females are surgically removed (so that their bodies don't make estrogen), LH levels still go up to initiate the breeding season at the correct time of year; that is, levels of LH appear to be controlled by some environmental factor.

There are also social influences on the biology of reproduction in animals. Nelson (1999) summarized some of them: If four or more female mice were housed

together in a cage, their cycles occurred less frequently. If they were then exposed to a male, they ovulated at the same time. In a study of albino mice, if a strange male was introduced into the cage of pregnant females, the females spontaneously aborted about 25% of the time. If the male who impregnated the female was re-introduced into the cage, there were no miscarriages. Female rats that were handled daily by researchers reached puberty at an earlier age than did rats who were not, and mice housed alone reached puberty sooner than mice housed with other females.

What does this mean for humans? There are not necessarily direct correspondences between animal and human research. Sometimes human physiology is simply different; sometimes, exactly the same. In addition, humans may have many influences where animals have fewer, so big, determining effects in animals may be mere suggestions in humans, one factor among many. On the other hand, the circadian research I discussed above was suggested by the possibility that shift workers and frequent travelers have fertility problems. Many social influences on human menstruation—synchronized menstrual cycles among college roommates, effects of stress—have been reported.

The possibility that intrigues me is this: We are individuals, but we are also intrinsically part of larger environments. Reproductive biology is about our inner organization of hormones, brain chemicals, goals and interests, but it is also about the viability and value of conception in specific social groups and physical environments. Our physiology is inside our skins, internal to us, but is also related to maintaining a state of balance with our physical and social environments.

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Averages
Paula Derry
May 27, 2013

Articles in the media often report research results with a number, for example the number of hot flashes per day or the severity of menstrual cramps. However, these are not facts in the way that "man bites dog" would be a fact. In part, this is because the numbers in research reports often are averages. Averages are useful summaries, but they also leave out a lot of information. Take shoe size. If the average woman's shoes are size 7, this does not mean that all women are size 7. It does not mean that a woman whose feet are size 8, 9, or 10 is abnormal or has a problem. At some point, a very large or small foot could mean that someone has a problem, but knowing where to draw the line requires knowing a lot more than the statistics. It means knowing something about the biology and biomechanics of feet. It means knowing about the context—for example, is a woman who wears a size 11 shoe 5 feet tall? or 7 feet tall? This is different from a situation where numbers have an absolute meaning. For example, if my temperature is 102 degrees, then I have a fever, because of the realities of the biology of my body and not because of what most people's average temperature is.

What is an average? There are a few common ways of computing this. The median is the score for which half of the people being studied have higher scores and half lower. If the scores of all of the people being studied are added together and then divided by the number of people, this gives us the mean. The standard deviation is a number that indicates variation around the mean. If whatever is being measured has what is called a "normal distribution" (which is most often assumed) then over 68% of measurements will be within one standard deviation, and over 95% within 2 standard deviations of the mean.

Take osteoporosis and osteopenia. Osteoporosis is a bone disease that typically develops in old age in which bone is fragile and more likely to fracture. This has been defined (World Health Organization, 2003) as a bone density measurement that is more than 2.5 standard deviations below that of an average 30-year-old woman. Osteopenia is having bone density that is not thin enough to be osteoporosis, but thinner than "normal," and is defined as bone density 1-2.5 standard deviations below that of a 30-year-old woman. These definitions are statistical, i.e., different from an average (young) woman. Sometimes women are told that they have bone disease based on these definitions. With regard to osteopenia, the assumption is that this is an early stage of disease that will get worse over time and become osteoporosis. Sometimes women with osteopenia are advised to use a medication to prevent the disease progressing. However, these statistical definitions have been controversial. For example (Los Angeles Times, 2011), other doctors assert that it is normal for bone to thin as women age and that only a small percentage of women with osteopenia go on to get osteoporosis. Some doctors believe that a diagnosis of osteoporosis itself requires more than low bone density—for example, that a woman has had a bone fracture or that other indications exist.

