



REVIEW ARTICLE

Evolutionary endocrinology: A pending matter[☆]

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Abstract Twenty years have passed since the foundational article of what is now known as evolutionary medicine (EM) was published. This young medical discipline examines, following Darwinian principles, susceptibility to certain diseases and how we react to them. In short, EM analyzes the final cause of the disease from a historical perspective.

Over the years, EM has been introduced in various medical areas in very different ways. While it has found a role in some fields such as infectious diseases and oncology, its contribution in other areas has been quite limited. In endocrinology, EM has only gained prominence as a basis for the so-called “diseases of civilization”, including diabetes mellitus and obesity. However, many experts suggest that it may have a much higher potential. The aim of this paper is to provide a view about what evolutionary medicine is. Some examples of how EM may contribute to progress of our specialty are also given. There is no doubt that evolution enriches medicine, but medicine also offers knowledge to evolution.

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Endocrinología evolutiva: una asignatura pendiente

Resumen Se cumplen veinte años de la publicación del artículo fundacional de lo que actualmente conocemos como medicina evolutiva (ME). La joven disciplina médica analiza, siguiendo los postulados darwinistas, la susceptibilidad hacia ciertas patologías y la manera cómo reaccionamos a ellas. En pocas palabras, la ME analiza, desde un punto de vista casi histórico, la causa final de la enfermedad.

Con el paso de los años la ME se ha introducido en las diversas especialidades médicas de forma muy diferente. Mientras que ha encontrado su papel en el campo de las enfermedades infecciosas o la oncología, su contribución en otros ámbitos ha sido bastante escasa. En endocrinología tan solo ha obtenido protagonismo como base para las conocidas «enfermedades de la civilización», entre las que se encuentran la diabetes mellitus y la obesidad. No obstante, muchos expertos apuntan que su potencial puede ser mucho mayor. El objetivo del presente trabajo es dar una visión sobre qué es la ME. Asimismo, se dan algunos ejemplos sobre qué nos puede llegar a aportar en el avance de nuestra especialidad. No hay ninguna duda

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que la evolución enriquece la medicina, pero también que la medicina ofrece conocimiento a la evolución.

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Introduction

Schematically, the theory of evolution is based on three main postulates. First, even within a species, organisms are not genetically homogeneous, but show some variations. Second, such variations determine, in some cases, differences in survival rates and reproductive efficacy. Third, natural selection (NS) tends to increase the frequency of variations in individuals who reproduce more, so that those variations increase over the generations.

In 1991, the evolutionary biologist George Williams and the psychiatrist Randolph Nesse¹ published the article that would lay the foundations of what we now know as Darwinist or evolutionary medicine (EM). Before them, very few scientists had approached disease from an evolutionary viewpoint,² and they did so in very specific fields.³⁻⁵ Darwin himself virtually did not address health and human disease in his vast literary output.⁶

In the words of Nesse himself, "EM uses an evolutionary perspective to understand why the organism is not better designed, or why diseases occur".⁷ Integration into the genome of genes that improve reproductive success and elimination over successive generations of genes that decrease biological efficacy would of course be expected.⁸ Based on such a principle, the evolutionary approach to medicine addresses the reason why NS does not eradicate the genetic variants that make us more susceptible to disease and only select the genes that make us more resistant.⁹ Thus, while the traditional approach of medicine investigates the immediate causes of disease, in an attempt to answer formal questions such as "what and "how", EM adds another dimension to that immediate explanation, searching for the "why".¹⁰ Moreover, EM is not only restricted to the evolutionary study of disease but also addresses the physiological responses of organisms to it, many of which often appear to be counterintuitive.¹¹ EM is therefore a historic branch of science, based on the study of the past, and attempts to reconstruct a particular scenario in order to be able to understand the present.

Twenty years after the foundational publication of Williams and Nesse, the new discipline has only made very modest advances and, contrary to the expectations of the authors, is still absent from the teaching programs of most medical schools.¹² In our specific specialty, EM is virtually nonexistent, with only a few exceptions. The purpose of this paper is to describe this undervalued medical discipline and to offer some reflections about it. In addition, some practical examples are given to demonstrate the high potential of EM in the field of endocrinology.

