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Darwinian medicine and mental disorders

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Abstract. Darwinian medicine applies the principles of evolutionary biology to the problems of medicine. It asks, for each disease, "Why has natural selection left the body vulnerable to this disease?" There are six possible kinds of answers: (1) novel environments, (2) co-evolution with pathogens, (3) constraints on what natural selection can do, (4) design trade-offs, (5) traits that increase reproduction at the expense of health and (6) defenses that are useful even though they are costly and aversive. These principles prove even more useful for understanding mental disorders than they do for understanding physical disorders. In particular, they offer psychiatry a diagnostic framework that distinguishes defenses from defects in the same way the rest of medicine does. It also calls attention to the utility of emotions, especially negative emotions. This knowledge will become increasingly essential as we gain new powers to use drugs to influence cognition and emotion. It can also help psychiatry to finally become recognized as a medical specialty just like any other.

Resumen. La medicina darwiniana es la aplicación de los principios de la biología evolutiva a los problemas médicos. Se pregunta, para cada enfermedad, "¿Por qué la selección natural ha dejado el cuerpo vulnerable a esta enfermedad?" Hay seis posibles respuestas: (1) un nuevo medio ambiente, (2) co-evolución con patógenos, (3) restricciones en la acción de la selección natural, (4) compromiso de diseños, (5) rasgos que incrementan la reproducción a expensas de la salud y (6) defensas que son útiles incluso si son costosos y provocan rechazo. Estos principios parecen ser incluso más útiles para la comprensión de las enfermedades mentales que para la comprensión de desórdenes físicos. En particular, se ofrece a la psiquiatría un marco de diagnóstico que distingue defensas de defectos del mismo modo que lo hace el resto de la medicina. También llama la atención sobre la utilidad de las emociones, especialmente las negativas. Este conocimiento se irá convirtiendo en esencial a medida que se desarrollan nuevos fármacos que influyen en el

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conocimiento y las emociones. También ayudará a que la psiquiatría sea reconocida finalmente como una especialidad médica más. © 2006 Published by Elsevier B.V.

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1. Introduction

The frustrations of trying to understand mental disorders were a powerful motivation for development of one branch of Darwinian medicine. As I finished my psychiatry residency, all the usual subspecialties seemed too narrow. Psychoanalysis, behavior therapy, family therapy or so-called biological psychiatry each seemed to have a hold of a different leg of the elephant. The integrative framework of the time, the "biopsychosocial model", seemed full of good intentions but lacking in substance.

Then, thanks to conversations with biologists and reading Williams, Wilson, Dawkins, Alexander and Mayr, among others, it suddenly became clear that all biological phenomena needed two kinds of explanation and that medicine was using only one half of biology. It was looking only for proximate explanations for how the body works and the mechanisms that explain why one person gets sick and another does not. Few doctors were asking why the body's mechanisms are the way they are and, in particular, why so many are so vulnerable to failure. The evolutionary half of biology had yet to be applied to medicine.

The situation was somewhat better for studies of behavior. By the early 1980s, evolution was the established foundation for understanding animal behavior, but it was only beginning to be applied to human behavior [1,2]. The time was ripe to begin to use evolution to understand behavioral and emotional problems. In the intervening decades, progress has come slowly, but we now are at the point where an evolutionary approach can help not only to explain vulnerability to specific disorders but also to provide a framework to unify psychiatry. The route to this goal is, however, via first understanding why diseases exist at all.

While I was working on my long-standing interest in the evolution of senescence [3], I began looking for an evolutionary biologist who might want to tackle the problems of medicine. In a remarkable bit of good luck, George Williams, the very architect of the most interesting evolutionary explanation for senescence, among his many contributions [4], was at the same time looking for a physician who wanted to take an evolutionary look at disease. When we began talking, it soon became clear that asking evolutionary questions about disease was a novel venture that might be very useful. Early on, we recognized that we were not trying to explain the evolution of disease, but instead wanted to know why natural selection had left the body so vulnerable to so many diseases. The key was to ask why natural selection had not shaped a body less vulnerable to disease [5].

Such questions about why we are all alike in our vulnerability are fundamentally different from most medical research that attempts to find out why some people are different in ways that results in disease. As Tinbergen and Mayr have emphasized so effectively, these are fundamentally different questions and both deserve their own independent answers [6,7].