Or take the number of days in the normal menstrual cycle. The stereotype is that the average menstrual cycle is 28 days long and that regularly recurring cycles are what is healthy. A study published in 1967 by Treloar and colleagues presents some of the complexities that this stereotype ignores. Assuming that there is one average menstrual

cycle length for all women leaves out important information about changes that occur over time, across a woman's adult life. The average cycle length when a large group of women were studied was indeed 28 to 26 days (median length). However, this was for women aged 20-40. During the first few years after menarche and the last few years before menopause, median cycle length was over 30 days. Even more striking is the amount of variability from one woman to the next, and how this variability changes over time. Among 20-year-old women, for example, the cycle could be anywhere from 24 to 38 days, or occasionally less or more. However, the first year that periods began, these differences between women were larger--cycle length was between 18 and 83 days. Variability between women decreased for about 8 years, but, as I have said, even when women were most similar (at ages 20-40) there were still big differences among them. Variability increased again about 8 years before menopause; the last year before menopause, women had cycle lengths from 18 to 80 days. An individual woman's cycle lengths changed over her life span; further, cycle lengths varied from month to month as well as over a span of years in ways that were very different for different women.

Averages have useful information. However, it's always important to know what the numbers mean in order to interpret them. This is important for knowing what an average means, and it's always important to remember that an individual's reality may be very different from the picture derived from finding an average for a large group of people.

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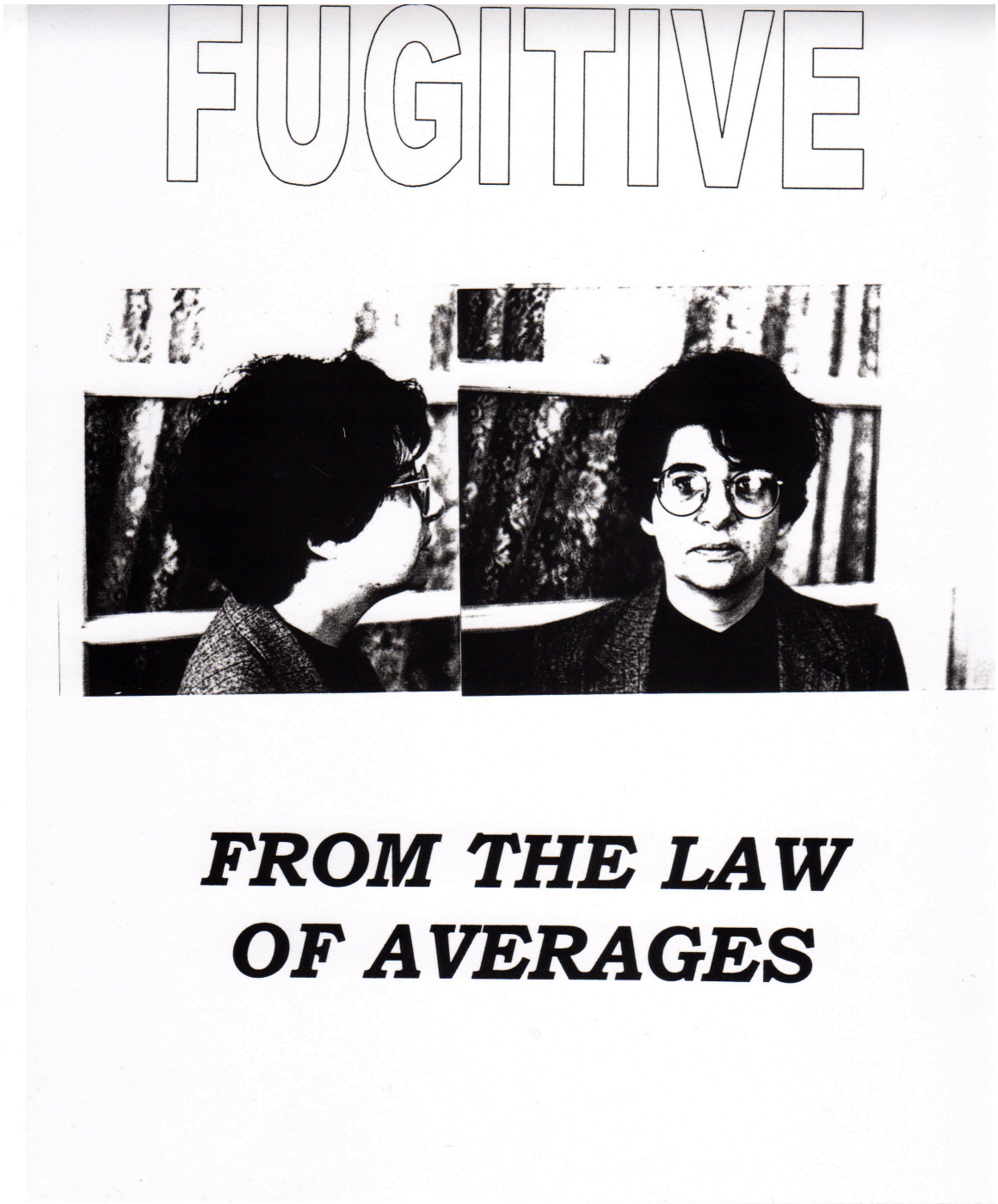

