Research Commentary

Evolutionary Thinking as a Tool in Pharmaceutical Development

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ABSTRACT The rapidly expanding technologies involving chemical synthesis and screening, genomics, and bioinformatics are leading to the point where every gene product can be modulated as a therapeutic target. Thus, pharmaceuticals increasingly offer the potential to control disease processes. While great strides in understanding disease processes can come from this mechanistic approach (addressing “how?” questions), complete understanding is impossible without addressing the ultimate causation of disease processes. By addressing ultimate (“why?”) questions, evolutionary thinking provides a firm theoretical framework for all biological processes, including those relating to disease. Of practical relevance for pharmaceutical development is an increased awareness of evolved responses and potential consequences of bypassing these defenses. Examples involving reproductive medicine, components of the acute phase response, apoptosis, and axonal regeneration are discussed. Drug Dev. Res. 52:439–445, 2001. © 2001 Wiley-Liss, Inc.

Key words: evolution; pharmaceutical preparations; reproduction; acute-phase reaction; apoptosis

INTRODUCTION

Tremendous strides are being made in biomedicine and pharmaceutical development through ever-expanding technologies such as molecular biology, computing, and high-throughput screening of compounds for efficacy. It may be anticipated that the functions of every gene product will be discovered and that the activity of every gene product can be modulated by a potential pharmaceutical. Thus, pharmaceuticals will offer the ability to manipulate virtually every disease process. Researchers are comfortable seeking to understand function in terms of how processes work and what each component does; i.e., the proximate or mechanistic function. However, every biological phenomenon also has a function in terms of why the process and components exist, i.e., the ultimate or evolutionary function. Unfortunately, the evolutionary function is frequently ignored. This commentary will emphasize that the complete understanding needed for effectively and safely modulating disease processes requires consideration of evolutionary as well as mechanistic function.

Evolutionary thinking can offer useful perspectives for medicine in general [Stearns, 1999] and for pharmaceutical discovery and development in particular. The term “Darwinian medicine” was introduced in 1991 in an effort to bring to medicine the great advances in understanding that evolutionary theory had brought to biology [Williams and Nesse, 1991]. The goal of Darwinian medicine is to understand why medically related phenomena are the way they are. This has practical implications for pharmaceutical development.

Phenomena that appear to be paradoxically harmful, costly, or defective are ripe for careful examination. Systems and processes that appear overly prone to malfunction also merit evaluation from an evolutionary viewpoint. Illustrative examples to be discussed include: the low survival rate from conception to birth, morning sick...

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ness, components of the acute phase response, cell death, and the limited regeneration of axons in the central nervous system. Careful examination of the evolutionary or ultimate function of a trait or phenomenon is especially important in pharmaceutical development because it is becoming increasingly easy to therapeutically “correct” apparent defects. The evolutionary approach asks why apparent defects persist, especially those that should be simple for natural selection to have corrected.

A first, and key, step is to determine whether or not a phenomenon or condition is an adaptation or is a maladaptation or dysfunction. Nesse and Williams [1998] categorized evolutionary explanations for disease vulnerability, including: host defenses, genetic conflict, design trade-offs, historical design constraints, and environmental changes such that the phenomenon is no longer adaptive. Whether a phenomenon is an adaptation may depend on the individual circumstances. Evolutionary concepts pertaining to aging emphasize that diseases of aging are in part due to reduced selection pressure for survival in postreproductive life [Kirkwood and Austad, 2000]. Similarly, traits harmful in the elderly can be selected for if they are even slightly beneficial earlier in life [Williams, 1957], e.g., a high propensity for blood clotting can be beneficial early in life, although especially harmful later. Another aspect of Darwinian medicine notes that many chronic human diseases (e.g., diabetes, atherosclerosis, hypertension, and certain cancers) occur because of “discordance between our current life-style and the one in which we evolved” [Eaton et al., 1988]. On the other hand, Cochran et al. [2000] used evolutionary thinking in suggesting that there may be an infectious component to many chronic diseases. In regard to host defenses, Ewald [1980] noted that in infectious diseases it is critical to determine which party, the pathogen or the host, is benefiting from the phenomenon or condition. Genetic conflict, not limited to host–pathogen relationships, has implications critical to understanding the basis for evolved responses. In this commentary I will concentrate on the value of recognizing host defenses or, more broadly, evolved responses, in pharmaceutical development.