Infectious diseases: The pioneers

The strength of the evolutionary argument varies depending on the type of pathology, but is the greatest in infectious

diseases.³ Williams and Nesse applied the principles of NS to four great examples, in which infection was analyzed in most detail.¹ The simplest and best known case is pathogen resistance to antibiotics. This is an evident and visible example of ongoing, real time evolution. Genetic acquisition by pathogens of tools that make them immune to certain antibiotics was already noted in Fleming's day^{13,14} when investigators became aware that the antibiotic against anti-antibiotic struggle had started many million years before.¹⁵ In fact, host-pathogen interaction is the evolutionary result of hundreds of thousands of years during which both contenders have advanced in an arms race intended to optimize their effects. The clinical translation of an infectious disease, i.e. the symptoms and signs that guide our diagnosis, is the final consequence of the sum of the mechanisms used by the pathogen, the defensive tactics of the host, and the tricks used by both to overcome its opponent's strategy. Thus, the clinical picture is merely a still photo which is the consequence of an evolutionary process. EM has thus allowed us to understand that fever, diarrhea, and cough^{7,16,17} are defensive mechanisms which have evolved to cope with infection, and that the current trend to manipulate or reduce them, so ignoring their true role, may be harmful.

Another question of concern for EM is the understanding of the presence of certain allele variants that make us vulnerable to given diseases and have no apparent evolutionary advantage. Surprisingly, various hypotheses proposed in recent years appear to show that heterozygosis for those genes provides protection against other diseases, most of them infectious in nature and highly prevalent in the past.¹²

Evolutionary oncology: Cancer from another perspective

After infections, oncology is another field of interest for EM. Here, the evolutionary fight between host and pathogen is replaced by the no less tense competition between cells that form part of the same pluricellular organism: cancer and development are two sides of a same coin, as they both have been modeled by the same evolutionary processes.¹⁸ Multicellularity requires the social cohesion of cells that form an organism and the strict prohibition of "clonal escape". From an evolutionary viewpoint, cancer is a reversion to unicellular selfishness.¹⁹ Although medicine reveals to us the various elements favoring cell malignization, the first such element is the basis itself of the principle of Darwinism, as there is no evolution without variation. On the other hand, that same variation is the basis for neoplastic transformation. Increasing research in evolutionary oncology in recent years has resulted in a body of literature large enough to warrant the publication of specific treatises.²⁰

One of the most interesting contributions is the view of carcinogenesis itself as a phenomenon governed by

evolutionary laws, an idea already pointed out more than three decades ago.²¹ The evolutionary alternative to the theory that tumorigenesis is a process where a normal cell experiences a number of progressive genetic changes that eventually convert it into a neoplastic cell is the concept that the cell follows in such a process the same principles explained in the Darwinian scheme.⁶ From this perspective, any neoplasm may be seen as a large population of genetically and epigenetically heterogeneous individual cells.²²

More recently, the evolutionary view of stem cells has provided new data for medical oncology. Stem cells are essential for the renewal and increased longevity of higher organisms, but also represent a source of vulnerability, and many of the most common tumors are currently thought to originate from those cell populations.²³

However, the evolutionary approach does not only help to find theoretical responses, but has also contributed to improving antineoplastic treatments. Darwinian understanding of cancer has led to the construction of more sophisticated models of carcinogenesis, creating mathematical models borrowed from evolutionary and population biology.^{24,25} The objective is to find more effective, safe, and individualized therapies. Thus, the realization that the administration scheme of chemotherapy (pulsed or continuous) may modify response and induce tumor resistance has been one of the most recent contributions of EM.²⁶

The list of contributions of evolutionary biology to oncology is endless, and reminds us of basic questions. Examples of such questions include, among others: Why are we humans so vulnerable to cancer, much more so than primates, our close relatives, and even more as compared to creatures so different from us as reptiles? How has evolutionary pressure helped bring about an immune system so apparently permissive of tumor development?

