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David R. Rubinow: Triggers and susceptibility–reproductive steroids and the regulation of affective state

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This Genomic Press Interview explores Dr. David R. Rubinow's transformative contributions to reproductive psychiatry through his journey from a major in philosophy and history to becoming a leading researcher. Rubinow fundamentally changed how we understand mood disorders linked to hormonal changes by discovering that women with conditions like premenstrual dysphoric disorder (PMDD), postpartum depression, and perimenopausal depression have normal hormone levels but respond differently to hormonal fluctuations, a concept he termed "differential sensitivity." This breakthrough shifted treatment approaches from attempting to normalize hormones to targeting the abnormal responses themselves. His research directly contributed to the development of brexanolone (Zulresso), the first FDA-approved medication specifically for postpartum depression, which works through novel neurosteroid mechanisms rather than traditional antidepressant pathways. After 27 years at the National Institutes of Health (NIH), where he served as National Institute of Mental Health (NIMH) Clinical Director and founding Chief of the Behavioral Endocrinology Branch, Rubinow joined UNC-Chapel Hill in 2006 as Chair of Psychiatry, a position he held until 2019. During his tenure, he founded the UNC Center for Women's Mood Disorders, established the nation's first peripartum inpatient unit and first NIH-sponsored fellowship in women's mood disorders, and led the department to consistently top-10 national rankings in NIH funding. A member of the National Academy of Medicine since 2012, Rubinow has authored over 400 scientific publications and served as president of both the Society of Biological Psychiatry and the American College of Neuropsychopharmacology. The interview reveals how serendipity shaped his career trajectory, from an unexpected fellowship with Bob Post to leadership positions while maintaining parallel passions for music and woodworking. His philosophy of "bringing the chisel when sent for the hammer" reflects the thoughtful approach that has characterized his research. Rubinow's work has validated the experiences of millions of women whose hormone-related mood symptoms were previously dismissed, establishing reproductive psychiatry as a legitimate subspecialty with evidence-based treatments.

Figure 1. David Rubinow, MD, University of North Carolina at Chapel Hill, USA.

Part 1: David R. Rubinow, MD – Life and Career

Where were you born, and where do you live now?
I was born in Hartford, Connectucut and since 2006 I have lived in Chapel Hill, North Carolina, USA.

Could you give us a glimpse into your personal history, emphasizing the pivotal moments that first kindled your passion for science?
My interest in science evolved from unlikely origins: my majors in philosophy and history in college. What I enjoyed in those two areas were the discipline of questioning in philosophy and the opportunity for creative linking of ideas in history. During my residency in psychiatry at Yale, I was exposed to some of the country's pioneers in biological psychiatry, but my interests remained primarily clinical. I was going to be a consultation-liaison (CL) psychiatrist. However, completing a two-year fellowship at NIH would ensure that I understood research methodology sufficiently to critically read the literature (rather than having to rely on the stories and post-hoc justifications that often characterize many published papers). It was as a fellow working with Bob Post in the National Institute of Mental Health (NIMH) intramural program that I learned that I liked science, particularly the operations reminiscent of my studies of history and philosophy: the creation of isomorphs between areas or facts that were not connected but that, when connected, offered novel insights into the area of focus.

Please share with us what initially piqued your interest in your preferred area of research or professional focus.
Over my first few years at the National Institutes of Health (NIH), I had three disconnected areas of "specialization." First, Bob gave me access to spinal fluid (in addition to the hundred or so spinal taps that I ultimately

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performed) and suggested I study CSF somatostatin in the affective disorders of the patients in our research unit. In addition to reading about this hormone, which I knew virtually nothing about, I spent some time in the laboratory of Seymour Reichlin at Tufts to learn how to perform radioimmunoassay. Sometime later, Bob provided me with a laboratory where I could run assays for hormones (primarily cortisol) and subsequently perform PCR for genes of interest in the Unit on Peptide Studies in Bob's Section. Second, I maintained my interest in CL psychiatry, and I suggested to the then-clinical director of NIMH, Robert Cohen, that I create a research CL service out of what was then an exclusively clinical service. As a third-year fellow, I was appointed head of the intramural CL service, and we generated a variety of interesting findings, including one of the first demonstrations of cognitive dysfunction in HIV-positive patients, stress axis sensitization following repeated administration of immunotherapy, and neuropsychiatric complications associated with alpha interferon administration.