**Evolved Responses/Defenses**

The recognition of evolved responses or defenses is particularly relevant to pharmaceutical development so that the potential consequences of bypassing those defenses can be predicted. The defense or evolved response, at either the cellular or whole body level, is a reaction to a potentially harmful situation. In many instances the evolved response is a compensatory mechanism to maintain homeostasis. Often the evolved response is effective because it is an unpleasant condition to be avoided, as in the case of acute pain, hunger, thirst, muscle exhaustion, or anxiety. Ultimately, selection is for reproductive success—the individual’s comfort rarely plays a role [Nesse and Williams, 1998]. Because evolved responses/defenses are generally costly and are often unpleasant and involve tissue harm, they are prime targets for pharmaceutical intervention. In most cases, though, targeting the evolved response does not get at the underlying cause of the problem.

Evolved responses may be obvious—acute pain and clotting are examples. Other defenses are well understood, but require some medical knowledge to recognize; e.g., inflammation as a defense against infection. The function of other defenses can be rather subtle, such as spontaneous abortion and other pregnancy responses, components of the acute phase response, and apoptosis. Other apparently harmful phenomena that are induced by our own gene products, such as failure of axonal regeneration in the central nervous system, should be considered in the broad context of why they evolved.

We all practice Darwinian medicine for therapies where the consequences are obvious. Aspirin inhibits platelet function, thereby reducing the risk of myocardial infarction. The cost is the increased risk of bleeding, a risk worth taking except for those more likely to be involved in accidents or combat or needing surgery. Patients are made aware of this risk. Similarly, corticosteroids are extremely useful for inhibiting inflammation and immune responses, at the risk of infection or increased mechanical injury (in sports). This is common knowledge. The risks are known and the risks are appropriately considered. However, some evolved responses are much more subtle. Consideration of why these phenomena evolved is crucial to safely inhibiting them.

The point of this commentary is not to discourage targeting evolved responses for pharmaceutical intervention. Rather, it is to encourage the recognition of an evolved response/defense that is being targeted and to encourage understanding the context in which the response evolved (i.e., its evolutionary function). In many instances defenses are useful only infrequently, but when useful they may be life-saving. With the advent of modern medicine, particularly anti-infectives, surgery, and good supportive care, many defenses can be safely bypassed. But without knowing if a disease condition is indeed an evolved response/defense, we risk being taken by surprise. For pharmaceutical development this surprise may be manifest as 1) lack of efficacy in preclinical or clinical studies, 2) as unacceptable “side effects” in clinical studies, or 3) as rare but serious consequences arising after the drug is marketed. In our present litigious society, it is not enough that the overall benefits of the drug outweigh the risks. The risks of therapy must be understood and conveyed to the patient.
EXAMPLES OF POTENTIAL THERAPEUTIC TARGETS INVOLVING EVOLVED RESPONSES

High Incidence of Pregnancy Loss

The incidence of pregnancy loss, estimated at 60–80% from the time of fertilization and 30–40% from the time of implantation [Roberts and Low, 1975; Haig, 1999; Lockwood, 2000], appears excessively high for a phenomenon that has had ample time to be perfected. This apparent inefficiency is especially paradoxical since it involves reproduction, which is fundamental to evolutionary fitness. The concept of genetic conflict, in which the genetic interests of two or more genetic entities are not identical, offers a useful perspective and is a key concept in evolutionary thinking. In medicine, genetic conflict is important in host–pathogen interactions, in host–tumor cell interactions, and even between genes within a cell (e.g., viral vs. host genes, pro-neoplastic vs. anti-neoplastic genes). Genetic conflict plays a central role in reproduction, involving female–male and parent–offspring interactions. Haig [1993, 1999] has applied genetic conflict theory to maternal–conceptus interactions. The resulting analysis has permitted an understanding of reproductive endocrinology that would otherwise be impossible. In the case of the high incidence of pregnancy loss, the genetic conflict is between the mother and the conceptus (which is only 50% related to the mother) and when infections are involved genetic conflict also involves the infectious organism.