Brisdelle for Hot Flashes

Paula Derry

October 14, 2013

The North American Menopause Society held its annual meeting Oct. 9 to 12. An article posted a few days earlier stated that hot flashes would be "extensively discussed" at the meeting because "temperature control is such a preoccupation for menopause." There would be 13 presentations on low-dose paroxetine mesylate (brand name Brisdelle), "the first nonhormonal treatment for hot flashes to be approved by the US Food and Drug Administration." A link was provided to an article about the FDA approval.

The article about the FDA approval is titled "Brisdelle okayed as first nonhormonal Rx for hot flashes." However, the content of the article states: "The first nonhormonal drug for hot flashes associated with menopause was approved by the US Food and Drug Administration (FDA) today despite an agency advisory committee having rejected it as too much risk for minimal benefit. ….The FDA's Advisory Committee for Reproductive Health Drugs voted 10 to 4 against recommending approval. …The FDA is not obliged to follow the advice of its advisory committees, but …it usually does."

With regard to risks, the same article states: "Critics said the drug's minimal superiority to a placebo did not outweigh the risk for suicide ideation and osteoporosis, 2 adverse events associated with paroxetine. …The drug's label features a boxed warning about the increased risk for suicidality. The label also warns clinicians that paroxetine mesylate can reduce the effectiveness of the breast cancer drug tamoxifen if taken together, increase the risk for bleeding, and comes with the risk for serotonin syndrome."

Risks might be worth it if they are unlikely and there is a large benefit. In testing paroxetine did better than placebo, so it was accurate to state that the medication had an effect. However, the absolute advantage of the medication compared to placebo was small. For example, at week 4 of the study, 60% of the women taking the medication reported relief but so did 48% of the women taking a placebo; at 12 weeks, 47.5% vs. 36.3%.

Some clinicians with patients with severe hot flashes, and some women themselves, have had the experience that serotonin reuptake inhibitors (the class of drugs that includes Brisdelle) have worked. The article on the FDA approval speculates on why the medication was approved: "In a news release, the agency seemed to explain why it overrode the recommendation of its advisory committee when it came to paroxetine mesylate. 'There are a significant number of women who suffer from hot flashes associated with menopause and who cannot or do not want to use hormonal treatments,'

said Hylton Joffe, MD, director of the Division of Bone, Reproductive and Urologic Products in the FDA's Center for Drug Evaluation and Research."

For women with severe hot flashes, an effective treatment is needed. Yet, surely, a treatment with potential side effects should pass a high bar before being FDA approved.

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Cause and Effect
Paula Derry
November 11, 2013

Does menopause cause an increase in health problems ranging from heart disease to bone disease to psychological depression? One issue is that many of these claims have been criticized as being overblown both by professionals within the medical community and by critics outside it. Another issue is that when problems are linked to menopause, the suggested solution has often been estrogen supplements (postmenopausal hormone therapy)—since after menopause a woman's body produces far less estrogen—rather than seeking more complex causes, solutions, and mechanisms.