Asking about the body's design is also somewhat different from the well-established body of knowledge about evolution and disease, namely, the large body of knowledge on the evolution of pathogens [8]. With antibiotic resistance, you can watch natural selection happening in the lab, or even more frightening, in the general population as useful antibiotics one by one become useless as bacteria evolve resistance. Knowledge about such pathogen evolution is crucial for medicine, has direct benefits, and is an essential component of Darwinian medicine, but we wanted to focus instead on why selection leaves us vulnerable.

It the midst of all the wonderful progress described in this volume giving deeper understanding of specific diseases, it is important to emphasize that the most important advances offered by an evolutionary approach to disease are as simple as they are powerful. The single most important advance is recognition that medicine has, so far, made use of only one half of biology [9]. Asking evolutionary questions about why natural selection has left our bodies vulnerable to disease will bring us deeper understandings of the body and disease, understandings that will make medicine and public health more effective. The previous common answer to this question has been "natural selection is a random process that can't create perfection, so of course the body will be vulnerable to disease". This is, indeed, one reason why we are vulnerable to disease, but it is only one. The other five also need careful consideration.

2. Six reasons for vulnerability

The reasons why we are left vulnerable to disease can be summarized in six categories [9,10]. The first two, mismatch and co-evolution, reflect the slowness of natural selection. If selection were much faster, these vulnerabilities could be overcome. The next two, constraints and design trade-offs, reflect limits on what selection can do no matter how much time is available. The last two, reproductive success at the expense of health and defenses, are not really vulnerabilities at all, but they need to be on the list because they so often are confused with design deficits. Each reason for vulnerability deserves brief mention with an example or two from physical diseases to provide the foundation for proceeding to the mental disorders (Table 1).

3. Novel environments

We live in an environment vastly different from the environment we evolved in and much disease arises from the mismatch. Examples abound, from the current epidemic of obesity, to drug abuse and even breast cancer. These disorders were rare when humans

Table 1
Six evolutionary reasons for vulnerability to disease

1. Mismatch between our bodies and novel environments
2. Co-evolution of hosts and fast-evolving pathogens
3. Constraints on what natural selection can do
4. Design tradeoffs
5. Traits that increase reproductive success at the expense of health
6. Defenses that are useful even though aversive

lived in small groups on the African savannah. They were rare not only because people lived less long. Even adjusted for life span atherosclerosis, drug abuse and breast cancer are vastly more common. Much of the difference comes from diet and activity levels. Most physicians recommend keeping cholesterol levels below 200 mg/dl, but even at these levels many people die from heart attacks. In today's indigenous populations, cholesterol levels are in the range of 120 to 130 and heart attacks are rare, even in older adults [11].

Breast cancer is also much more common in modern societies. The crucial environmental factors seems to be birth control and bottle feeding, which together greatly increase the number of menstrual cycles. In populations without birth control, women have an average of just over 100 menstrual cycles in a lifetime, while modern women have on average over 400 [12,13].

Myopia is another example. The rate is quite consistent at about 30% in modern populations and variation in nearsightedness arises mostly from genetic differences. Does this mean it is a genetic disease? Consider that myopia is rare in people who have not been to school. The genes that cause myopia are not defects, but "quirks" that cause no harm except when they interact with an environment that includes early reading. When the genes interact with early reading, nearsightedness is very likely.

Novel environmental factors should be the first suspect for common chronic diseases that strike modern people much more frequently than those living in a more natural environment. Such diseases account for at least half of hospitalizations. This does not mean that we would be better off living as hunter-gatherers did. But it does help to focus the search for the causes of these diseases [14].

4. Co-evolution

We remain vulnerable to infectious disease simply because pathogens evolve so much faster than we do. In fact, it is amazing that multicellular organisms can exist at all in the face of competition from pathogens that evolve 10,000 times faster than we can. This is the simple explanation for our continued vulnerability to plague, influenza and rhinoviruses to say nothing of HIV.

Co-evolution has another cost, however. Each defense we evolve is a new selection force shaping a counter-defense in pathogens, which then further shapes our defenses in a never-ending arms race that results in mechanisms as expensive and dangerous as the nuclear weapons in the cold war. Many autoimmune disorders result from such arms races, especially when pathogens imitate our antigens making it difficult to attack them without also damaging our own tissues. Rheumatic fever is a good example.