Perhaps the major cause of pregnancy loss is due to genetic/developmental defects, and these typically occur very early in pregnancy [Roberts and Low, 1975; Hermonat et al., 1997; Lockwood, 2000; Semprini and Simoni, 2000]. The genetic conflict arises because the mother’s overall genetic interests are served by early and high reproductive success. The conceptus’ genetic interests are served by its own survival and the resources it can extract from the mother at the expense of its siblings. Genetic conflict theory recognizes that the conceptus is 50% related to its full siblings (both in the womb and from other pregnancies) and is 25% related to half-siblings (from a different father), so there are limits to the resources it is expected to extract. The mother benefits by allotting her limited resources (nutrients and time) to maximize her reproductive efforts. If the conceptus is defective and unlikely to survive and reproduce, then early (rather than later) pregnancy loss can be seen as an example of one of many stages of maternal selection to maximize her lifetime reproductive contribution to future generations. This maternal selection includes mate selection and the male–female genetic conflict involved in sperm selection by her reproductive tract and egg (explaining why the female reproductive tract requires millions of sperm to fertilize one egg). Maternal selection for high-quality offspring continues during implantation, through pregnancy, and even beyond [Wedekind, 1994].

Another important cause of abortion or premature delivery is infection. Viral infection is thought to be important early in pregnancy [Hermonat et al., 1997]. Bacterial infection has come to be recognized as an important cause of premature delivery, a major problem in obstetrics [Goldenberg et al., 2000]. Although there have been numerous attempts to therapeutically delay delivery, it has not been feasible to delay delivery by more than a week except with the use of antibiotics [Goldenberg and Rouse, 1998]. Besides the risk of infection to the fetus, reproductive tract infection can compromise the mother’s subsequent reproductive efforts. In addition, pregnant women appear to be at increased risk from a variety of infectious diseases [Brabin, 1985; Diagne et al., 2000]. In this context, pregnancy loss during uterine infection can be viewed as a maternal defense against carrying a defective (infected) fetus and as a means of clearing the infection. Intrauterine infection during pregnancy is a three-way genetic conflict—among the two hosts and the pathogen. Inflammatory mediators (e.g., prostaglandins) and proteases are mechanistically associated with delivery [Goldenberg et al., 2000; Lu and Goldenberg, 2000]. Because inflammation is an evolved response to infection, it is logical that inflammation would also be associated with delivery, as an ultimate defense against uterine/fetal infection.

The practical implication is that drugs that directly inhibit pregnancy loss or delay premature delivery are countering a maternal evolved response, and therefore involve some level of risk. On the other hand, potential drugs that function by reducing genetic or developmental defects or by preventing infection get to the underlying problem, and thereby obviate this risk.

Morning Sickness

This is a paradoxical phenomenon that had long been in need of an evolutionary explanation. Since morning sickness seems harmful (to the mother and possibly to the embryo) and is hormonally induced, why does it persist? One of the more well-known applications of Darwinian medicine principles is the hypothesis that morning/pregnancy sickness is actually a maternal defense against toxins in foods [Hook, 1978; Profet, 1992;
Flaxman and Sherman, 2000]. Profet noted that many foods, especially bitter-tasting vegetables, contain a variety of toxins (evolved for the plant’s defense) and that maternal aversion to them is strongest during embryogenesis. In this early part of pregnancy, development is especially sensitive to teratogens, but nutritional demands of the embryo are rather low. The key data supporting her hypothesis are the prior clinical studies showing that morning sickness is associated with a reduction in miscarriage. In a recent review of relevant clinical studies confirming this beneficial effect, Flaxman and Sherman [2000] noted that the frequent aversion to meat during early pregnancy may be related to the ease with which meat becomes contaminated. In applying maternal–fetal conflict theory to morning sickness, Profet [1992] suggested that the embryo, acting through placental hormones, is making the mother sick to protect itself from ingested toxins. Again, this is not to say that morning sickness should not be treated. We need to recognize, however, that without understanding why morning sickness exists unpleasant consequences could occur that affect the patient and her child.