For example, although heart disease has many causes, during the 1990s many professionals recommended hormone therapy as being uniquely effective at preventing heart disease. At one time, a middle-aged woman who was depressed ran the risk of a professional assuming that she was suffering from a hormone imbalance without a careful evaluation of her distress.

While there is more attention today to looking at what causes problems and the best way to solve them, there is still a fundamental lack of understanding of basic processes. Even if menopause is linked to a problem, that doesn't in itself tell us the mechanism by which this happens, or the best way of solving the problem. Suppose, for example, it had turned out that research established (it hasn't, but suppose it had) that a woman's risk of heart disease increases because of menopause. If this was because changes in estrogen levels result in changes in a woman's metabolism, then lifestyle changes might solve the problem by revving up her metabolism even though a hormonal change caused it. Further, some other cause might be present. Perhaps some women who feel old or are busy become less physically active at midlife. Or perhaps some women who are depressed start eating more dessert. Or perhaps (as seems to be the case) heart disease risk simply increases as people get older.

For a wide variety of problems related to menopause, it would be great if more research looked at basic causes, complex mechanisms, and individual differences.

The "Choosing Wisely" Campaign: Don't Routinely Test for Osteoporosis Until Age 65
Paula S. Derry
June 25, 2012

On June 13, 2012 the medical website Medscape posted an interview with the president of the American Academy of Family Physicians (AAFP) on AAFP's involvement with the "Choosing Wisely" campaign. "Choosing Wisely," according to the article, **is an initiative of the American Board of Internal Medicine Foundation that has come up with evidence-based recommendations from 9 organizations about questionable medical tests and procedures. The organizations are mainstream medical groups like AAFP. The goal is to use these recommendations as the basis for discussions between doctors and patients.**

According to the article, one of AAFP's top five recommendations is that women should not be routinely screened for osteoporosis at the time of menopause. In fact, except for women who have high risk factors, screening should not begin until age sixty-five. The same recommendation was made by a Choosing Wisely group in 2011 and was also the judgment of the U.S. Preventive Services Task Force. This is in contrast to a common practice among physicians to order a DEXA screening test to measure bone mineral density (BMD) around the time of menopause and to prescribe medication for women who score low on the test beginning at this time.

Here's some background: The word "osteoporosis" at one time meant a medical condition in which bones are fragile and break easily; low bone mineral density was a risk factor for osteoporosis. However, low BMD also came to mean that a person had the disease itself rather than a risk factor for it. "Osteopenia" means that BMD is not as low as in osteoporosis but lower than a statistically-defined normal amount. One perspective by physicians and medical groups has been that since menopause and the transition to menopause are associated with declining BMD, it makes sense to test BMD at this time and to begin treating women, often with medication, if a screening test shows low bone density. Osteopenia as well as osteoporosis might be treated. A different perspective is that osteoporosis involves bone becoming so fragile that it fractures; BMD is only one of the factors that contribute to bone fragility; many factors (including lifestyle) contribute to bone strength and to whether a woman will break a bone. Further, since osteopenia is defined statistically, it may not really indicate a problem (as in Lake Wobegon, where everyone wanted their children to be above average).

What are factors indicating osteoporosis or risk of osteoporosis before age 65? Some of them are: if a bone fractures for what seems like no good reason (e.g., if you haven't had a hard fall or something else like it); if you've lost height; if you've been prescribed steroids for long periods of time; if you have certain other diseases like thyroid problems. There are many other factors that statistically predict increase risk. FRAX is an online tool that can be used to estimate risk. However, it is based on things like sex, height, weight, and medical history, and does not take lifestyle measures (whether you

exercise, have ways to avoid falls, etc.) into account. Many websites have additional information (e.g., National Institutes of Health, National Women's Health Network).

Some reasons behind recommending that women should not routinely be screened for osteoporosis until age 65 are: the rate of fracture does not go up until after age 65; there is little evidence that using medication helps women with osteopenia; the medications used to treat osteoporosis are good medicines for women who need them but carry risks, so women who don't clearly need them or will benefit from them shouldn't be using them. Thus, the Choosing Wisely initiative recommends that unless a woman has high risk factors to suspect osteoporosis, screening tests should not be ordered until a woman is 65.