Nobody questions today the help that an evolutionary view may provide to the study of cancer,²⁷ and Merlo et al. even think that it would be interesting to integrate evolutionary biologists into oncological research groups.²²

Evolutionary endocrinology

The term "evolutionary endocrinology" has rarely been used in the scientific literature, and when used it usually refers not to the human clinical setting, but to the experimental study of other species.²⁸ Endocrinology has attracted interest in evolutionary biology as a means of analyzing its influence on animal behavior, morphology, and development, i.e. it is its "compared endocrinology" side that has been used.²⁹ Its focus on humans has also been on the impact of hormones as mediators of vital strategies,³⁰ which are defined as the set of characteristics that determine the survival and reproductive success of organisms, and which have therefore been selected to maximize biological efficacy.³¹ It has been postulated that the endocrine system guides the organism through its ontogenetic roadmap and is in turn an integral part of the mechanisms that provide it with the plasticity and dynamism required for its adaptation to specific settings.³² As recently stated by Williams,³³ no doubt exists that the hormone system is critically involved in the adaptation and evolution of complex characteristics, maybe to a greater extent than in any other physiological system.

Evolutionary endocrinology has thus not been claimed as a specific component of EM. Despite this, there are different examples that may be used in order to appreciate that our specialty should also take advantage of the Darwinist legacy to achieve a deeper understanding of the field.

Predisposition to certain diseases: thrifty genotypes and diseases of civilization

NS does not work like a fortune-teller, but operates with the limited genetic variations at hand, choosing the most effective variations for the specific moment at which it is operating. The result is that any environmental change makes its action obsolete, and if the change is fast, the imbalance worsens. Over the past 10,000 years, humans have led changes in life conditions. Our genotype has remained anchored in the Stone Age, while our phenotype advances through the 21st century at breakneck speed.³⁴⁻³⁶ The conflict has resulted in the so-called "diseases of civilization",^{37,38} most of which belong to the realm of endocrinology. Endocrinology has thus entered the evolutionary discipline through the back door, sometimes even unconsciously. The pioneering work of Neel on thrifty genotypes³⁹ and subsequent criticism and reinterpretations of his theory⁴⁰⁻⁴⁴ have made us familiar with the idea that obesity,⁴⁵⁻⁴⁸ diabetes mellitus,^{49,50} or insulin resistance⁵¹⁻⁵⁴ are the evolutionary legacies of our ancestors. In recent years, a myriad of researchers have attempted to show the existence of candidate genes as part of the hypothetical thrifty gene.⁵⁵⁻⁶⁰ However, Darwinian explanations for the "diseases of civilization" often lack the necessary rigor and should be more thoroughly analyzed.⁶¹ It should be noted that the majority of studies on this subject have been the work of biologists and even anthropologists, while only a few studies have been published by endocrinologists.

Safer treatments

EM questions the efficacy of the use of laboratory animals as clinical research models. Humans diverged from rodents some 70 million years ago. It should also be noted that, once species are differentiated, their genetic distance tends to increase.⁶² This is especially transcendental in drug safety and efficacy studies, and an unfortunate and fatal example is found in diabetology.

Troglitazone was the first thiazolidinedione marketed for treatment of type 2 diabetes mellitus. It was approved for clinical use in 1997 and withdrawn from the market in 2000 after 94 cases of severe hepatotoxicity had been reported,⁶³ of which 65 proved fatal.⁶² The mechanism of troglitazone toxicity has not been fully elucidated,⁶⁴ but prior studies in rodents had shown no relevant hepatic effects. During the development phase of troglitazone, the mechanism by which it improved insulin resistance was not known. It is now known to activate PPAR γ /RXR. Retinoid X receptor (RXR) is an orphan receptor that heterodimerizes with another nuclear receptor called PXR (pregnane X receptor). PXR in turn activates the expression of CYP3A, a member of cytochrome p450 implicated in the metabolism of more than 50% of commonly used drugs. Troglitazone activates PXR and is metabolized by CYP3A. Jones et al.⁶⁵

