

The emerging synthesis of development and evolution: A new biology for psychoanalysis

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Significant transformations have taken place in our understanding of evolution and development since the late nineteenth century, when the two seemed so closely related; at that time, the ideas of Charles Darwin, Ernst Haeckel, and other biologists played a prominent role in Freud's creation of psychoanalysis. During the twentieth century, as biological research reached the molecular level, biological concepts of development and of evolution veered progressively further from each other and further away from psychoanalysis. Then most recently, in response to a flood of discoveries in the last two decades, the long-separated fields of developmental and evolutionary biology have come together in the creation of a new field, informally referred to as "Evo-Devo." In this paper, I trace these remarkable changes, and discuss how these recent advances have returned biological concepts to a closer alignment with psychoanalytic principles regarding the role of early experience in long-term developmental change and the importance of the role that early parent-infant interactions play in shaping our lives and those of our children. I have illustrated the changes in our thinking that have taken place over the past half century by describing the different ways that I have thought about, puzzled over, and been enlightened by these changing concepts in the course of my psychobiological research on the roles of the mother-infant relationship in the development of a relatively simple model organism, the laboratory rat.

Keywords: developmental theory; early separation; evolution; attachment; mother-infant interaction; epigenetics

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Introduction

Since the creation of psychoanalytic theory, significant changes have taken place in how biologists view the relationship between the two great historical processes in biology: development and evolution. In the last decades of the nineteenth century and into the first years of the twentieth, the biological theories of evolution and of development created by Charles Darwin and Ernst Haeckel were a great influence on Freud's thinking and that of other early psychoanalysts during the formation of psychoanalytic theory. As George Makari described in his recent book (Makari, 2008), these two great "laws" of biology gave Freud a theory of psychological development: a view of the nature of the child, and a mechanism for the long-term effects of early social relationships.

During the first decade of the twentieth century, however, biologists' understanding of development and its possible role in evolution began to veer away from the nineteenth-century consensus, and continued to widen the differences between biological and psychoanalytic theory throughout most of the twentieth century. Remarkably, discoveries in the last two decades have

resulted in a new set of changes in how biologists view development in relation to evolutionary processes, bringing biological theory to a position that is again more compatible with psychoanalytic thinking.

In this paper, I will trace these changes in our concepts of development and evolution over the period since the origins of psychoanalysis in the last quarter of the nineteenth century. And I will look more closely at how conceptual changes taking place over the past half century affected the ways in which behavioral scientists approached their research into the biology of early development and the long-term effects of the mother-infant relationship. I will illustrate these changes with examples of how my own research thinking, as a psychoanalytically oriented psychiatrist, changed over this period of time. I will argue that the recent changes in biological theory have brought biology much closer to psychoanalysis at a fundamental level, changes that could restore some of the synergy that initially supported the creation of psychoanalysis.

I The dawn of evolutionary biology and psychoanalysis

The three scientists most closely associated with the nineteenth-century "laws" of biology (or theories, as we

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refer to them today) were Charles Darwin, Ernst Haeckel, and Jean-Baptiste Lamarck. The theory that most closely related development to evolution was the “biogenetic law,” championed by Ernst Haeckel, which grew out of the observation that in advanced species, early embryonic development passes through stages resembling adults of more primitive species. That is, human embryos progress from a single cell to what resembles a worm, to a fish, to pig, to monkey, before appearing clearly as a human, in a progression that appeared to reenact the course of evolution.

First described by Fritz Muller in a short book he sent to Darwin upon its publication (Muller, 1864), these observations were incorporated by Darwin into his fourth edition of *The Origin of Species* (1866) as further evidence for the existence of evolution. Darwin was helped in translation from Muller’s German by a young biologist, Ernst Haeckel, who went on to become the strongest supporter of Darwin’s theory on the continent, and beyond (see the recent re-evaluation of Haeckel’s contributions by Robert Richards, 2009). Haeckel went on to explore and expand the implications of Muller’s observations to create what he called “The Biogenetic Law,” taught to generations of high school biology students as the principle, “Ontogeny Recapitulates Phylogeny.” This simple phrase seemed to unite the fields of development and evolution. It was embraced by most scientists throughout the last half of the nineteenth century (Haeckel, 1897), and continued to influence evolutionary thinking well into the twentieth. Thus, early human development was seen by Haeckel, and by most late nineteenth-century biologists, as a much shortened “recapitulation” or reenactment of evolution, so essential an insight that Haeckel wrote: “This is the thread of Ariadne; only with its aid can we find any intelligible course through this complicated labyrinth of forms” (Haeckel, 1874, quoted in Gould, 1977, p. 79).

Essential for this “recapitulation” to be linked with the much longer timescale of evolution was some process by which changes in one generation could be represented in the next, a process Darwin called “descent,” or in modern terms, “heredity.” For Haeckel, and for most other biologists of the time, this was the “law of use and disuse” that has been for so long attributed to Jean-Baptiste Lamarck as the “inheritance of acquired characters.” But this “law” did not actually originate with Lamarck, nor did he claim special credit for it. For Lamarck, “the law of nature by which new individuals receive all that has been acquired in organization during the lifetime of their parents is so true, so striking, so much attested by the facts, that there is no observer who has been unable to convince himself of its reality” (Lamarck, 1815, quoted in Burkhart, 1984, p. xxix). What Lamarck did claim credit for, and with which Darwin and others after him vigorously disagreed, was

the idea that the “law of use and disuse” was of sufficient consequence to explain how organisms had become diversified into the many classes, orders, genera, and species that Lamarck had so beautifully described in his work as a systematist (Burkhart, 1984). Lamarck’s explanation for the origin of species was discarded in favor of Darwin’s brilliant insight that natural selection was responsible for evolution. As an unintended consequence of the vigorous defense of Darwin’s theory by Haeckel and many others, the original idea for the “inheritance of acquired characters” was (falsely) attributed to Lamarck along with the repudiation of it as the primary mechanism for the origin of species.

But the “law of use and disuse,” both as an explanation for developmental change, and for the transmission of that change into subsequent generations, was of great interest to Darwin as well as to his contemporaries.

May we not suspect that the vague but very real fears of childhood, which are quite independent of experience, are the inherited effects of real dangers and abject superstitions during ancient savage times? It is quite comfortable with what we know of the transmission of formerly well-developed characters, that they should appear [in the descendants] at an earlier period of life, and afterwards disappear. (Darwin, 1877, quoted in Sulloway, 1983, p. 245)

Over the ensuing 150 years, reports of such transgenerational effects continued to be repeatedly debated, then discredited, as examples of “Lamarckian inheritance,” and revived again, well into the twentieth century. As examples of such long-term effects of developmental experience were reported periodically, they were disregarded as “exceptions” for which no mechanism was known. Only in the twenty-first century, as we learn more about mechanisms for the regulation of gene expression in development, are transgenerational effects again beginning to be widely accepted, as I will describe below.

The sense in which Haeckel’s “biogenetic law” continued to be accepted by scientists well into the twentieth century was stated in the encyclopedic volumes *The Science of Life* written by H. G. Wells, his son G. P., and Julian Huxley in 1934:

Tens of thousands of animals do recapitulate the past during their development ... and in none of these ... cases is this departure intelligible save on the view that in so doing they are repeating phases that were once final forms in the earliest evolution of the race. (Wells, Huxley, & Wells, 1934, p. 369).

But the analogy for Haeckel’s concept of “recapitulation” often made by scientists of Freud’s time, was in relation to memory. As Gould summed it up:

The general form of the argument was simple: ... Instincts are the unconscious remembrance of things learned so strongly, impressed so indelibly into memory, that the germ cells themselves are affected and pass the

trait to future generations. ... Thus, ontogeny is the organism's memory of its past history. (Gould, 1977, p. 96)

Haeckel's "biogenetic" principle, and the "law of use and disuse," played a major role in Freud's thinking, both in the formation of psychoanalytic theory in general, and its metapsychology in particular. As described by George Makari (2008) in his recent book on the historical influences in the creation of psychoanalysis:

In 1914, when Freud wrote a preface to the third edition of the *Three Essays on Sexuality*, he baldly stated that the human "... disposition is ultimately the precipitate of earlier experience of the species. Carrying inside them the cumulative weight of evolution, the child is driven by archaic, perverse impulses. In civilized societies, these forces were hidden and rendered unconscious. But under the veneer of progress, there lay a primal sexual force that was vital to life itself." For years afterward, Freud would look to children, savages, and primitives, arguing that they all lived free from repression. In these beings, one could circumvent the problems of knowing what was normally forgotten and impossible to apprehend with interior observation. In them it was possible to grasp the mystery of the unconscious. This position was plausible only because Freud and many of his readers, following the famed biologist Ernst Haeckel, believed that all human history lay somewhere in our minds (2008, pp. 117–118).