Components of the Acute Phase Response

The acute phase response is a systemic response to infection that also occurs as part of severe trauma and late-stage cancer. As a typical defense it has a number of costly and/or unpleasant components, including fever, listlessness, iron and zinc sequestration, and anorexia/catabolic metabolism leading to cachexia. Yet exactly how each component of the acute phase response functions continues to be an enigma. Since each of these components can be induced by host cytokines acting on specific receptors, and this response has existed throughout vertebrate history, it is safe to say that, overall, each of these components provides more benefit than harm. Fever has long been suspected of playing a role in defending against infection, although exactly how it does so is not entirely clear [Kluger et al., 1996]. The widespread use of fever-reducing drugs suggests that in the majority of cases there is no harm in reducing it; and occasionally fever, as a metabolically costly and potentially tissue-damaging response, may be inappropriately excessive to the infectious threat at hand [Kluger et al., 1998]. The challenge is in understanding the circumstances when an evolved response is likely to be important versus when it can or should be bypassed.

The antinutritional components of the acute phase response seem especially paradoxical. Just when the body should be gathering nutritional resources to mount a strong immunologic defense, iron and zinc are sequestered from most tissues, anorexia develops, and overall metabolism becomes catabolic and apparently inefficient (e.g., loss of amino acids, inefficient use of ketones, insulin resistance) [Long, 1977; Beisel, 1995]. Zinc, in particular, plays numerous key roles in stimulating immune responses [Zalewski, 1996; Shankar and Prasad, 1998]. Tremendous efforts have been expended in combating the antinutritional components of the acute phase response, with the justification that it is a maladaptation with no beneficial role [Espat et al., 1995; Tisdale, 2000]. Other investigators, with an evolutionary bias, recognize that it is an evolved response, one that could easily be selected against if it were more harmful than beneficial [Murray et al., 1978; Hart, 1988; Langhans, 1996]. Iron sequestration is becoming widely recognized as a means of denying a key nutrient to pathogens, particularly extracellular ones [Weinberg, 1984]. Zinc sequestration can also inhibit bacterial and fungal growth [Radke et al., 1994; Santhanagopalan et al., 1995]. It has been suggested that anorexia functions to keep iron (and zinc) levels low [Michie, 1996]. However, the difficulty in accepting these mechanisms as the complete answer is that they do not address intracellular pathogens. Also, it has not been clear that the host would not be harmed at least as much as the pathogen by nutrient deprivation.

A recent hypothesis addressing these concerns combines three principles of apoptosis: 1) nutrient deprivation (particularly of zinc) is a pro-apoptotic stimulus, 2) the most damaged / least functional cells preferentially undergo apoptosis, and 3) apoptosis of infected cells (which are dangerous by fostering the infection) is a host defense [LeGrand, 2000a]. Thus, it is hypothesized that preferential apoptosis of infected cells, enhanced by generalized nutrient restriction, is a means for controlling intracellular infections that complements the benefits of directly keeping nutrients from extracellular pathogens. Again, once the true role of the components of the acute phase response is understood, then the risks of abrogating these components can be reduced.

Apoptosis

There has been a major shift in the perceived significance of cell death within the last decade. Except for limited conditions such as in embryogenesis, cell death had been generally viewed as a pathologic event. With the recognition that cell death can be initiated by the cell itself (apoptosis), this view is changing. Apoptosis is widely recognized as being crucial in development (especially in the brain), in proper immune system function, and in control of neoplasia and viral infections. Apoptosis is becoming recognized as playing a role in inhibiting aging (by allowing replacement of poorly functioning cells) [LeGrand, 1997; James et al., 1998] and in controlling intracellular infections in general [Williams, 1994; LeGrand, 2000b]. Despite published reviews of apoptosis emphasizing the conditions where it appears to be harmful, aberrant, or unchecked, apoptosis is clearly...
an important evolved response. As such, one should give careful consideration before declaring that apoptosis is excessive.