showed that troglitazone activates PXR at concentrations similar to those required to activate PPAR γ . This effect is not seen in rodents at equivalent doses, and it has been suggested that the hepatotoxicity of the drug may be related to its action on PXR. We, therefore, see that the potential severe adverse effect of the molecule may have been gone unnoticed because of the undue extrapolation to our species of the results obtained in experimental animals. It is now known that marked differences exist between rodent and human PXR. PXR is a promiscuous nuclear receptor with an affinity for xenobiotic substances that has substantially diverged during evolution.⁶⁵ Marked differences between the various species analyzed in the amino acid sequence of PXR ligand binding domains clearly suggest an extraordinarily rapid and divergent evolution of the gene,⁶⁶ possibly due to particular selective pressures.

However, evolution explains divergent responses not only between species but also between individuals of the same species. Genetic variety is the basis of pharmacogenetics, the branch of pharmacology dealing with the application of molecular technology to the study and development of drug research. The objective is to be able to achieve the most adequate treatment for each patient.⁶⁷ This means an improved efficacy with less side effects. The understanding of intraspecific genetic variability linked to evolution is essential if this objective is to be achieved. In endocrinology, this should help us to improve the inherent flaws in hormone replacement therapies.⁶⁸ This will allow us to decide, possibly once and for all, the adequate doses of thyroxine in hypothyroidism, hydrocortisone in adrenal insufficiency, or GH in GH deficiency.^{68–70}

GH: friend or foe?

One of the characteristic events in critically ill patients (with multiple trauma, extensive burns, or sepsis) is their hypercatabolic state, i.e. increased protein turnover and the resultant negative nitrogen balance. Severity of protein dysregulation is related to prognosis and recovery time. This is why treatment of these patients with growth hormone (GH) was proposed more than two decades ago.^{71,72} GH is one of the most potent anabolic agents. However, the theoretical assumptions on which this treatment was based were brought into question after the 1999 article by Takala et al.⁷³ reporting the results of two studies, one Finnish and the other multinational. In both studies, the mortality rate of critically ill patients who had received GH was virtually two times greater than that of patients not given GH. The main causes of death were multiorgan failure and sepsis.⁷³ The Takala et al. article led to GH treatment being discontinued, but some authors have subsequently questioned the conclusiveness of its results. For example, Raguso et al.⁷⁴ reviewed 42 studies reported and concluded that the mortality rate of critically ill patients does not appear to increase after GH administration, and that the risk of sepsis does not appear to be increased. More than 10 years later, the controversy continues. It is currently postulated that critically ill patients pass through two consecutive, well differentiated phases.⁷⁵ In the most acute phase, GH levels are increased, but there is some degree of resistance to its action because its target hormone (IGF-I) is markedly decreased (possibly due to

interaction with some inflammatory cytokines).⁷⁶ The initial phase is followed by a more chronic phase where a true GH deficiency exists. Some authors have suggested that GH administration would be beneficial in this second phase.⁷⁷

GH is a highly pleiotropic hormone whose role in critically ill patients should be contextualized within the complex stress response system. This sophisticated system is once again the result of evolution and has to be located in the habitat for which it was selected. In the past, seriously ill patients were not admitted to an ICU, did not receive vasoactive drugs, and were not supported with mechanical ventilation. The stress response program is the sum of various "subroutines" with a predominant participation of the neuroendocrine and immune systems. It was positively selected as the best possible response in the setting of critically ill mammals in the past. Today, however, we would have to assess the global significance of the program to be able to determine which of those subroutines continue to be adequate and which have become obsolete (much in the same way as diseases of civilization are analyzed). In the specific case of GH, it has been suggested that in the first phase of the critically ill patient (elevated GH, GH resistance, and decreased IGF-I) the aim should be to provide the beneficial effects of GH, such as immune system activation, but without the specific somatotrophic effects of IGF-I. The end result would be a reassignment of energy expenditure to the most necessary functions for that specific situation.⁷⁶