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Understanding Research: Expert Opinion Isn't Enough
Paula Derry

Many of us do our own health research, either because we have a specific question or simply to keep up with the news. If we don't read the original scientific articles, we rely on experts to provide summaries in newspapers, magazines, or on a variety of websites. It seems as though by choosing sources judiciously we should be able to count on finding information that is accurate. However, relying on authority, whether this authority derives from a writer having scientific or medical training, or the writer being a professional journalist, or some other reason, is not enough.

I thought about this recently when I saw an article on Medscape, a website for health professionals, especially physicians, called "Early menopause doubles CVD risk regardless of race." A summary of a new journal article, it was highlighted on the Medscape home page for many days. It began: "Women who experience early menopause--before their 46th birthday--are twice as likely to suffer from coronary heart disease and stroke as women who don't enter menopause prematurely, and this finding is independent of traditional risk factors." Johns Hopkins University, where one of the authors is employed, issued a press release entitled "Early Menopause Associated With Increased Risk Of Heart Disease, Stroke" which also begins: "Women who go into early menopause are twice as likely to suffer from coronary heart disease and stroke, new Johns Hopkins-led research suggests." Similar articles appeared in Medline+ (a National Institutes of Health and National Library of Medicine website), a BlueCrossBlueShield healthcare news and many print newspapers.

So, what was in the original scientific article? The article was published in *Menopause*, which, like many journals, does not post its articles free online for nonsubscribers. Many academic libraries do not carry this journal. However, if a reader does get the original article, these are some of the details: The women in this research were studied for a number of years. The researchers collected information about many predictors of circulatory problems (smoking, diabetes, etc.). The women were also asked at what age they had reached menopause. If this was when they were younger than 46, they were classified as having an "early menopause" whether menopause was caused by surgery (ovaries removed) or occurred naturally. The researchers looked at whether the women developed heart problems or strokes, and created mathematical models to study which predictors of these problems were important.

Twice the number of women with "early menopause" had heart problems compared with women who reached menopause later. This is what is called "relative risk." The "absolute risk" numbers were: 3% of the women with early menopause had heart problems compared with 1.4% of those who did not; for stroke, the numbers were 2.6% vs. 1%. This is still a difference, but not as dramatic as a twofold increase. In addition, the way the strength of the association was mathematically computed was to first predict heart problems and stroke with more usual predictors: age, risk factors like diabetes. The difference in risk due to menopause was in the uncertainty left after all these other factors had already been taken into account. Further, we don't know whether the "early menopause" group had other associated characteristics leading to a health difference—if they were unhealthy in other ways. The authors, for example, state that if

a woman had a family history of heart problems, and if this was mathematically taken into account before looking at menopause, then early menopause was no longer a predictor of her having a problem. In accounting for results, the article cannot distinguish between surgical and natural menopause, which differ in many ways.

It is true that, in the media accounts of this research, if a reader reads the entire article, qualifiers do appear embedded in the article in some of the sources. Some do say that the number of women in the study who developed heart problems or strokes was small; that this was a correlation, not a cause-and-effect association; or that when family history of cardiovascular disease was taken into account the relationship disappeared (although in Medscape, the author of the study was quoted as saying that "the pattern was still similar"). A piece of misinformation that reappeared in some of the sources was that the increased risk was similar whether the women had early menopause naturally or because their ovaries had been surgically removed. The research article clearly states that the authors did not have sufficient power (in research this means, basically, enough subjects to get an accurate answer to the question) to determine this.

I was puzzled why so much publicity was given to this study. In my opinion, it did provide some interesting, suggestive results and contributed information about women from a range of ethnic groups (who have been understudied in the past) but the study's results were modest and inconclusive. However, what the article did do was to claim to support the underlying assumption that menopause and heart disease are related, an idea that keeps re-occurring in the professional literature, even stated as though it is a fact, although the evidence for it has been at the very best arguable and weak. A recent SMCR blog by Chris Hitchcock analyzed media misreporting of the results of another research project intended to test this relationship. In the study I am discussing, highlighting weak data that seems to suggest a relationship between menopause and ill health, blurring the distinction between natural and surgical menopause, contribute to this meta-message. Ages 40 to 45 would be considered within the normal age range for menopause by many professionals, but is here defined as creating health risks. I would hate to think that meta-messages promoting ideas that menopause is unhealthy and causes risk of heart disease contributed to the perceived importance of the article.