5. Constraints

There is much natural selection cannot do. Some useful mutations never occur, others are created then lost by mere chance. Some harmful genes go to fixation by chance. However, there are many other reasons selection cannot make the body perfect. Especially important is path dependence. Most aspects of the body depend of other aspects in ways that suboptimal designs can never be set straight. Just like the pattern of keys on a QUERTY keyboard, once things go a certain way, there is no going back. Among the results are the wandering path of the recurrent laryngeal nerve around the

subclavian artery and the unfortunate long detour the vas deferens takes around the inguinal vessels. The very eye itself is inside out, with the nerves and arteries between the light and the receptors.

6. Trade-offs

Other apparent imperfections arise from trade-offs that are unavoidable in any design, whether from natural selection or human engineers. Our stomachs could be less acidic, but only at the cost of increased infection. Our eyes could see a mouse at half a mile like a hawk's eye can, but then we would not have color vision, depth of field and a wide angle of view. Our bones could be stronger, but then they would be heavier and less flexible. Our immune systems could be more aggressive, but only at the cost of more damage to our own tissues. No trait is perfect; all are compromises.

7. Reproductive success at the expense of health

This is a special kind of trade-off. If a gene somehow increased reproductive success, it will spread in the population even if it harms health. Do such genes exist? The exemplars are behavioral tendencies that increase mating success. The elephant seal commands his harem on a small patch of beach for an entire mating season, defending them against all other males. But the cost is an inability to go out into the ocean to feed. By the end of the season, the male elephant seal has lost hundreds of pounds and few are ever able to regain the strength to again will the competition for a patch of beach. For humans, mating competition is not quite so brutal, but males do die at about three times the rate of females in the early adult years [15]. These excess deaths arise from many causes, although the majority are from vigorous competition and associated reckless behavior.

8. Defenses

Fever, pain, nausea, vomiting and fatigue are not diseases, they are useful defenses. Their expression is regulated by mechanisms shaped by natural selection. Most are aversive, so they seem like problems. However, people who lack an ability to experience pain or an ability to cough die young. If natural selection shaped these defenses, then how can we so safely use drugs to block them? The answer is summarized in the "smoke detector principle" [16]. The costs of expressing defenses is so low compared to the cost of not expressing a defense when it is needed, that natural selection shaped mechanisms that expresses defenses often when they are not needed in order to ensure that they are always expressed when they are needed. Closely related is "The Clinician's Illusion", the tendency to think that defenses are abnormalities, instead of recognizing them as adaptations. Both the smoke detector principle and the clinician's illusion have special important applications in psychiatry.

9. Mental disorders

Some mental disorders, such as Alzheimer's disease, are readily recognizable as diseases little different from diseases such as diabetes or stroke. Other mental disorders,

however, are different from medical problems like diabetes. Behavioral problems such as addiction or episodes of violence get tangled up in our notions about will and self control. Other disorders involve emotions that seem useless such as jealousy and depression. While all mental disorders arise from brain mechanisms, only some are caused by primary neural abnormalities. Many more seem to involve problems more at the software than the hardware level. A theme of evolutionary psychiatry is that mental disorders are indeed real medical disorders no matter where they originate. However, bringing a genuine medical model to psychiatry changes the focus substantially from simple description of syndromes, to a search for the life situations that arouse aversive emotions. More about that in a moment. First, it is worth noting that, compared to other medical disorders, mental disorders are anomalous on several counts.

First, mental disorders are vastly common, affecting about half the population. Most of these common disorders are dysregulated emotions, mainly excessive anxiety and depression, but addiction is nearly as common. While some medical disorders such as arthritis are very common, no other disorders compare to mental disorders in terms of their impact on disability adjusted lost years (DALYs) for adults [17]. For women of reproductive ages in modern societies, over 25% of all DALYs are attributed to depression. The next most common disorders are schizophrenia, bipolar disorder, traffic accidents and obsessive compulsive disorder. Together, they account for about two thirds of the DALYs. Next on the list is osteoarthritis, the first ordinary medical disorder on the list.

Why do mental disorders so dominate in causing disability and early death. It is partly that they are common, but mostly because their onset tends to be at about the age of reproductive maturity. This is a remarkable and often overlooked fact. No other group of medical disorders arises at this age except those directly related to pregnancy. That is for the good reason that natural selection tends to select for modifier genes that shift the expression of deleterious traits later and occasionally earlier in life. The onset of many mental disorders at the age of first reproduction is an important clue.