Thus, the biological processes of evolution and of development were intertwined in the minds of biologists in the latter years of the nineteenth century. As part of that synthesis, early experience was accepted as a major force in shaping later development, even extending into the next generation. This scientific climate formed a strong theoretical base for Freud's thinking and for the growth of psychoanalytic theory; but in the world of biology, the basis for this synthesis began to fade in the dawn of the twentieth century.

II The century of the gene

In a very few years, between 1900 and 1910, there came a paradigm shift in biology. The rediscovery, in 1900, of Gregor Mendel's work on heredity in pea plants (Mendel, 1865/1966) and a growing appreciation of the cellular research of August Weismann (1894) led to the strong conclusion that the units of heredity were discrete entities, soon named "genes," that were isolated from the environment in special germline cells until they were passed over unchanged to the next generation. The very idea of transgenerational effects, presumed to act only on germline cells, soon became "heresy" to biologists. Concurrently, the advent of new experimental methods for studying early development at the microscopic level in the laboratory created a new field, embryology, and revealed that, when studied closely, the paths of normal

development in a number of species failed to follow the sequences of their evolutionary ancestors, severely limiting the generality of Haeckel's "law of recapitulation."

The advent of the field of embryology and its rapid specialization isolated the study of biological development from the whole field of evolutionary biology, a schism that lasted throughout most of the twentieth century. However, it was the discovery and naming of the "gene," its location, molecular structure, and finally its mechanism of action that was to dominate our understanding of evolution in the twentieth century. The first implications were for our understanding of heredity, then of variation, and most important for our topic, the unexpected role of genes in the processes of development – an area of research that only began at the close of the twentieth century.

In the decade from 1936–47, a general agreement was reached among the fields of experimental genetics, paleontology, population genetics, and natural history, that is still referred to as "The Modern Synthesis" (Hall & Olson, 2003, pp. 69–70). Evolution was reconceptualized as changes in gene frequency represented in populations. The evidence seemed overwhelming that the transmission of genes from one generation to the next was the (only) mechanism for heredity, that spontaneous mutations in genes and the chance recombination of genetic variants during sexual reproduction fully explained variation, and that natural selection influences evolution simply through determining which individuals are able to pass their genes on to the next generation. This gene-centric view of evolution may have reached its clearest expression in the popular book *The Selfish Gene* (Dawkins, 1976).

Meanwhile, development as a biological science, now redefined and renamed embryology, became a victim of scientific compartmentalization that further isolated it from evolutionary theory on the one hand, and from the burgeoning field of genetics on the other. As a part of this growing specialization, developmental psychology and psychoanalytic developmental theory grew up in the early twentieth century without any substantial links to the evolutionary or developmental biology of its time. Only in mid-century, in the newly emerging fields of ethology in Europe and comparative psychology in the United States, was there much interest in viewing the development of mind or behavior from a biological perspective.

Thus, just as psychoanalysis was beginning to grow as a profession in the first decades of the twentieth century, its connections to the scientifically accepted biology of evolution and development had vanished, although Freud, and even some prominent biologists, still depended on those concepts well into the twentieth century. Freud had already abandoned his "Project for a Scientific Psychology" (Freud, 1895), for the very good

reason that the neurobiology of the day was not sufficiently advanced to allow any clear paths to be imagined between the “structures” of mind and brain. No wonder that Freud and most other psychoanalysts gradually retreated – or some might say advanced – throughout the twentieth century, into a psychology that was independent of biology and for some, of science itself.

III Starting out to study behavioral development at mid-century

In my psychiatric training in the 1960s, I was taught to understand my patient’s illnesses in terms of the events of their childhood, as they remembered them. I became adept at creating psychodynamic developmental formulations, but I knew this was more art than science. Nevertheless, I was left with a respect for the long-term shaping effects of early experience, and the importance of the parent-child relationship.

I had been drawn to the idea that the behavioral biology of development could be studied in animal models when I was in college in the 1950s, through the work of the pioneering neurobiologist, J. Z. Young (1951), who was studying cellular physiology of learning and emotional behavior in the giant neurons of the octopus, two decades before the epic cell/molecular studies of Kandel in the sea hare, *aplysia* (Kandel, 1976). In 1961, I heard Harry Harlow describe the short- and long-term effects of maternal deprivation in rhesus monkeys. However, it was reading the European ethologists, Konrad Lorenz, Nikolaas Tinbergen, and Jakob von Uexkull (Schiller, 1957) during my training in the Department of Animal Behavior at the American Museum of Natural History with Ethel Tobach, that most encouraged me to embark on a most unusual line of research for a psychoanalytically-oriented psychiatrist in the 1960s.

Since so many advances in medicine had come from the experimental study of animal models, I wondered whether this approach could lead to a better understanding of the biological basis for the developmental effects of early experience that I felt were decisive for my patients at the New York State Psychiatric Institute. We were taught almost nothing about development in medical school, beyond the fact that pediatric patients differed in many ways according to their age. In my post-doctoral training in animal behavior, I attended a major international meeting on development at the Centennial of the American Museum of Natural History in 1969. (For the proceedings, see Tobach, Aronson, & Shaw, 1971.) I was astonished at how many points of view were represented and how strongly developmental scientists disagreed with each other. It was not simply

the absence of any widely accepted theory; it seemed to me that nobody really understood development at all.

The most widespread and vociferous disagreements seemed to be whether early behavior and the environment exerted any substantial effects on development. In the field of embryology, the traditional core of developmental studies, the preeminent authority, Viktor Hamburger, put it this way: “... the differentiation of the central and peripheral organization of the nervous system proceeds to advanced stages without the benefit of functional activity, sensory feedback, or environmental stimulation” (Tobach et al., 1971, p. 51). Another viewpoint on the role of experience in development, one that appealed far more to me, was articulated by Daniel Lehrman, perhaps the most creative figure in the field of behavior development at the time (Rosenblatt, 1995), which he called the “natural history approach” (ibid, p. 465). To paraphrase Lehrman, the naturalist’s questions differ from the behaviorist who wants to find out how a young animal develops the ability to do something *he* wants the animal to do (usually the infant seems to take a very long time to do any of those tasks). The naturalist, however, wants to find out how a young animal develops the ability to do something the *animal* wants to do (and therefore finds many forms of early learning).

Unfortunately, the scientific climate represented in this fascinating conference resulted in the appearance of factions, usually represented in research societies of like-minded individuals with shared interests and theoretical orientations. I cannot say that psychiatry or psychoanalysis was one of those for me at that time. But two small societies, the American Psychosomatic, and after its founding in 1968, the International Society for Developmental Psychobiology, became my scientific “support groups.” My “home,” however, became the new department of psychiatry at Montefiore Hospital/Albert Einstein College of Medicine, where a remarkable small group of psychoanalysts came regularly to research conferences and we researchers, who also continued to see patients and teach psychotherapy to residents, came to (clinical) Grand Rounds, where I learned that some psychoanalysts viewed a biological approach to the development of behavior as fundamentally related to psychoanalysis, and capable of contributing to its growth as a field, in the same way such an approach had contributed to its origin.

Is there a developmental biology of the mother-infant relationship?

When I started out in animal model research, in the mid-1960s, I had no idea that any of Freud’s interests in early development could be studied in animals less evolved than primates. Since the mother-infant relationship was, at that time, conceived of solely in terms of the inner experience and the emotional responses generated,

primates were considered the only suitable animals besides humans for investigating these questions. As one of my colleagues asked, “How would an infant rat even know that its mother was gone?” But there were, and still are, tremendous impediments to research in primates, not the least their housing cost, lengthy development, and small number of offspring per generation. However, European ethologists, studying fish, insects, carnivores, many species of birds, and even bees, had shown that relatively complex social behaviors have evolved in these more “primitive” species (translated and compiled in Schiller, 1957). Indeed, as our research has progressed, again and again I have been surprised to find unexpected biological processes in the early development of laboratory rats that seem to resemble – and literally to “embody” – the psychological concepts we use to understand early mental and emotional development.