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Ethics in Wonderland: The SUPPORT Study
Paula Derry
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Arthur Caplan is a well-known ethicist, the head of the Division of Medical Ethics at New York University's Langone Medical Center. On June 11, 2013, Caplan posted an article called "Get real: No need to overdo risk disclosure" on the medical website Medscape. According to basic ethical standards, subjects in research projects are supposed to give written informed consent, which means among other things that they are informed of possible risks that a decision to participate in the study might cause. The Office of Human Research Protections (OHRP) of the U.S. Department of Health and Human Services criticized researchers in a large project called SUPPORT for failing to clearly disclose the study's risks. In his Medscape article, Caplan disagreed with OHRP and argued that strict, inappropriate requirements for consent discourage important research. His sentiments were echoed in a recent editorial in the *New England Journal of Medicine*, a major respected journal. In contrast, SUPPORT is criticized in a *New York Times* editorial entitled "An Ethical Breakdown" and by watchdog organizations like the Alliance for Human Research Protection and Public Citizen (many of the critical documents are on the Alliance for Human Research Protection website

Here's some background: SUPPORT was a large study of how best to treat very premature babies. These babies often need to be given oxygen to help them breathe. However, if too little oxygen is given, there is a risk of death or brain damage; if there is too much, the babies may develop an eye problem called ROP or blindness. Enter SUPPORT. According to the researchers, their goal was to determine the best oxygen level to get lowest risk of blindness without increased risk of death. This amount had already been narrowed to 85% to 92% oxygen saturation (a measure of the oxygenation of blood) in medical practice; the researchers wanted to find out where within this range is best. Infants in the research were randomly assigned to experimental conditions; in one condition, babies were given enough oxygen to bring the oxygen saturation measure to the lower end of the range (averaging 85%); in the other condition, the higher end (averaging 92%). The researchers found that infants receiving less oxygen did, indeed, have fewer eye problems than did infants given the higher amount, but more of them died.

The critical letter from OHRP stated that the consent forms that the mothers of the babies signed should have clearly stated, but did not, that an increased risk of blindness (for babies in the higher oxygen condition) or death (for babies in the lower oxygen condition) was possible. The ethicist Caplan objected to this. He argued that the researchers were comparing two standard medical practices, since 85% to 92% is the standard range used by doctors. In his view, the current way that doctors decide how much oxygen to use within that range is "a coin flip"; randomly assigning babies to the experimental groups was simply comparing two treatment approaches currently in use to see which one is best and involved no increased risk than the babies would otherwise face. He distinguished this from studies that introduce a new treatment, where informed

consent about risks is a different matter. Caplan stated: "I believe that this research is highly ethical" and expressed concern that overly strict rules will hinder needed research. The *New England Journal of Medicine* editorial also objects to the OHRP letter. The editorial states that the OHRP's finding that subjects should have been informed of an increased risk of death was based on hindsight. The editorial quotes the researchers, who state that "there was no evidence to suggest an increased risk of death" for infants receiving the lower levels of oxygen before their study was done. The editorial laments that OHRP has "cast a pall over the conduct of clinical research" and "strongly disagree[s]" with their letter. SUPPORT, in the editorial's view is "a model of how to make medical progress."

What is the controversy? First, with regard to the idea that what was being compared were two versions of standard care, although Caplan does not state this in his article, the OHRP letter specifically addressed this point. In real clinical practice, a range of 85% to 95% exists, but in this study only the extremes were used. As the letter states:

> According to the study design, on average, infants assigned to the upper range received more oxygen than average infants receiving standard care, and infants assigned to the lower range received less. Thus the anticipated risks and potential benefits of being in the study were not the same as the risks and potential benefits of receiving standard of care.