Another anomaly and clue is the massive comorbidity of mental disorders [18]. In most epidemiological studies, a small proportion of the population, about 15%, tends to have over half of the diagnoses. People with anxiety are likely to also have depression, drug users are likely to have depression or bipolar disorder, and individuals with schizophrenia or obsessive compulsive disorder or eating disorder are likely to also have depression or anxiety disorders. This massive comorbidity should tell us something important about mental disorders.

Finally, the heritability of mental disorders is notable [19]. It is not far off to generalize globally that about half of the variation in vulnerability to most mental disorders arises from genetic variation. More surprising is the increasing likelihood that our efforts to find specific genes that account for specific disorders will be disappointed. So far, we have found no specific genes with major effects on the major mental disorders, not even for those like schizophrenia and bipolar disorder that are overwhelmingly heritable. These diseases greatly decrease Darwinian fitness. Why, then, hasn't natural selection eliminated the responsible genes? This is an evolutionary question, one that cannot be answered by proximate studies.

The utility of an evolutionary approach to mental disorders is best illustrated by specific examples. First, however, an evolutionary perspective offers a framework to beginning to

make sense of the confusion that surrounds psychiatric diagnosis. The primary problem arises because the criteria are intentionally based on no theory at all. This was a reaction to the domination of psychoanalytic ideas and it has helped to bring objectivity to diagnostic criteria. However, it also ignores the most fundamental distinction in the rest of medicine that between diseases and symptoms of diseases. When a patient comes to a physician complaining of a cough, the doctor does not look up the diagnosis in a table of cough disorders. Instead, the doctor knows that the cough is not the disease, the cough is the body's useful response to a disease. Observation of a cough sets off a search for what is arousing it. Likewise for fever, vomiting and pain. In psychiatry, however, there are a variety of diagnoses for anxiety disorders and mood disorders. Some psychiatrists continue to search for the causes using a detailed interview probing about every aspect of a patient's life. This is a truly medical model for psychiatry, one that distinguishes disorders from symptoms and that goes looking for what is causing a symptom. Other practitioners go directly from diagnosis to drug treatment, however, never looking for what might be arousing this emotion in this person's life now.

In many cases, this does no more harm than giving aspirin to someone with a fever. Also, since individuals vary so much in their reactions to life circumstances, it is often hard to recognize how experiential factors interact with these predispositions to give rise to disorders. However, failing to look for the causes of a negative emotion is as serious a medical error as failing to look for the cause of cough or fever.

The evolutionary version of the medial model for psychiatry suggests three broad categories of mental problems [20]. First are those, such as schizophrenia, autism, obsessive compulsive disorder and bipolar disorder, which arise from primary brain abnormalities with high heritability. Here the evolutionary question is why the responsible genes persist despite their dire effects on fitness. Second are disorders of emotional or behavioral dysregulation such as addiction, anxiety and depression. Here the question is how those responses are useful, how they are usually regulated and why the regulation mechanisms have failed. Third and finally, there are affective states that are aversive or socially unacceptable but nonetheless normal, or at least useful for the genes. Examples in each category illustrate the breadth of what evolution offers to psychiatry.

10. Schizophrenia

Existing data have long documented the overwhelming effect of genetic differences on schizophrenia. Recent data confirm that the Darwinian fitness of individuals with schizophrenia is very low, about half that of average [21]. One popular notion has been that schizophrenia is somehow useful, a variation that gives advantages in certain situations. However, the combination of increasing evidence for brain damage and the very low Darwinian fitness of individuals with schizophrenia makes this implausible. Some have suggested that having someone with schizophrenic tendencies might assist the group, but such ideas are inconsistent with modern understanding of the limits of selection at the group level. More plausible are suggestions that the genes that cause schizophrenia are advantageous except in combination with certain other genes or environmental situations. Recent data on the families of siblings of schizophrenics contradict this; sibs of schizophrenics have families of exactly average size. It could be that the benefits do not

increase family size in modern societies, so further investigation of relatives of schizophrenics is warranted. But the experiences of those who have interviewed many such relatives suggest no special abilities and many mild cognitive deficits.

What kind of evolutionary explanation might apply? It may be simple constraints. Data showing increasing risks of schizophrenia with increasing parental age are consistent with as much as a quarter of schizophrenia arising from new mutations in sperm [22]. Genome studies should eventually determine if this is correct.