A prime example of seemingly harmful apoptosis involves that of helper T cell lymphocytes in HIV infection. T cell apoptosis can occur following cell infection or even by contact with HIV proteins. Because helper T lymphocytes are at the heart of an effective immune response, their apoptosis has been seen as a fundamental problem and as a target for intervention [Gougeon and Montagnier, 1993; Ameisen, 1994; Famularo et al., 1997]. On the other hand, these cells are infected or at imminent risk of becoming infected and thus pose a danger to uninfected cells. More recently, the value of having HIV-infected cells die is becoming recognized [Antoni et al., 1995; Sandstrom et al., 1996; Chinnaiyan et al., 1997; Sieg et al., 1997].

While apoptosis is a costly defense, the alternative of having infected cells survive and continue producing viruses is even costlier. Early vigorous therapy involving a combination of antiviral drugs at the earliest sign of HIV infection is proving to be especially beneficial [Rosenberg et al., 2000]. As mentioned, the ideal means of controlling disease is to get at the root cause. In this case, stopping viral replication and spread should take precedence over inhibiting the effects of the virus, since the effects may well turn out to be host defenses.

One other potential therapeutic area is the seemingly excessive apoptotic loss of germ cells due to toxins (e.g., chemotherapy) or radiation. Particularly in females this can lead to infertility and to premature menopause, since the supply of female germ cells does not replenish itself after birth (why this should be is an important question in need of an answer). By using inhibitors of apoptosis, it has become possible to keep oocytes that have been exposed to chemotherapeutic agents or radiation from undergoing apoptosis [Morita et al., 2000]. Apoptosis of oocytes is simply an earlier step in the maternal selection for offspring quality. In contrast to selection through pregnancy loss, there is no genetic conflict between the mother and her oocytes, except in the case of anti-apoptotic mutations arising in the germ line. As with inhibiting pregnancy loss, inhibiting apoptosis of oocytes may come with an increased risk of defective conceptuses.

**Limited Axonal Regrowth in the CNS**

When a specific cell type has an unusual restriction one should suspect there is an evolved reason for the restriction. Examples include the limited replication of postnatal neurons and cardiac myocytes and the limited regenerative outgrowth of axons in the CNS. Since axons in the peripheral nervous system can readily regrow, one should suspect that there may be a functional reason why this does not occur within the CNS. Thus, it should be no surprise that proteins have been found that actively inhibit axonal regrowth in the CNS [Chen et al., 2000; GrandPre et al., 2000]. With the knowledge gained from the study of mice with deletion of these genes and the further development of antagonists of these CNS axon growth inhibitors, we are close to understanding the evolutionary rationale for limited axonal regrowth in the CNS.

**CONCLUSIONS**

It is clear that evolutionary thinking greatly facilitates an understanding of the overall disease process. While in some of these examples experts have arrived at the same conclusions without consciously using evolutionary thinking, one simply has to recognize that a phenomenon is an evolved response (although this is not always easy) to reach the question of what might happen if the response were to be bypassed. This question, derived by evolutionary thinking, is crucial to pharmaceutical development because it is at the heart of drug safety.

Consideration of evolutionary principles can have both a moral and financial rationale in pharmaceutical development. The value of recognizing defenses has been mentioned, but there are numerous instances where abrogation of evolved responses (relieving the symptoms) has provided immeasurable relief to patients—and pharmaceuticals take most of the credit. It is obvious, however, that the ideal pharmaceuticals are those that directly address the root cause of the disease, such as anti-infectives, anti-neoplastic drugs, or protective agents. In the final analysis, the physician and the patient must be made aware of the potential trade-offs of therapy, and evolutionary thinking is an essential tool in recognizing those trade-offs.

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**REFERENCES**