One of the strongest influences on my thinking at that time was the “rebel” psychoanalyst, John Bowlby, who conceptualized infant attachment and the separation response as deriving from the strong affective “bond” that exists between an infant and its mother, even in some species of monkeys. When this emotional bond is severed by separation, Bowlby proposed, there ensues a sequence of traumatic emotional states: the “biphasic protest–despair response,” in which an initial burst of calling and active search behavior is followed by a long decline in behavioral responsiveness accompanying an affective state resembling despair (Bowlby, 1969). But it seemed to me that there was a circularity in this line of reasoning, for if the response to separation was explained by the existence of the bond, how could the existence of the bond be established by the response to separation? Perhaps there was more to be learned, I thought, remembering what Bowlby had written in one of his early papers:

I emphasize ... my belief ... that ethology will prove a fruitful approach to psychoanalytic problems ... With ethological concepts and methods it is possible to undertake a far-reaching program of experimentation into the social responses of the preverbal period of infancy, and to this I attach much importance. (Bowlby, 1958, p. 365)

Early separation

I was led to a new way of thinking about early separation by unexpected results in our laboratory. We found that two-week-old rats, about the age they are first able to live in the lab without their mother, nevertheless showed a number of responses to maternal separation, such as slowing of behavior, markedly lower cardiac rate, decreased thermogenesis, and a rapid fall in growth hormone levels, but also increases in non-nutritive sucking, behavioral reactivity, and corticosterone secretion, all of which developed slowly in the hours following

removal of the mother from the home cage, each on their own time schedule (reviewed in Hofer, 1994). To our surprise, we found that this was not an integrated psychophysiological stress response, as in Bowlby’s proposed “despair” phase of the response to disruption of an emotional “bond.” Instead, it was the result of the removal or loss of a number of different behavioral and biological interactions with their mother that had regularly occurred prior to separation. We found that the behavioral and physiological systems of the infant were each regulated (that is, maintained at a certain level or in a certain pattern or rhythm) by different components of the mother–infant interaction prior to separation: by the mother’s licking, warmth, odors, suckling, milk, and by the timing or rhythm with which these interactions occurred. When these regulators were all lost at once, all the regulated systems responded by changing their levels or rhythmic patterns. We called them “hidden maternal regulators” because they were not apparent when simply observing the mother interacting with her offspring. These findings appeared to be good evidence for a psychobiological symbiosis in which maternal behavior and nursing physiology interact with widespread infant physiological and behavioral systems in a shared homeostatic system (Hofer, 1990).

We, and others since, have found that these hidden maternal regulators control and shape the levels of hormones, blood pressure, and sleep over extended periods of development. For example, the finding that levels of growth hormone in rat pups were regulated by vigorous tactile stimulation similar to their being licked and groomed by their mothers, was translated to a clinical setting involving very low birth weight in human premature infants, by Saul Schanberg and Tiffany Field (Field et al., 1986). They found that the preemies’ weight gain and overall growth while isolated in an intensive care unit could be significantly increased over a period of days by providing an intervention of stroking and limb movement – just 15 minutes, three times a day – and this intervention allowed the infants to leave the intensive care unit six days earlier than a control group of infants that received traditional care.

These long-latency responses to separation closely resembled the “despair” phase in Bowlby’s biphasic response, but what about the more familiar acute “protest” phase with the familiar calling and “searching” behavior? In this case, we found that infant rats responded immediately to separation when we gently removed first their mother and then littermates one by one from the home cage. As soon as the last pup awoke, it began a vigorous and prolonged series of vocalizations (in the ultrasonic range, 35–45kHz), as it moved around its home cage (Hofer & Shair, 1978). Previously the ultrasonic vocalization (USV) of rodent pups had been thought to be due to rough handling and to being picked

up and placed in a novel, and colder environment, rather than specifically to separation from mother and littermates. This “protest”-like response could be reduced by providing different sensory elements of the infant’s mother and littermates, such as a soft synthetic fur, a warm environment, or maternal odor, singly or in combination. The importance of odor was made clear by the failure of pups to show their usual USV quieting, or “comfort” response when deprived of their olfactory sense (Shair, Masmela, & Hofer, 1999).

This early response to separation in rat pups closely resembled the properties of a “protest” response; and the rapid cessation of USV calling upon reunion with littermates or mother, resembled the “comfort” response in the Bowlbian attachment system. But here again, as in the several systems and processes involved in the slower evolving responses to separation described above, we found that the vocal response of the infant was in fact “regulated” over different sensory pathways – odor, texture, warmth, and contour – each contributing, additively, to the quieting response to reunion (Hofer & Shair, 1980).

The vocal response of the infant mammal to isolation in a novel environment has been viewed since Darwin’s time as an early developing anxiety-like behavior, and presumed to have evolved to alert and attract the mother to the separated infant (MacLean, 1985). We, and others (Panksepp, Newman, & Insel, 1992; Insel, 1992), began to explore the neural systems underlying this response of the pup to isolation, and found an almost uncanny similarity to human anxiety in the neurotransmitter systems involved. A number of drugs that are effective in clinical anxiety states in humans produced robust decreases in the rate of the pups’ isolation calling response, such as benzodiazepines and serotonin receptor binding drugs. Remarkably, substances known to produce disintegrative anxiety in adults, such as pentylenetetrazol, a convulsant, greatly intensified the rat pup’s USV response to isolation (reviewed in Hofer, 1996).

How is a “bond” formed?

I found myself surprised again that rat pups should so resemble humans, even in the neurochemistry underlying their immediate vocal response to separation. But another component of human attachment seemed even less likely to be represented in the early development of rats: the establishment of a “bond” between the infant and its mother. The use of the word “bond” was essentially metaphoric. Even today, “bonding” is used very loosely to refer to what seems like a “glue” that holds mother and infant close to each other. Bowlby thought that the “tie” between the human infant and mother was built up slowly through essentially unknown processes embedded in the first year after birth. He drew on the work of Konrad Lorenz (Schiller, 1957) and other ethologists who had

studied the almost instantaneous “imprinting” of goslings and chicks on their mothers in the first hours after their emergence from the egg, as an evolutionary predecessor of the different and far slower process of bond formation taking place in mammals. But no such process had yet been found.

It is small wonder then, that developmental psychobiologists in the 1970s did not even think of studying the formation of attachment in the rat. The word “attachment” was not used in most of our discussions of early development, except for work in primates. Thus, it was not surprising that the first research to reveal the formation of such a “bond” grew out of studies on the development of more basic processes. Regina Sullivan, a doctoral student in our lab, with Steven Brake, was studying the acquisition of odor preferences by repeatedly pairing a reinforcer, milk, to a hungry pup in association with a neutral odor such as lemon oil, and then assessing very young pups’ preference for that odor, versus another unfamiliar odor, in a choice test. Another possible reinforcer, stroking the pup with a soft brush to simulate licking by its mother, also produced rapid olfactory learning. Then, as a control to show that ordinary, non-reinforcing stimulation alone was ineffective, Sullivan tried firm pressure on the pup’s tail, and then a very mild electrical current. To our surprise, the pups rapidly learned to seek out and stay near any novel odor previously associated with these forms of stimulation, even when strong enough to be clearly aversive, judging from the pups vigorous escape behaviors. Since one of the lesser-known characteristics of imprinting in newly hatched chicks was the rapidly learned preference for following specific moving models that had previously been paired with mild electric shock, we allowed ourselves to think that Sullivan might have discovered an imprinting-like process that could be responsible for the development of the powerful inclination of mammalian young, including humans, to prefer and stay close to their own mothers. Perhaps this was how an “attachment bond” was formed. However, we gave the published results a much more carefully articulated title: “Olfactory guided orientation in neonatal rats is enhanced by a conditional change in behavioral state” (Sullivan, Hofer, & Brake, 1986).

It took a number of years, and much further research on the underlying biological processes, before most biologists accepted that the infant mammal’s psychological “bond” is made up of memories and associated affects established by a simple associative learning process. Sullivan has gone on to discover that the bond formed in rat pups when mild electric shock was used to “reinforce” the association, occurred only during an early “sensitive” period, from birth to mid-infancy (Sullivan, Landers, Yeaman, & Wilson, 2000). However, this sensitive period could be extended by daily repetition of the association, as occurs with abusive human mothers.