Another possibility is the cliff-edge effect that was originally proposed by David Lack and colleagues to explain the number of eggs birds lay [23]. Some individual traits, such as height, egg number, speed or intelligence, may confer increasing fitness benefits but extremes of the trait may lead to catastrophic failure for some individuals. For instance, horses bred for speed have increasingly long and thin cannon bones, making them faster, but more vulnerable to a broken leg. If high intelligence or verbal ability has given a major selective advantage in recent millennia, then selection could have pushed these traits quickly to levels so extreme that some individuals "fall off the cliff" because some crucial system fails. This does not necessarily mean that the trait itself causes the failure. It could be, for instance, that a process of neural pruning tunes the system to function efficiently and that a slightly excessive pruning causes schizophrenia. Superficially, it seems that this theory would imply that close relatives of patients would have special abilities. However, this does not necessarily follow. The sibs of race horses who break their cannon bones may not be any faster than average race horses. Nonetheless, selection pushing all race horses to extremes explains why they all are vulnerable. The apparent rapid selection for special human mental abilities could well create comparable vulnerabilities.

Bipolar disorder could arise from related factors, but the remarkable productivity and sexuality of people with bipolar disorder suggests a stronger case for the possibility that genes causing bipolar disorder give a selective advantage, or are at least neutral [24]. The missing foundation for understanding of bipolar illness is knowledge about what mood is for. Put another way, we need to look for the disadvantages experienced by individuals who lack any capacity for mood variation.

Autism is another highly heritable disorder with devastating effects on fitness. Here the crucial clue is the extreme male biased sex ratio. Some have claimed this reflects an extreme version of the male brain [25]. But it also seems likely that the disorder could arise from some abnormality of imprinted genes, which are expressed only if they come via the mother or only if they come via the father. A strong case has been made for such factors influencing the IGF2 genes in the causation of very large or small babies [26]. Individuals with Turner's syndrome offer a natural experiment because they have only one X chromosome and no Y chromosome. If the X comes from the father they tend to be mentally fairly normal, but if the X comes from the father, rates of ADHD and other disorders are high [27].

11. Anxiety disorders

It is easy to recognize the utility of anxiety. It protects us in dangerous situations. A detailed evolutionary assessment of anxiety disorders offers several useful conclusions, however [28]. The first is that not all anxiety disorders are disorders at all. Some are

certainly simply the extreme high end of a normal distribution. Because the anxiety is aversive, it is easy to call it a disorder. We will have to wait to better understand just how and when anxiety offers advantages to know when anxiety levels are truly harming fitness.

The second insight is related. Just as there are disorders of excessive anxiety, there are disorders of deficient anxiety, the hypophobias. Patients do not complain of too little anxiety so they do not come to clinic requesting drugs to increase anxiety levels. Instead, patients with hypophobia are likely to be found in the emergency room, the court room and jail.

Another evolutionary insight is about the subtypes of anxiety. Much ink has gone into trying to decide if they are fundamentally different or fundamentally the same. From an evolutionary view, however, they are subtypes partially differentiated from a more generic precursor.

12. Emotions in general

Most mental disorders are emotional disorders, but many mental health clinicians have only a dim notion of what emotions are. Emotions are special states shaped by natural selection to adjust multiple aspects of the body and mind to foster effective coping with the adaptive challenges that arise in a particular kind of situation [29,30]. Emotions are software for the mind, adjusting the machine to cope with current tasks. There is a good evolutionary reason why essentially all emotions are either positive or negative. Any situation that did not pose a threat or an opportunity would not shape a special state. The positive emotions seem normal and the aversive emotions seem maladaptive but this is an illusion. No emotion is useful or not except in relation to a particular situation. There has been great emphasis on disorders of excessive negative emotion or deficient positive emotion. An evolutionary perspective suggests the need to exert equal effort for understanding disorders of excessive positive emotion and deficient negative emotion. A functional perspective on emotions is one of the more profound contributions evolution offers to psychiatry.

13. Depression

Depression is a world wide scourge. It seems maladaptive at any level of severity and it causes far more disability and death than any other psychiatric illness, nearly as much even as cancer and heart disease. Recent efforts have looked to the brain to find the responsible abnormalities. There are certainly brain mechanisms that mediate mood and they certainly are abnormal in many who suffer from depression. However, there are good reasons to think that mild states of low mood are useful. If they were not, they would not exist. An evolutionary perspective suggests that we are missing the most fundamental information needed to understand depression, namely, the normal functions of normal low mood [31]. With that information in hand, we can make faster progress unraveling the mechanisms that regulate mood as a basis for understanding why they go wrong so often.