The evolutionary view of changes detected in severely ill patients may give us the key to determine the suitability of GH treatment and to establish the effectiveness of other strategies whose clinical use is controversial,^{78,79} such as treatment with glucocorticoids,⁸⁰ vasopressin,⁸¹ or thyroid hormones.⁸²

Future prospects

Only evolution can give us the necessary clues for understanding aspects which we accept without questioning but which, in fact, we do not understand. For example, we are used to accepting that only the free fraction of a hormone is metabolically active and its protein bound form only represents a "circulating reservoir". Since the free fraction of most hormones only represents 1–5% of the total hormone, why is such a high amount of molecule produced for such a low performance? Such "waste" is intolerable from the Darwinist viewpoint and there should be a reasonable explanation for it, particularly since stress situations for that given hormonal axis increase the free fraction in a derisory percentage. We may thus wonder whether transporter proteins are, as we have now started to think, something other than mere containers and should rather be considered as functional elements in hormone dynamics.

There is no doubt that the future of our specialty has many open fronts. One of them is the improvement of our understanding of the remote causes of such prevalent diseases as diabetes mellitus or obesity, whereas other diseases also have aroused less evolutionary interest. For example, why is the thyroid gland the organ most commonly affected by human autoimmunity?

As previously noted, another great challenge in endocrinology in the next few years will be the

individualization of adequate doses for hormone deficiencies, an objective for which evolutionary endocrinology may be of great help. For example, the high interindividual variability in levels of most hormones needs first to be understood. The limit accepted as physiological is much higher for endocrine parameters as compared to other variables.³³ All the foregoing tells us that each patient is different and that genetic variations determine specific hormonal profiles which depart from the so-called tyranny of the golden mean.³³

Finally, evolutionary endocrinology should be of help for avoiding errors made in the past and for facing the future with tools which are safer both when treatment is administered and when new diagnostic or therapeutic strategies are assessed. EM should undoubtedly be helpful for facing the new challenges posed by society. We must take advantage of it as a guide for devising a consistent approach to increasingly demanding problems which are not strictly medical, such as what could be called the "endocrinology of esthetics" or the "endocrinology of ageing".⁸³

Conclusions

An engineer who faces recurrent problems in a machine he has designed should not only examine the specific problem, but should also analyze the original design to understand the root of the problem.¹⁹ EM is a discipline that complements current medicine. Its unified principle allows for an adequate understanding of human biology and disease,¹¹ provides a historical perspective, and stresses aspects often not considered in our current technified science. For example, EM emphasizes interaction between the organism and the environment, showing that disease cannot be understood without a deep knowledge of both.⁹ EM offers principles that may be applied at any level of biological systems, becoming a unifying frame for a global interpretation of biological events which would otherwise appear unintelligible.⁸⁴

After regretting the delay of medicine with regard to other biological sciences, the extensive work by Williams and Nesse ended with a song of hope for the future of what they called in 1991 the "dawn of EM".¹ They had no doubt about what EM could contribute to modern medicine and proposed changes in order to have it taught at medical schools. They also expressed their wish that future textbooks would add to the usual sections devoted to epidemiology, etiology, diagnosis, and so on a new section called "evolutionary considerations". However, they were aware of the difficulty of bringing about such a change and proposed a more modest start consisting of the creation of interdisciplinary programs involving geneticists, physiologists, microbiologists, chemists, anthropologists, and psychologists, as well as specialists from the different areas of clinical medicine. The first steps are being taken in various parts of the world.⁸⁵ Endocrinology, one of the most dynamic biomedical disciplines^{69,70} and a pioneering one in so many aspects, should not be left outside this current. This is the challenge we face. Nepomnaschy et al.³² recently stated that anthropologists are in a privileged position to lead the study of evolutionary endocrinology as a driving force of life strategies. However, we endocrinologists should

not renounce the medical dimension provided by Darwinian theory.

Conflicts of interest

The author states that he has no conflicts of interest.

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