Interestingly, the brain and neurotransmitter systems mediating this early aversive learning (locus coeruleus and noradrenergic beta receptors) are different from those mediating positive association learning (primarily the later-maturing amygdala). Changing the timing of maturation of these two systems, using neuropharmacologic and neuroendocrine manipulation, Sullivan showed that the early period of aversive learning could be prolonged; and by advancing the normal rise in adrenal corticosterone levels to an earlier age, amygdala maturation was accelerated and positive association learning replaced aversive learning at an earlier age (reviewed in Moriceau & Sullivan, 2005; see Section IX for a fuller discussion of human parallels).

Sullivan's recent work has shown that experiencing these early aversive olfactory learning contingencies (but not unpaired shock and odor) has the long-term effect of enhancing adult depression-like behaviors; whereas re-introducing that specific odor during adult testing reduced these depressive responses, perhaps functioning as a "safety signal" (reviewed in Landers & Sullivan, 2012). These findings may provide a biological basis for the strong attachments of abused human infants as well as their long-term vulnerability.

The role of latent theory in biological research

Why were we so often surprised at our results? I think this came unwittingly from our (preconscious) concepts of evolution and development as separate processes, in which we vastly underestimated the extent to which basic developmental processes have been conserved by evolution over vast reaches of time. We believed that the developmental processes involved in attachment – the formation of early attachment bonds, the kinds of interactions taking place during early relationships, and the presence of long-term effects due to early experiences between mothers and their infants – had only evolved to a primitive degree in non-human primates. The neurobiological substrates underlying these developmental processes, we thought, were almost certain to be absent in species from which primates had evolved. We humans operated at the level of affect, memory, and inner experience, we told ourselves, whereas lower mammals such as the laboratory rat, were driven by instincts, reflexes, and what the ethologists had named "fixed action patterns." We could not easily imagine a level of biological processes that could mediate what seemed to be "innately human" behaviors and developmental effects in less evolved animals. After all, we thought, "animals operate at the biological level, whereas humans live in a psychological world."

Also, we did not appreciate sufficiently the implications of the "levels of organization" concept that recognizes events taking place in us simultaneously at

molecular, cellular, organ systems, cognitive/emotional, and experiential levels. But we were on our way toward realizing that, in these laboratory animals, we were seeing a set of biological/behavioral processes that we have inherited in our evolution (in modified form) and that continue to underlie and literally *embody* the simultaneous psychological processes we are attempting to understand in our patients (see Section IX). Paul MacLean, the legendary neuroanatomist, described this idea in his book, *The Triune Brain* (1990), in his fantasy of the psychoanalytic patient lying down on the couch bringing with him a horse and a crocodile.

IV Are there major long-term effects of early social experience?

Increasingly, we were finding novel physiological and behavioral processes that seemed to underlie many of the psychological constructs we have used to understand early social development. And we found that these processes acted to shape biological as well as behavioral development over the short term. However, for the effects of such early experience to extend into adulthood would require some form of persisting change in developmental processes that would extend well beyond the duration of the mother-infant interaction. We use psychological concepts such as personality, temperament, or character formation to help us understand the extended effects of early social experience into adulthood. Unfortunately, the climate of opinion among biologists and some physiological psychologists in the 1970s was that well-documented examples of such long-term effects of early environments were exceedingly rare, and those few could not be explained by any known biological mechanism.

However, a clear implication of our discovery of "hidden regulators" within the mother-infant relationship was that they might constitute a developmental mechanism that could mediate the long-term effects of early experience, so essential to psychoanalytic thinking, and so difficult for biologists to accept as real. It occurred to us that early weaning was a naturalistic early experience that would withdraw all "maternal regulators" at once, yet allow survival of offspring. Previous work (Ader, Tatum, & Beels, 1960) had shown that this early, permanent separation experience raised the susceptibility of adult rats to gastric ulceration (during prolonged immobilization) to 30%, with controls showing only occasional ulcers. In following up this lead, Sigurd Ackerman, Herbert Weiner and I (Ackerman, Hofer, & Weiner, 1975) took a developmental approach. We separated the mothers from their litters at 15 days postnatal age (weaning in the wild is at 25 days and in most labs, 21 days), and later immobilized their offspring in small wire mesh cages at different ages, using separate

experimental groups, ranging from as early as two days after separation to late middle age at 200 days; normally weaned rats were also subject to immobilization at the same time points.

No rats developed gastric ulcers if immobilized two days following early weaning, at 17 days of age; however, following immobilization at 30 days of age (in early adolescence), nearly 100% of the early separated rats showed ulcers, compared to only 5% of the normally weaned controls, and the ulcers were larger, deeper, and far more likely to cause major bleeding than those occurring at any other ages. There was a smaller, but still robust effect of early separation that substantially increased vulnerability during late adolescence and early adulthood, whereas the normally weaned age groups continued to show minimal (5–10%) levels of gastric ulceration. But in late adulthood (200 days), nearly 50% of the normally weaned controls had developed vulnerability to the stress of immobilization, whereas, surprisingly, the early weaned rats had developed *resistance* to the stress by this age, only 25% of them showing ulceration (Ackerman et al., 1975).

It was clear that early weaning had produced a profound shift in the whole developmental course of the offspring's vulnerability to stress. And it seemed possible that this could be understood as the result of the premature loss of all maternal regulators at once, thus affecting a number of the offsprings' physiological and behavioral systems, altering their developmental paths to create this complex, changing pattern of vulnerability to stress over the lifespan.

Could the effects of early experience extend to the next generation?

At this point, a clinical psychology intern, Neil Skolnick, suggested the possibility that, as adults, the "quality" or amount of the maternal behavior of the previously early weaned rats could be reduced or disrupted as a result of their early separation from their own mothers. He proposed that such a reduction in effective mothering of her offspring could produce a vulnerability to stress ulcer in those pups, even if they themselves were normally weaned. This seemed to us an overly simplistic translation of clinical thinking to our animal model, and was likely to be a waste of time. Fortunately, we found funding to allow him to take a year off to see what would come of it. He found that early weaning did actually reduce the amount of time that these females later spent with their own pups, and when they were allowed to wean their own litters normally, their pups became twice as vulnerable in adulthood to stress ulceration as the offspring of normally reared females, just as Skolnick had supposed.

Ackerman and I were first astonished and then certain that some mistake had been made. We repeated

the study with careful supervision, and added two new groups: normally reared pups cross-fostered to previously early weaned mothers, and the pups of early weaned mothers cross-fostered to normally weaned mothers. First, the results replicated Skolnick's earlier finding that increased vulnerability to stress ulcer was produced in the adult offspring of early separated mothers. However, the cross-fostered groups showed clearly that the vulnerability could not be due to the change Skolnick had observed in early weaned mothers' maternal behavior. Instead, it was transmitted to the next generation through the early weaned mothers even when their offspring were reared by normally-weaned mothers (Skolnick, Ackerman, Hofer, & Weiner, 1980). Apparently the vulnerability was transmitted either during the affected offspring's embryonic and fetal development within the intrauterine environment provided by their early weaned mothers, or by some even earlier effect on their mother's germline cells during or after her early weaning from the affected offsprings' grandmother.

Now we had ventured beyond the limits of our knowledge, for we seemed to have stumbled upon a clear-cut example of the "inheritance of acquired characters," so disputed even in the late nineteenth century. However, a brief literature review brought up two other published examples of transgenerational effects, involving the adult offspring of female rats that had been exposed to toxins prior to mating. So we cited these sources along with our results, in a paper we submitted to the journal *Science* that was quickly accepted, a sign of some growing interest in unexpected developmental processes (Skolnick et al., 1980). Subsequently, the National Institutes of Health (NIH) put together a small meeting to explore the possibility of special funding for studying this kind of heritable developmental effects. But the geneticists present were unenthusiastic, since so little was known that could suggest a possible molecular genetic mechanism for these observations.

V When expected long-term effects of early experience do not occur

It must seem to the reader at this point that any major disruption of the mother-infant relationship should have readily discernible effects on the social behavior of the young. But we soon found out that this was not necessarily true. At that time, we were trying a new approach: rearing rat pups without any postnatal maternal interaction as an experimental baseline, to which we could add various elements of the normal interaction based on the "hidden maternal regulators" we had previously found. Such complete maternal deprivation is complicated by rat pups' exquisite olfactory discrimination that prevents them from sucking on any artificial nipple. But a way

had been found to rear rats with minimal or no postnatal experience of their mother, by raising them alone, on their usual bedding, in plastic cups floating in a warm bath that imparted a rocking effect whenever the pup moved. Pups were fed through an indwelling gastric cannula connected by fine plastic tubing to a warm milk supply. There was one maternal behavior that had to be simulated: the anogenital licking, provided by the dam, that stimulates her pups' emptying of bladder and rectum, something that does not occur spontaneously until 8–10 days post partum. This could be done using an artist's brush two to three times a day.