When could states of pessimism and low motivation be useful? When all available options involve costs and risks that are greater than anticipated benefits, the best thing to do is nothing. When an individual is unable to find a way to get something crucial to his or her core meaning in life, then efforts in other domains will be poorly spent. It may be

better to pull back and wait and consider other routes to the goal or possibly even giving up a major life goal. This insight has immediate application in the clinic. One patient became depressed when he realized that his fiancée was socially out of his league and would never really marry him. Another had devoted her life to keeping her daughter off drugs, but as soon as the daughter left home, she moved in with a drug dealer leaving her mother helpless and distraught. In both cases, depression resolved only when the goal was given up.

Far from suggesting that all depression has the same origins, an evolutionary perspective suggests that there are many different kinds of depression with many different etiologies. Some may arise from brain mechanisms unrelated to those that normally regulate mood. Others start from personality problems, drug abuse or bipolar genetic tendencies. New evidence suggests that different precipitants for depression give rise to different symptoms of depression [32], thus encouraging consideration of the possibility that what appears to be a consistent syndrome may actually be a collection of emotional responses different situations involving loss or inability to reach crucial goals. An extensive body of knowledge in psychology supports some of these ideas [33,34]. Evolution inspired attention to the functions of mood could bring modern psychology to psychiatry.

Any discussion of the potential utility of a syndrome as devastating as depression is prone to misunderstanding [35]. An evolutionary approach does not say that depression is useful, only that low mood is useful and that we cannot know when more intense states of low mood are or are not useful until we better understand their functions and normal regulation. The smoke detector principle and the clinician's illusion certainly apply here. The analogy with physical pain helps to prevent misunderstanding. The capacity for pain is normal and useful and people who lack it die young, but chronic pain is common, abnormal and devastating. Depression is mental pain, useful in general and in some situations, but prone to excess expression in some situations.

14. Understanding individuals

A behavioral ecological perspective offers a framework for understanding individual human lives that can begin to link the clinician's detailed understanding with larger frameworks that reveal common patterns. For instance, every life consists of a sequence of activities, pursued for a certain length of time. Why do we eat for 30 min or so and then go on to something else instead of eating for a minute every hour or a few hours every few days? Why do we socialize for a few hours, and then tire of it and seek solitude. Why do we get lonely when see few friends? Why do we so often feel torn between doing something that benefits ourselves now versus doing something that will help someone else now at some personal cost? In broad outline, the answer is that all organisms must constantly make decisions about where to invest their time and resources. This is not a personal problem or a pathology of modern life, it is the essence of decision-making for all animals. Far from a cold impersonal view of humans as simple animals, an evolutionary perspective encourages a deep understanding of individuals. Furthermore, it tends, done right, to encourage a deep empathy for the real difficulty of their life situations.

15. What evolution offers psychiatry

An evolutionary approach to psychiatry will eventually ground the field in the well-established principles used to understand the normal behavior of all other organisms [20,36]. This foundation for understanding human behavior should provide the kind of functional understanding of normal function that physiology provides for the rest of medicine. This framework may be able to provide the long-sought connections among proximate studies at different levels and the many kinds of interventions that now are seen as competing. Diagnosis needs not remain atheoretical. We can begin to separate those disorders that arise from defects from those that are dysregulated defenses. Taken together with a deeper understanding of individuals and how relationships work, evolution provides much of the missing foundation for understanding mental disorders. It encourages a truly medical, truly biological model for psychiatry. This means something very different from the current preoccupation with proximate brain mechanisms. Instead, it means separating symptoms from diseases and looking at the interactions among all levels that result in mental disorders in some individuals. This knowledge will be helpful.