Further, in real clinical practice, physicians would be making decisions about where within this range to aim, and how much oxygen a particular infant needed. Caplan assumes that random assignment in the experiment was no different than a physician making a decision. In my view, this is a pretty big assumption. Since the researchers compared infants receiving higher vs. lower levels of oxygen, but did not compare either group with a control group of infants getting real standard care, we do not have evidence whether the babies did better, the same, or worse, than babies given genuine standard care. We know that babies receiving less oxygen in the experiment had fewer eye problems than did babies receiving higher amounts, but we do not have definitive evidence of whether they did better or worse than babies receiving usual care.

With regard to the argument in the Editorial that the OHRP was using hindsight by faulting researchers for not warning of risks that could not be anticipated before the research was done, again, what was in the letter was not cited: the OHRP letter specifically states that the literature had already suggested that death might be a risk of participating in the study:

> While it would have been unwarranted to predict, ahead of time, specific outcomes (i.e., which infants developed which outcomes), the researchers had sufficient available information to know, before conducting the study, that participation might lead to differences in whether an infant survived, or developed blindness, in comparison to what might have happened to a child had that child not been enrolled in the study.

In addition, the OHRP letter faulted the researchers for listing possible benefits while not disclosing possible risks in the consent forms:

> Although the consent form did not identify a single specific risk relating to the randomization to high or low oxygen ranges, it did include a section that was quite specific in noting possible benefits to participating infants from the change in oxygen ranges. That paragraph observed that "[t]here may be benefits to your child directly, including . . . a decrease in the need for eye surgery as a result of exposure to oxygen." It did go on to point out that since it was not known in advance which treatment a particular child would be randomized to, it was "possible that your baby will receive no direct benefit."
> …The form does not say that there may be a greater or lesser risk of death depending on whether the infant is in the lower or upper range group. …While the form says that being in the lower range group may result in the benefit of decreasing the chances of developing severe [eye problems], in the "Possible Risks" section it does not say that being in the upper range group may result in the greater risk.

As I stated above, watchdog groups including the Alliance for Human Research Protection and Public Citizen, a New York Times editorial, and others, have criticized the SUPPORT study as "an ethical breakdown". The articles by these groups catalog a number of other criticisms and give additional details. For example, in standard medical practice a physician would be evaluating an infant's need for oxygen in an ongoing manner, but in SUPPORT the physicians were given false readings (depending on the experimental group the baby was assigned to) from instruments measuring oxygen level.

Research is important in making medical progress. No doubt about it. And research with vulnerable people is fraught with ethical dilemmas and problems. It is a truism that the goals of research and clinical care are not the same. However, national reputations of researchers, ethicists, or journals, are not guidelines for what information to trust in evaluating research or deciding to participate in a study.

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Fun Facts About Menstruation
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Menstruation occurs because the inner lining of the uterus (called the endometrium) has undergone changes that prepare for pregnancy. If there is a fertilized egg, the uterus will be able to provide a hospitable and nurturing environment. If a woman doesn't become pregnant, the inner lining is shed, in a discharge that includes cells, fluid, and blood; we call this menstruation.

Fun fact #1: Menstruation is a rarity, perhaps an oddity, in nature. Most animals don't prepare a lining in advance just in case pregnancy occurs. They have hormonal cycles, which are called estrus cycles, but not menstrual periods. Most primates (monkeys, apes, and us) menstruate (Nelson, page 262).

Fun fact #2: The endometrium is shed in layers during menstruation (Voda, page 62). That is, although cells are dying, blood vessels are leaking, and other changes are occurring, this breakdown occurs in the form of shedding of layers, not in a random cataclysm.

Fun fact #3: Most of the endometrial material that is eliminated is resorbed, not menstruated (Voda, page 62). That is, your body typically clears away material that is no longer useful or is waste. Suppose, for example, you bang your finger hammering a nail and get a bruise. Over time, the black-and-blue area at your injury, with its injured cells, blood, and other material, returns to normal as your body clears away the debris. Similarly, according to Voda, most of the endometrial material is resorbed; menstrual flow is a minority of the material being shed.

Fun fact #4: Why do women (or monkeys and apes, for that matter) menstruate? Answer: There are theories, but no one knows.

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