We planned to add simulated elements of maternal interactions to massively deprived pups to determine which combinations would support the development of the pups' vocal quieting ("comfort") response to their mother's body. We did worry that the pups' ultrasonic vocalizations themselves might not develop under these artificial conditions. But, as it turned out, we did not need to be concerned. The artificially reared pups, in what we thought would be the control group, not only showed vigorous ultrasonic vocalization responses to being placed alone in a test cage, they showed complete "comfort" quieting responses upon contact with their anesthetized dam that they had not experienced since the day of their birth, two weeks previously. The only abnormality observed was that artificially reared pups vocalized at higher rates than normal for their age, similar to rates of younger pups (Hofer, Shair, & Murowchick, 1989).

When Gilbert Gottlieb, a leading figure in the field of behavioral development, and often ahead of his time (Gottlieb, 1987) saw these results, he wryly "congratulated" me for demonstrating the strong effects of "inapparent" early experiences (no genetic "blueprints" for him!). But these results were not our only surprise. Later, using pups that had not been part of any previous studies, but instead were "weaned" as juveniles from their tubes and cups but remained isolated until they were early adolescents, nevertheless showed normal "rough-and-tumble" social play, with its intricately timed reciprocal interactions, in their first encounter with one of their similarly isolated age-mates. In comparing videotapes of these play sessions with those of normally weaned juveniles, Susan Brunelli and I could not distinguish between the two tapes. However, quantitative slow motion analysis of the tapes was not done, and other research has shown subtle differences after extensive play deprivation (van den Berg et al., 1999; Pellis & Pellis, 2010).

How can we explain these results, when other developing behaviors and physiological responses had shown major long-term effects as a result of far more subtle changes in the mother-infant interaction? Previously, I had given little thought to the question of how

evolutionary selection pressures could have acted on the developmental processes we had been studying. But now the questions posed by our recent results seemed to suggest that when we found a developing trait to be readily shaped by features of the animal's early maternal environment, this was likely to have been the result of two features in its evolutionary history: (1) the presence of an adequate level of variation among individuals in the degree to which maternal interactions contributed to the development of that trait and (2) a history of natural selection for those interactions that provided developmental outcomes that had been advantageous in the environments encountered in its evolutionary past (see Section VIII). Conversely, evolution of traits whose development depends *minimally* on maternal interaction were likely to have evolved when: (1) individual variation in the developmental path for that trait had been scant within that population, or (2) if their past environment had favored variations in the development of traits that were minimally influenced by their interactions with their mothers; for example, in environments that necessitated long maternal absences. Possibly such an environment played a role in the evolution of species such as the rabbit whose only contact with her pups occurs in a single nursing bout of about five minutes each day. The role and importance of such "maternal effects as adaptations" (as they were later named) was virtually unknown in the late 1980s when we were trying to understand our findings, but became much better recognized within a decade (Mousseau & Fox, 1998) and have formed a field of their own (Mousseau, Uller, Wapstra, & Badyaev, 2009).

Thus, I was led on a search for what was known about the evolution of development, and to a more basic question I had not asked myself before: when and how did life forms with a developmental phase first appear in the fossil record, and what selective pressures were likely to have shaped the nature of developmental processes over time?

VI Searching for a theory of development

As I was trying to digest the surprising findings described above and make some sense of them in evolutionary terms, I was asked an unexpected question by a graduate student I met at an international meeting. She asked, "What is it that you would most like to discover in your research?" Nobody had ever asked me a question quite like that. I hesitated, and then I found myself saying, "I'd like to discover a simple principle that explains development the way Darwin's phrase 'descent with variation and selection' explains evolution." As soon as the words left my mouth, they sounded wildly over-ambitious, but they kept coming back to my

mind, and some years went by before I realized they were based on an entirely misguided concept of the relationship between development and evolution.

I had been thinking along the lines of the “Modern Synthesis” that had conceptually disengaged evolution from development, and I had been assuming that these two “historical” processes in biology constituted entirely different kinds of biological change over time. Then, at the end of the 1980s, I read Steven J. Gould’s book, *Wonderful Life* (Gould, 1989). In it he described the discovery of the “sudden” appearance of multicellular animals in the fossil record, after billions of years of only single cell bacteria and protozoa. These new life forms appeared in what geologists consider a very short time period, between about 570 and 540 million years ago, a tiny interval in the 4-billion year course of evolution.

The original discovery, in 1909, by James Doolittle Wolcott, had been misinterpreted, and thus its extraordinary implications were missed. But in 1985, that fossil record was re-interpreted by Charles Knight, and is now known as the Cambrian “explosion.” For in this geologically tiny period of time, fossils of the ancestors of all the major classes (Phyla) of animals appeared in recognizable form, some closely resembling those we are familiar with today, such as the fish, lobster, and clam. Others look quite fantastic. Gould’s conclusions from Wolcott Knight’s “Burgess” shale fossils centered on its implications for evolutionary processes: the demonstration that the evolution of a vast diversity of forms was not necessarily slow and gradual, as is much of evolution. As previously described by Eldredge and Gould (1972) other increases in diversity occurred in the aftermath of mass extinctions caused by sudden environmental catastrophes or impact of comets. These extinctions were essentially random and sudden in their effects – in contrast to the far slower adaptive processes envisaged by Darwin and represented in the “modern” synthesis.

What struck me about this “sudden” appearance of diverse multicellular organisms was that they all shared a common feature: their many cells were seamlessly fitted together into a single animal with many different organs and body parts, by a newly evolving process that we now call “development.” Before this evolution of development, cells lived independent lives or formed into loosely knit colonies. During the period preceding the Cambrian, the more advanced protozoa, the algae, amoebas, and flagellates, are generally thought to have evolved almost all the major capabilities of cells needed to form multicellular animals, such as rapid multiplication, directed movement, cellular adhesion, reproduction (both sexual as well as asexual), and even cellular differentiation (the capacity of a cell to produce a daughter cell very different from itself, which has sometimes been viewed as limited to multicellular organisms). Furthermore, these unicellular

behaviors and functions often occurred in response to changes in their environment or to signal molecules released by other nearby cells, much the way molecular interactions would soon come to regulate the development of multicellular animals. What was missing in these protozoa was the organization of their cell/molecular processes into a linear series of events involving many such cells and the grouping of different cells into interconnected body parts and organs, including a central nervous system. (For a review of this area, see Maynard Smith & Szathmari, 1999, and for more recent discoveries, see Donoghue & Antcliffe, 2010).

In the Cambrian explosion, this form of dynamic organization appeared for the first time. Development was a product of evolution: the individual, episodic, and parallel processes of protozoa became the multiple, sequential, and linear processes of multicellular development (Wilkins, 2002). Genetic evidence suggests that the foundation for this turning point was laid by a gradual increase in the complexity of the genome of unicellular forms prior to the Cambrian “explosion” (Srivastava et al., 2010). And new geologic findings have shown evidence of specific geochemical and physical environmental processes linked to seawater chemistry during a major expansion in shallow marine habitats at that time (Peters & Gaines, 2012).

The rapid appearance of a wide variety of different animal types at that time suggests that the new life process that made them, that is now called development, not only possessed mechanisms for increasing the variation present in each generation, but also novel mechanisms for heredity that would have made possible such an acceleration in the rate of evolutionary change. This example of the “evolution of the capacity to evolve” (Carroll, 2002) has interesting implications for our understanding of development, for it allows us to see it for the first time as one of the great creative forces in evolution. Development is not a separate historical process, to be considered separately from evolution, as I had assumed in my reply to the graduate student’s question described above. This new perspective also turns on its head Haeckel’s view of development as a “re-enactment” of evolution, and evolution as “the mechanical cause” of development. (For an analysis of the implications of the Cambrian “explosion” and its place in the origins of “Evo-Devo,” see Goodman & Coughlin, 2000).

For the three billion years of life on Earth prior to this time, the only mechanisms for creating *heritable* variation among the single celled organisms inhabiting the Earth during that long period had been genetic mutation, and later, with the evolution of sexual reproduction, the recombination of genetic “alleles” from each parent cell. But now, with the new forms of variation created in the Cambrian “explosion” by this life process

we now call development, came the potential for a new category of heritability by which new developmental paths could be transmitted to subsequent generations, through various forms of transgenerational effects. For example, the embedding of eggs, embryos, and fetuses within the protective internal environments of female fish, birds, and mammalian mothers not only functions to promote the survival of her immature young, but also serve as “inherited environments” that provide links between generations potentially capable of transmitting the effects of events in their own generation to the next (Danchin et al., 2011). Similarly, in the postnatal period, developmental effects can be transmitted across generations postnatally, through the previously described “hidden regulators” operating within the mother’s interactions with her infants.