References

[1] Alcock J. Animal Behavior: An evolutionary approach. 4th ed. Sinauer, Sunderland, Mass; 1989.
[2] Tooby J, Cosmides L. Evolutionary psychology and the generation of culture: Part I Theoretical considerations. Ethol Sociobiol 1989;10:29–50.
[3] Nesse RM. Life table tests of evolutionary theories of senescence. Exp Gerontol 1988;23:445–53.
[4] Williams GC. Pleiotropy, natural selection, and the evolution of senescence. Evolution 1957;11: 398–411.
[5] Williams GW, Nesse RM. The dawn of Darwinian medicine. Q Rev Biol 1991;66:1–22.
[6] Mayr E. How to carry out the adaptationist program? Am Nat 1983;121:324–33.
[7] Tinbergen N. On the aims and methods of ethology. Z Tierpsychol 1963;20:410–63.
[8] Ewald P. Evolution of infectious disease. New York: Oxford University Press; 1994.
[9] Nesse RM, Williams GC. Why we get sick: the new science of Darwinian medicine. New York: Vintage Books; 1994.
[10] Nesse RM. Maladaptation and natural selection. Q Rev Biol 2005;80:62–70.
[11] Eaton SB. Human, lipids and evolution. Lipids 1992;27:814–20.
[12] Eaton S, Pike M, Short R, Lee N, Trussell J, Hatcher R, et al. Women's reproductive cancers in evolutionary context. Q Rev Biol 1994;69:353–67.
[13] Strassmann BI. The biology of menstruation in *Homo sapiens*: total lifetime menses, fecundity and nonsynchrony in a natural fertility population. Curr Anthropol 1997;38:123–9.
[14] Eaton SB, Strassmann BI, Nesse RM, Neel JV, Ewald PW, Williams GC, et al. Evolutionary health promotion. Prev Med 2002;34:109–18.
[15] Kruger D, Nesse R. Sexual selection and the male:female mortality ratio. Evol Psychol 2004;2:66–85.
[16] Nesse RM. Natural selection and the regulation of defenses: a signal detection analysis of the smoke detector principle. Evol Hum Behav 2005;26:88–105.
[17] Murray CJ, Lopez AD. Global mortality, disability, and the contribution of risk factors: global burden of disease study. Lancet 1997;349:1436–42.
[18] Kessler RC, McGonagle KA, Zhao S, Nelson CB, Hughes M, Eshelman S, et al. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States: results from the national comorbidity survey. Arch Gen Psychiatry 1994;51:8–19.
[19] Tsuang MT, Tohen M. Textbook in psychiatric epidemiology. 2nd ed. New York: Wiley-Liss; 2002.
[20] Nesse R. Evolutionary psychology and mental health. In: Buss D, editor. The evolutionary psychology handbook. John Wiley and Sons.

[21] Shaner A, Miller G, Mintz J. Schizophrenia as one extreme of a sexually selected fitness indicator. Schizophr Res 2004;70:101–9.
[22] Malaspina D, Corcoran C, Fahim C, Berman A, Harkavy-Friedman J, Yale S, et al. Paternal age and sporadic schizophrenia: evidence for de novo mutations. Am J Clin Genet 2002;114:299–303.
[23] Nesse RM. Cliff-edge fitness functions and the persistence of schizophrenia. Behav Brain Sci 2004;27:862–3.
[24] Wilson DR. Evolutionary epidemiology and manic depression. Br J Med Psychol 1998;71:375–95.
[25] Baron-Cohen S. The extreme male brain theory of autism. Trends Cogn Sci 2002;6:248–54.
[26] Haig D. Genomic imprinting and kinship. New Brunswick, N.J: Rutgers University Press; 2002.
[27] Skuse DH. Imprinting, the X-chromosome, and the male brain: explaining sex differences in the liability to autism. Pediatr Res 2000;47:9–16.
[28] Marks IM, Nesse RM. Fear and fitness: an evolutionary analysis of anxiety disorders. Ethol Sociobiol 1994;15:247–61.
[29] Nesse RM. Emotional disorders in evolutionary perspective. Br J Med Psychol 1998;71:397–416.
[30] Tooby J, Cosmides L. The past explains the present: emotional adaptations and the structure of ancestral environments. Ethol Sociobiol 1990;11:375–424.
[31] Nesse RM. Is depression an adaptation? Arch Gen Psychiatry 2000;57:14–20.
[32] Keller MC, Nesse RM. Is low mood an adaptation? Evidence for subtypes with symptoms that match precipitants. J Affect Disord 2005;86:27–35.
[33] Gilbert P. Depression: the evolution of powerlessness. New York: Guilford; 1992.
[34] Nesse RM. Evolutionary explanations for mood and mood disorders. In: Stein DJ, Kupfer DJ, Schatzberg AF, editors. The American Psychiatric Publishing textbook of mood disorders. Washington DC: American Psychiatric Publishing; 2006.
[35] Nettle D. Evolutionary origins of depression: a review and reformulation. J Affect Disord 2004;81:91–102.
[36] McGuire MT, Troisi A. Darwinian Psychiatry. Cambridge, MA: Harvard University Press; 1998.