Third, my interest in reproductive psychiatry, a field that did not exist at the time, stemmed entirely from an interaction with my Branch Chief, William Bunney. He shared concerning information from an endocrinologist about four patients who had attempted suicide during the latter part of the menstrual cycle, and he directed me to investigate this important clinical observation. In my reading, I learned about premenstrual syndrome (PMS), a condition that had received limited attention in medical education at that time. The existing literature was inconsistent and lacked methodological rigor, so I spent three weeks with a junior fellow, Pete Roy-Byrne, comprehensively reviewing all available research and writing a methodologic review to help establish more precise diagnostic criteria. The paper was accepted without revision, and a few months after its publication, I was asked to serve as a consultant to the Food and Drug Administration (FDA) regarding their consideration of progesterone as a therapy for PMS. At that point, I had not yet had the opportunity to work directly with patients experiencing the disorder, which made me acutely aware of the responsibility that came with being viewed as an expert based on our systematic review. This experience reinforced my commitment to combining rigorous research with clinical practice in this underserved area.

I continued to work in these three areas. However, I increasingly focused on reproductive studies in my lab (examining sex differences in cellular signaling and, ultimately, in transcriptional differences in cells from women with reproductive mood disorders) and clinically, particularly following the arrival of my third fellow, Peter Schmidt, who became my primary collaborator for the next 40 years.

We would like to know more about your career trajectory leading up to your most relevant leadership role. What defining moments channeled you toward that leadership responsibility?

Well, my career trajectory was primarily determined by serendipity – being in the right place at the right time. Had I not been at Yale, I likely would never have gone to NIH (eight or nine residents in my year ended up there!). Had the director of CL at NIH not been about to retire, I would not have become head of the CL service. If the Clinical Director and Scientific Director of the NIMH IRP had not been retiring, I likely would have left after my two-year fellowship (the Yale Residency instills an interest in systems and politics, and I wanted to see what was going to happen). If not the head of the CL service, I likely would not have been appointed Clinical Director of the IRP. If I had not supervised Bob Golden on the CL service, he would not have recruited me to replace him as Chair at UNC. If not for the wonderful friends I made at professional meetings (often presenting the reproductive science that interested few in our larger field), I would not have been elected president of the Society of Biological Psychiatry and the American College of Psychopharmacology. You get the idea – show up and be open to opportunities.

What is a decision or choice that seemed like a mistake at the time but ended up being valuable or transformative for your career or life?

I tend to be so obsessionally impaired when making a decision that by the time I have made it, I am good with it, irrespective of the outcome. I did make one decision that I immediately regretted and almost immediately reversed. When Bob Post offered me the fellowship position, I turned it down because I thought I would prefer to be in a lab more closely related to my clinical interests (despite my thinking that he was a good guy). After I hung up the phone, I realized that I had made a big mistake. I called him right back and said that I would be grateful to accept his invitation. Had I not gone to work with Bob, who gave me tremendous freedom and support, I am not sure that I would have ever stayed at NIH and would have missed the opportunity to learn how much I loved science and the luxury of being an investigator. The lesson I learned is that the quality of your relationships with work colleagues exceeds in importance what you imagine they can do to advance your career. It is all about relationships.

What habits and values did you develop during your academic studies or subsequent postdoctoral experiences, that you have maintained throughout your life?

The habit left over from college is the canine approach to work – full on for brief periods, then stop. I cannot learn and retain information incrementally, so I immerse myself in a topic for brief periods, focusing intently on it, and then move on to something else, cycling repeatedly through different areas. Having multiple areas of interest (hormonal receptor pharmacology, clinical phenomenology, CL, administration, private practice) allowed me to remain engaged despite my distractibility. The principal value that guided my work was conveyed to me by my grandfather, as relayed by my father: "When you are sent for the hammer, bring the chisel." In other words, think about what you are doing: carefully articulate your questions, anticipate the confounds, and do it right.

Please tell us more about your most relevant focal points – past or present – within your chosen field of science.