Thus, I gradually began to see that the evolution of multicellular development provided new mechanisms for Darwin’s two major evolutionary processes, variation and “descent”: a prime example of the evolution of the “capacity to evolve” (Carroll, 2002). Development evidently became an integral part of the evolutionary process at the time of the Cambrian “explosion,” and thus, any question about how development works should be approached through a better understanding of the “simple” processes of evolution referred to in my answer to the graduate student’s question at the meeting a decade earlier (as described in the first paragraph of this section, VI). In addition, as our knowledge of genes and how their expression is controlled have continued to grow exponentially in the last decade of the twentieth century and the first years of this one, genes have come to be understood as playing a central role in development as well as in heredity, and even to be centrally involved in the short- and long-term effects of experience on development. All of this showed me clearly how the “simple theory of development” I had been hoping to discover was to be found in a newly expanded theory of evolution itself.

VII The new genetics of development and the birth of evo-devo

Since the discovery of genes as the mechanism of heredity at the beginning of the twentieth century, the assumption of biologists has been that different species of animals were produced by different genes. If species evolved through selection based on the random mutation of genes, larger and more complex animals, like ourselves, were assumed to have a greater number and variety of genes, with a large proportion of the new genes being entirely novel. The different paths of development in different species, and similarly between individuals, were assumed

to result from a direct expression of their different genetic makeup.

These assumptions underlay the twentieth-century biological view of development as resulting from the innate expression of inherited genes over time, a view that left little conceptual basis, and no molecular/genetic mechanism, for interactions with the environment to affect the course of development. It is not surprising, therefore, that biology grew ever more distant from psychoanalysis, which continued to identify early experience as a key factor in development. But since the full sequencing of DNA in a number of species, these twentieth-century views of development have been radically modified, and the first changes in this direction came, unexpectedly, from the direct application of new genetic tools to developmental processes themselves (reviewed in Nusslein-Volhard, 2008). We have learned that humans have no more genes than chickens and fewer than corn! Moreover, the genes that are active in development are widely shared by animals as distant on the evolutionary tree of life as flies and humans – which share 99% of developmental genes. We have come to realize that the differences between species, and evolution itself, resulted not so much from the creation of novel genes by mutation, but through changes in the patterns and timing of activation within groups of shared developmental genes (Carroll, 2005).

These “regulatory” regions of DNA are situated within the intervals between genes, and they function as a series of switches controlling the transcription of the “structural” or protein-coding genes. These switches are organized into circuits, and the circuits into complex networks; thus, the development of the embryo resembles a “Lego” block assembly, rather than the formation of a crystal, or the sculpting of a riverbed, metaphors that had been used in previous theories of development (Haraway, 2004). This block assembly nature of the developmental process allows a wide variety of structures to be produced from a more limited supply of building blocks.

With this insight into the molecular genetics of development, the new field of evolutionary developmental biology (informally known as “Evo-Devo”) has gradually become recognized over the past two decades, and development is now being understood as driven and organized by complex patterns of gene regulation (Hall & Olson, 2003). The inbuilt flexibility of these developmental circuits underlies their capacity for rapid adaptation to changes in the organism’s external environment, such as forced migration, drought, cold, famine, or crowding, without the need for the slow processes of selection from random mutations. For example, in the rats I described earlier (see Section IV), different weaning times could model a real-life event precipitated by

changes in the natural environment that offspring must adapt to over a few generations.

Such adaptive changes in the course of development, called “facilitated variation” by Kirschner and Gerhart (2005), are made possible through the re-use of existing genetic regulatory networks, in new combinations and patterns, as part of the physiological and behavioral responses of each individual to its changed environment, as it develops. If an environmental change, and the new patterns of gene activation induced by it, persists over a number of generations, as in famines or droughts, this altered developmental path could become stabilized through conventional natural selection, even over such short time periods, through the re-assortment (during sexual reproduction) of genetic alleles involved in the newly adaptive pathway. In this way, these environmental influences on development over generations can become represented in the genome, and thus make the transition to a more “fixed” form of inheritance.

Until the last few years, the word “epigenetic” was used to refer to developmental processes that took place through an interaction between an organism and its environment (“regulative” development), in contrast to “mosaic development,” referring to the stepwise construction of animals based on the genetic information present in the fertilized egg (Raff, 1996). In the last decades of the twentieth century, there was a gradual shift of thinking among neuroscientists toward an acceptance of the importance of epigenetic development, for example, the discovery of “activity-dependent processes” in the development of neural systems underlying behavior (Purves & Lichtman, 1985). But the term “gene-environment interaction” was generally treated with a dismissive air by basic-level neuroscientists, in the absence of any known molecular/genetic site or mechanism for the environment to actually interact with a gene.

The “epigenetics” revolution

In the last few years, however, the word “epigenetics” has come to be used in a new sense as the title for a new field. One of its origins was in our growing understanding of how cells can become so different during development, becoming liver or skin, kidney or brain cells, despite having identical DNA. It was found that when cells divide, some genes in daughter cells become silenced, whereas other genes are activated.

This exquisitely orchestrated regulation of gene activity by messenger molecules was found to result from minute local changes, or remodeling, of “chromatin,” the three-dimensional molecular scaffolding that the long DNA strands are wrapped around and partially embedded in. Once thought to represent inert “packing material” for DNA, we now know that local changes in

the histone protein structure of chromatin, with the addition or removal of small molecules such as methyl groups (particularly to cytosine molecules in DNA), can initiate or silence the expression of specific genes. Because these local molecular changes, or “marks,” are situated outside the sites of genes on the long DNA strands, and do not alter the underlying DNA sequences, they were termed “epigenetic.” (For a lively and readable account of this new field, see Carey, 2012.) This rather concrete use of the “epi” prefix did not in itself connect these molecular/genetic mechanisms to the processes of developmental epigenesis described above – at least not at first.

Where genes and environments interact

In the past decade, an ever growing number of studies have been published linking environmental influences on development to epigenetic mechanisms, ranging from natural changes in ecology to the effects of specific environmental toxins and even the origins of cancer (Gilbert & Epel, 2009). I will focus on one line of work, closely related to the research I have been describing in this paper, that is closing the causal ring between a particular set of maternal behaviors directed toward her offspring early in their development, and the expression of adaptive behaviors with their supporting physiological responses in her adult offspring, even extending to the next generation. These studies provide a molecular/genetic mechanism for the long-term effects of the “hidden maternal regulators” we had described many years previously.

In 1997, Michael Meaney and his colleagues at McGill (Liu et al., 1997) produced evidence that mothers with naturally occurring differences in levels of two of the maternal regulatory interactions we had found to have long-term effects (the licking and grooming of her young, and her nursing in a high arched position; Myers, Brunelli, Squire, Shindeldecker, & Hofer, 1989), produced long-term changes in adult measures of anxiety and corticosterone responses in their adult offspring. Since then, Meaney, his colleague Frances Champagne and others have shown that these and many other long-term effects of early maternal behavior are the consequence of changes in the activity of specific genes in areas of her pups’ brains, and in her adult offspring, that regulate a wide range of brain functions. These focused changes in brain gene expression were found to be the result of epigenetic processes, in the form of targeted epigenetic “marks” on specific genes, established by the different levels of maternal licking and grooming they had received as infants. Importantly, these effects did not depend on whether pups were reared by their own mother or by a cross-fostered mother with similar maternal behavior levels, eliminating classical genetic

or intrauterine pathways. These epigenetic cell/molecular effects continued to be expressed into adulthood, and in a series of studies were found to account for differences in anxiety levels, sexual behavior, learning and memory and, at the physiological level, CRF receptor density, corticosterone stress responses, dopamine signaling, and oxytocin receptor binding (reviewed in Cameron et al., 2005, and Champagne, 2010).

Furthermore, one of the adult traits affected was the maternal behavior of the adult offspring toward their own pups in the next generation – thus extending the initial effect across generations, to the grand-pups of the original mothers! This transgenerational effect that is such an important feature of human attachment could be traced to the effects of the different mothering patterns on estrogen-mediated oxytocin receptor levels in the pups' developing medial preoptic area – later to become the substrate for her maternal behavior toward her own pups in the next generation (Champagne, Diorio, Sharma, & Meaney, 2001; for a recent commentary on this and many other more recently described transgenerational effects, see Champagne, 2013). In humans, we tend to think of such an intergenerational effect as being mediated exclusively by developing conscious and unconscious *mental* processes in the formation of a maternal representation (or “internal working model” of human attachment). This raises the question of how inferred mental processes are related to, and may reflect underlying biological developmental processes. (See further discussion of this issue in Section IX.)

The epigenetic revolution has affected many areas in addition to the ones described above. For example, the burgeoning field of ecology and wildlife preservation has attached itself to evolutionary developmental biology by coining the new term “Eco-Evo-Devo,” and launching a new textbook integrating epigenetics, conservation, medicine, and evolution (Gilbert & Epel, 2009). There is now growing evidence for epigenetic mechanisms for early experience effects in humans that are similar to those previously described in animals: for example, in adult brains of suicide victims with histories of early life abuse, compared to brains of suicides without such histories (McGowan, 2009). Evidence in animals is accumulating showing that even germline cells (in testes and ovaries of parents) can participate in epigenetic environmentally-induced transgenerational effects on offspring behavioral development (Curley & Mashoodh, 2010). And most recently, there are many reports of new epigenetic regulatory roles for RNA (“large non-coding” and “micro” RNAs) that go well beyond the classic role of RNA as the “messenger” between DNA and the synthesis of new proteins, thus providing an additional pool of potentially useful variation (Eggleston, Eccleston, Marte, & Lupp, 2012).

Indeed, we are in a period of unprecedented change in our understanding of how variation is generated within the environment of the developing organism. As Philip Ball, an editor of the journal *Nature* wrote in April 2013, on the 60th anniversary of Watson and Crick's discovery of the structure of DNA, “We do not know what most of our DNA does ... this could be a celebration of the ‘known unknowns.’ ... Finally, for the Jubilee we should do DNA a favor and lift some of the awesome responsibility for life's complexity from its shoulders” (Ball, 2013, pp. 419–420).

The impact of “evo-devo”

The implications of these findings and ideas mark a true paradigm shift in the fields of evolution and development, comparable to the two very different revolutions in thinking that took place in the mid-nineteenth century and in the early to mid-twentieth century. From the Evo-Devo perspective, development and its capacity to generate variation is seen as a major participant and even a cause of evolution (Hendrikse, Parsons, & Hallgrímsson, 2007), turning on its head Haeckel's vision of evolution as the cause of development. We now understand many of the ways in which early experience shapes the behavior of the adult organism as part of that variation. And our new knowledge of the nature and roles of genes, and of the many novel mechanisms for their regulation during development, has restored our understanding of biology to a position much more supportive of Freud's formulation of psychoanalytic theory than at any time since the end of the nineteenth century. Ironically, it has been our understanding of biology that has changed to a view more congruent with psychoanalysis, rather than psychoanalytic thinking changing to accommodate the new biology, as has often been suggested by biologists, and even by some psychoanalysts; for example, Sandor Rado, for whom the lecture, on which this paper is based, was named.

VIII How did early mothering effects evolve?

The functions of development described in the last two sections, acting from the beginning of multicellular life, have evolved to create the overlap of generations and the long-term plasticity of developmental processes in response to interactions with the previous generation that we have found in our studies. Specific instances of responsiveness of a developing trait to a particular environment, such as the environments created by parents, are likely to be retained and shaped by natural selection during evolution when they provide a compelling advantage over many generations (see Section V). Such effects are actually common in nature and occur in

many species: first discovered in reptiles and insects (Mousseau & Fox, 1998), then in a variety of mammals (Maestripieri & Matteo, 2009; and placed in a broader perspective in Mousseau et al., 2009). Their evolutionary advantage stems primarily from their beneficial effects on the next generation, effects that are “anticipatory;” that is, they equip the offspring in advance for predictable environmental threats. For example, the genetic and epigenetic mechanisms underlying the timing of female sexual behavior, and later egg laying or birth, according to annual cycles of light and temperature, have been shaped during the evolution of many species, by selection for behaviors that anticipate the future needs of vulnerable offspring. In other words, young organisms evolve to be sensitive to their initial environment, as “communicated” through the mother, because that can give them the ability to develop adaptations even before they encounter challenging features of the particular environment in which they will function as adults.

In mammals, the mother is the complete first environment, and is part of the pup’s inheritance, an “inherited environment” (no longer an oxymoron). The mother-infant relationship is thus in a position to function as a matrix and template to guide and shape developmental patterns in her offspring. And the adaptations of immature animals to the early environments created by their parents are evolutionarily-shaped functions of development that may account for many of the stage-specific behavioral and physiological regulatory processes that we and others have discovered within the parent-infant interaction, and that account for the complex responses of infants to maternal separation. Furthermore, changes in the biological substrates of maternal behavior that are induced in the mother by stresses in her life may become “targets” for evolutionary selection because some of these promote the development of her young in ways that anticipate, and protect them against, similar stresses appearing during their adulthood. Such developmental variations are potentially heritable through altered maternal behavior being passed on to the next generation.

An example of just this kind of evolutionary developmental process can be found in research by Frances Champagne and Michael Meaney (2006). They showed that if pregnant female rats were subjected to stressful conditions, their later behavior toward their newborn pups was altered so that they licked and groomed them less. This, in turn, altered their pups’ development, so that as adolescents and adults, her offspring were pre-adapted to harsh conditions. Through epigenetic changes in the regulation of the pups’ developmental genes, they showed earlier maturing sexual and reproductive behaviors, and as adults, they were more aggressive and less anxious; and they were less likely to show extreme corticosteroid responses to stress in their lives. This

research reveals processes capable of modifying the developmental paths of offspring in the next generation to prepare them for the harsh conditions predicted by the mother’s own previous life experience. Such “predictive” adaptations provide a clear survival advantage and give us a reasonable account of how this form of long-term influence of maternal behavior is likely to have evolved within developmental systems by selection over generations. Anthropologists have described similar “matching” of early rearing patterns with different subcultures, for example, the very different levels of maternal care in tribes of hunters compared to tribes of farmers in neighboring African kinship groups (Fouts, 2010).

Paradoxical implications for human society

The pace of cultural evolution and the overall “acceleration of history” have resulted in a steady increase in the rapidity of intergenerational change in many human societies. As a result, evolved developmental systems predicting what sort of environment the children will grow up in, based on the prior life experiences of parents, may no longer be so adaptive. The “pathological” behavior of adolescents emerging from childhood experiences we now view as abuse and neglect may actually have been protective in primitive and unstable environments during our evolutionary past in which their lack of investment in social relationships, hyperactivity, aggression, short attention span, and rapid sexual maturation would have been adaptive. Now, with more rapid social evolution in a number of countries, these characteristics are hardly adaptive when such children find themselves in new charter schools and protective communities (Hofer, 2006).

IX Relating animal model research findings to mental development

Thus far, I have sketched out an evolutionary perspective on development that has helped us understand how the unexpected behavioral and physiological processes that we found in our research may have evolved, and how they fit into a new way of thinking about development itself. But another kind of question remains: what are the implications of this perspective and these research findings for an understanding of early *mental* development, the primary concern of psychoanalysis? I have previously used the phrase “component processes underlying the psychological constructs we use to understand attachment” to convey the idea that these biological processes “embody” the psychological constructs. And I think of the mental life of humans and the observed events and inferred processes of the psychoanalytic situation as having “emerged,” in both evolution and

development from the biological level of the behavioral and physiological processes we observed in our research.

I have used the words “emerge” and “embody” here because they seem to me to be the best and simplest ways to refer to the still mysterious processes through which the unconscious and conscious processes of humans derive from their bodies and brains. Both words are used in current research and theory in the sense of “emergent” properties in complex dynamic systems (Smith & Thelen, 2003) and “embodied” cognition (Overton, Mueller, & Newman, 2008), and they are currently being actively discussed and tested for their usefulness. They have the advantage of an intuitive simplicity that makes talking or writing about the relationship of biology to psychoanalysis somewhat less difficult. However, they tend to remain at the level of useful metaphors, while their translational basis remains a “work in progress.”