The most relevant focal point for me is the impact of reproductive steroids on brain function and their role in reproductive-related mood disorders. Reproductive steroids represent one of the most powerful systems for regulating brain and behavior, which makes teleological sense: without the ability to determine motivated behavior surrounding reproduction (and feeding), the species disappears. It turns out that, independent of reproductive behavior, reproductive steroids regulate virtually every signal transduction system, as well as the synthesis, metabolism, and function of all neurotransmitters and all elements of transcription (including all three mRNA polymerases). Their intracellular receptors represent points of convergence for multiple signaling pathways, and their metabolites (e.g., the neurosteroid allopregnanolone) exhibit their distinct signaling properties. Returning to serendipity, my demonstration of the role of reproductive steroids in PMDD when Steve Paul was the IRP Scientific Director led him to ask me to pitch a use case for allopregnanolone soon after he created Sage Therapeutics. That led to the first trial of brexanolone (conducted at UNC by Samantha Meltzer-Brody) in PPD and its subsequent FDA approval as the first neurosteroid therapeutic for a psychiatric disorder.

What were the key impact areas of your research topics?

The key impact areas of my reproductive research are phenomenologic and conceptual. The first phenomenologic impact was the demonstration that reports of PMS (later to be called PMDD) were strikingly unreliable and required prospective demonstration, formally introduced by an NIMH workshop that Susan Blumenthal and I convened in 1984. This permitted the generalizability of findings across studies, which previously was impossible. Conceptually, the most significant impact was the discovery of the phenomenon of differential sensitivity, which was revealed in studies that manipulated the reproductive axis blindly, as conducted by Peter Schmidt and me. Critically, these studies permitted us to identify and study women who had reproductive hormone-triggered affective syndromes, not based on history but instead as reflected by their response to the blinded hormone manipulation. We were able to show in all three reproductive affective disorders – PMDD, PPD, and PMD – that reproductive hormones did play a clear causal role in the precipitation of these disorders. However, we did so only in those susceptible to the disorder. In other words, there was no reproductive endocrinopathy: the hormones did trigger the dysphoric affective states, not because of abnormal levels but rather because of post-hormone signaling that resulted in a different

Figure 2. View from the Maine coast near Dave Rubinow's retreat. This landscape represents the convergence of natural beauty and intellectual contemplation that characterizes his ideal setting for reading, reflection, and discovering "connections between ostensibly unrelated topics."

behavioral response to the same hormonal signal. Much of the work that Peter, I, and our collaborators have undertaken has been directed toward defining this context of susceptibility, including Peter and David Goldman's demonstration of differential sensitivity at a cellular level using induced pluripotent stem cells. A related impact, described in the preceding section, is our contribution to the introduction of neurosteroids as a treatment for PPD. It is very gratifying (and a privilege) to be able to participate in the process of taking a new therapeutic modality from conception to FDA approval. Finally, our demonstration of the antidepressant efficacy of estradiol – independent of its impact on somatic symptoms – contributed to the voices that questioned the banishment of menopausal hormone therapy following the initial publication of the Women's Health Initiative.

What have you most enjoyed in your capacity as academic or research leader?
That is an easy one, albeit in two parts: 1) the privilege of mentoring and being helpful to others in their careers, and 2) partnering with trainees and colleagues to ask an answerable question that will move the field forward and contribute to healthcare.

At Genomic Press, we prioritize fostering research endeavors based solely on their inherent merit, uninfluenced by geography or the researchers' personal or demographic traits. Are there particular cultural facets within the scientific community that warrant transformative scrutiny, or is there a cause within science that you feel strongly devoted to?
You mention cultural facets within the scientific community, but clearly, the most important facets currently reside outside of it. This magnificent enterprise, of which we are a part, is under threat from cultural forces that benefit tremendously from our science but are willing to diminish it for political purposes. It is a travesty. Within the scientific community, of course, there is room for improvement. Notably, despite the laudable efforts of many grant reviewers, the process at times appears capricious, driven by a suspicion of novelty and by the loudest (often negative) voice in the room. I do not have recommendations for a better system.

Outside professional confines, how do you prefer to allocate your leisure moments, or conversely, in what manner would you envision spending these moments given a choice?
Woodworking, music composition and recording, exercise, fixing whatever machine or house-related system goes awry, being with my wife, Carly, in Maine, and playing golf with Don Rosenstein.

Part 2: David R. Rubinow – Selected questions from the Proust Questionnaire[1]

What is your most marked characteristic?
The absence of any outstanding characteristics.

[1]In the late nineteenth century, various questionnaires were a popular diversion designed to discover new things about old friends. What is now known as the 35-question Proust Questionnaire became famous after Marcel Proust's answers to these questions were found and published posthumously. Proust answered the questions twice, at ages 14 and 20. In 2003 Proust's handwritten answers were auctioned off for $130,000. Multiple other historical and contemporary figures have answered the Proust Questionnaire, including among others Karl Marx, Oscar Wilde, Arthur Conan Doyle, Fernando Pessoa, Stéphane Mallarmé, Paul Cézanne, Vladimir Nabokov, Kazuo Ishiguro, Catherine Deneuve, Sophia Loren, Gina Lollobrigida, Gloria Steinem, Pelé, Valentino, Yoko Ono, Elton John, Martin Scorsese, Pedro Almodóvar, Richard Branson, Jimmy Carter, David Chang, Spike Lee, Hugh Jackman, and Zendaya. The Proust Questionnaire is often used to interview celebrities: the idea is that by answering these questions, an individual will reveal his or her true nature. We have condensed the Proust Questionnaire by reducing the number of questions and slightly rewording some. These curated questions provide insights into the individual's inner world, ranging from notions of happiness and fear to aspirations and inspirations.

Among your talents, which one(s) give(s) you a competitive edge?
Recognizing undeclared motivations.

If you could change one thing about yourself, what would it be?
Reduced numbers of aging body parts.

What is your current state of mind?
Fatigue with the questionnaire.

What is your idea of perfect happiness?
Sitting on my deck in Maine in the morning with my wife Carly, a pot of coffee, and a dozen books of various kinds, reading bits of each and seeing the connections between ostensibly unrelated topics (see Figure 2).

When and where were you happiest? And why were so happy then?
Two answers: during college (expansive potential, meeting Carly, independence, sex, drugs, and rock 'n roll) and when my first-born daughter fell asleep on my shoulder when she was about 9 months old (just no better feeling than her trusting, completely comforted melting into my body).

What is your greatest fear?
Suffocating.

What is your greatest regret?
I have many small regrets (I should have said this, or I missed that, or I should have bought Berkshire Hathaway when it was first offered), but I fundamentally regret nothing.

What are you most proud of?
My daughters.

What do you consider your greatest achievement?
Parenting my daughters.

What or who is your greatest passion?
Learning.

What is your favorite occupation (or activity)?
Playing music (see Figure 3).

What is your greatest extravagance?
Woodworking equipment.

What is your most treasured possession?
It is probably my guitar, but most possessions are replaceable.

Where would you most like to live?
Somewhere on the ocean, maybe La Jolla.

What is the quality you most admire in people?
Altruist intelligence

What is the trait you most dislike in people?
Impositional intolerance.

What do you consider the most overrated virtue?
Unexamined faith/certainty.

What do you most value in your friends?
Sense of humor, irreverence, interpersonal presence, recognition of the gift of friendship.

Which living person do you most admire?
Both of my sons–in–law are uber-competent men who value friendship, family, and living life to the fullest.

Figure 3. A young Dave Rubinow with his guitar during his early career at NIH. His dedication to music composition and recording has provided a creative counterbalance to his research in reproductive psychiatry throughout his distinguished career.

Who are your heroes in real life?
My father and mother.

If you could have dinner with any historical figure, who would it be and why?
Christ – I would have many questions to ask.

Who are your favorite writers?
Walter Kaufmann, Bertrand Russell, Jo Nesbø, Gore Vidal, Robert Fuller, Katherine Stewart, and Michael Pollan.

Who are your heroes of fiction?
Reacher, Spenser, and Arya Stark.

What aphorism or motto best encapsulates your life philosophy?
Less a motto than the religion my daughter Katya created during her college years: Momentarianism, dedicated to increasing the number of moments in life characterized by awareness, awe, and unconditional gratitude.

A plane from Seattle, Washington, to Raleigh, North Carolina, USA.
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