When I was a resident, I remember one of my psychotherapy supervisors saying to me somewhat impatiently: “Don’t pay so much attention to what he (the patient) says, get him to look at what he’s doing!” His implication was that behavior is often the best clue to the content of the unconscious mind. Increasing evidence now shows that the brain circuits responsible for subjective feelings and even for abstract thinking in humans are clearly linked functionally to (and probably evolved from) far older circuitry that analyzes and processes our sensory experiences and motor acts at the behavioral level of organization (Panksepp, 2003; Kandel, 2012). The current concept of “embodied cognition” (Overton et al., 2008), Freud’s concept of the body ego (Freud, 1923), Damasio’s views on the role of the body in the origin of consciousness (Damasio, 1999), and the recently discovered “mirror” neurons which provide a means of concretizing (and oversimplifying) how empathy may be registered in the brain (Rizzolati & Sinigaglia, 2008), all illustrate different ways in which the many connections between body, behavior, and mind have played central roles in theory – while admitting our complete failure to conceive of how the physical processes of the brain can give rise to the subjective experiences of the mind.

With this perspective, I will revisit our research on the attachment “bond.” We know what a bond feels like in our own experience: the sense of an almost magnetic force, of being “pulled” forward toward the person, the flood of memories of past interactions, and a vivid mental image of the person. We could believe that such a state might exist in a baby, but it seems unlikely in an infant rat. However, the outward manifestations of the bond, the behaviors of intense activation, approach, and maintaining contact are similar in the two. The research question we asked was, how did these behaviors first develop? And we discovered that, even in a far less evolved species, the infant’s “bond” consists of a set of

memories and presumed associated feeling states, laid down through specific interactions with its mother. These can be viewed as constituting a simple mental representation of the sensations, contingencies, physiological/emotional states and actions previously experienced. Thus, it is highly likely that a human baby, and even a fetus learning to recognize its own mother’s voice (Fifer & Moon, 1995), also start to form internal object representations very early, and in a roughly similar way: through associative learning processes.

Further, we found that the process of bond-formation, in our model system, can be further analyzed into its component parts, as discussed above (and reviewed in Hofer & Sullivan, 2008). We found that during an early critical period, approach and huddling behaviors toward an object are learned – even if the stimulation associated with the sensory cues was so intense (like mild electric shock) that it elicited escape responses in the infant. And, if this early aversive learning experience was repeated each day, the “traumatic attachment” and the functioning of its neural substrate could be extended for many days past the end of the critical period, and even into adulthood (Landers & Sullivan, 2012). These findings closely resemble clinical findings in the infants of abusive mothers whose persistent strong attachment to their mothers is difficult to account for psychoanalytically. Perhaps when this form of “aversive learning” is repeatedly activated, this early experience can establish painful stimulation as something sought after (with or without any association with sexual stimulation), a primitive form of primary masochism (Freud, 1905; Freud, 1924).

Another finding from our experimental analysis of early attachment has been the discovery that specific maternal-infant interactions serve to regulate the basic physiology of developing infants (such as sleep states, body temperature, autonomic balance, level of general motoric activity, and adrenal and growth hormone levels) as well as their behavior patterns over time. These findings suggest a new way of understanding how different “qualities” of human maternal behavior, made up of different patterns and rhythms of intensity in these specific regulatory interactions, can have long-term shaping effects on development.

As soon as associative memories begin, infants start to function at a symbolic, as well as a sensorimotor, level at which regulatory processes originate. In infants of species with the necessary cognitive capacities, mental representations of caretakers are formed out of the individual units of their experience with regulatory interactions (as I described briefly in Section IV, and reviewed in Hofer, 1995). Once formed, these organized mental structures may be thought to act as superordinate regulators of biological systems underlying motivation and affect, gradually supplanting the sensorimotor, thermal, and nutrient-based regulatory systems found in younger

infants. Maternal warmth, patterns of touch, odor, rocking, and nursing are associated with the infant's clinging, reaching, and sucking. Since these behavioral interactions have the capacity to regulate powerfully many of the infant's biological homeostatic systems, this could add a physical dimension to these early representations, associating the physiological regulatory responses to more symbolic components of the representations.

Maternal "regulators" control neural systems mediating reward, arousal, and sleep, as well as motivational states such as thermoregulation and hunger. This could be a major reason that early caretakers arouse such widespread feelings of need and pleasure; and could help explain many of the "primitive" elements in dreams, fantasies, and bodily delusions. Likewise, the actions of early hidden regulators and their incorporation into mental representations may explain why early separation in children involves such deeply intense feelings of anxiety, anger, and despair.

In adults, we can think of biological systems being linked with internal object representations throughout their development accounting for the remarkable emotional and cognitive upheavals that take place in bereavement – even simply upon hearing of a death, for example, by telephone. And the psychological and physiological disorganization present in adult grief may be understood, at least in part, as the loss of the regulatory functions previously experienced during the course of a long relationship (Hofer, 1984; Shear & Shair, 2005). We already understand some of the neural components (for example, anterior cingulate and periaqueductal grey) in the generation and perception of these feelings, and key neurochemistries (including opioids, oxytocin, and prolactin) of this process (see Panksepp & Biven, 2012 for review) but much remains to be explored (Johansen, 2013).

What I am suggesting is that knowing about these bio-behavioral processes, and their evolutionary/developmental origins, may provide new ideas for analysts to use in deepening their understanding of the early phases of development of the unconscious mind, and its influence on the lives of their patients that is so crucial for the later development of mental life.

X Psychoanalysis in the light of evo-devo

The idea suggested in the title of this paper is that the emerging synthesis of developmental and evolutionary theory in biology can provide a new conceptual framework within which basic principles of biology and of psychoanalysis can find common ground. This new synthesis brings with it novel biological concepts and developmental processes that support and appear to underlie some of the existing observations, inferences,

and assumptions of psychoanalytic developmental theory. That is why I phrased my title for this paper as "A New Biology for Psychoanalysis." That is to imply that psychoanalysts, working so long in relative isolation from biologists since the end of the nineteenth century, have been presented with a rapid narrowing of the conceptual gap between the two disciplines, primarily through advances in biologists' understanding of evolution and development. This could be seen as a "gift" from biologists in the form of a new theoretical framework in their field within which psychoanalysts can venture further into the world of the new molecular neuroscience so elegantly prescribed for the field of psychoanalysis by Eric Kandel (2012).

In particular, the new concept of development as an integral part of the evolutionary process will benefit both psychoanalytic and biological understanding of development. Biologists can no longer consider biological development simply in terms of its functions in creating growth in the size and complexity of organisms, or describe its processes simply as a continuous series of interactions among the products of gene expression. As described in this paper, development consists of changes in a variety of systems evolved to create variation in traits, to maintain heredity through the creation of transgenerational templates, and to adapt immature organisms to a series of unique developmental niches. The functions of the various developmental processes are organized by their connections with each other in patterns of self-organization, by the effects of activity in their own and other systems, and by signals emanating from all levels of their environment. Progress in biology has therefore reaffirmed the central importance of childhood for the functioning of the individual and for the development of the species, which brings it much closer to psychoanalytic perspectives than it has been in a century.

For psychoanalysts, this progress in biology suggests that *mental* development as well should not only be conceptualized as progressing from the undifferentiated to the differentiated, from the primitive to the advanced, or as a series of steps in the formation of the self. Developmental phases do not simply function as steps toward adulthood, but have other functions as well, for which they were selected during evolution. For example, the mother-infant relationship functions not only to shape the development of affect regulation and mental representation, but also functions to create novel variations in psychological traits, to regulate physiology, to specify long-term effects in adulthood, and to facilitate their transmission across generations.

Finally, but perhaps most importantly, the major evolutionary function of development as a creator of variation underlies the uniqueness of the individual that emerges in the process of development and in the course of psychoanalysis. For all those trying to understand

development, “Evo-Devo” is a major advance because ever since the collapse of Haeckel’s “biogenetic law,” development could only be approached empirically (by biologists), or viewed through a cloud of competing theories (by psychoanalysts) and without a concept of how development is related to evolution.

Psychoanalysis has had its roots in biological evolutionary thinking since it was founded by Freud in the late nineteenth and early twentieth centuries. However, throughout the twentieth century, biology became identified with the “nature” side of an endless argument that forced a choice between “nature and nurture.” No wonder psychoanalysts grew away from their Darwinian roots and, to a considerable degree, from biology itself. Now, for the first time since the fall of Haeckel and Lamarck at the close of the nineteenth century, there is an opportunity for a dialogue on the subject between psychoanalysts and biologists that can benefit both fields. In this paper, I have discussed how developmental psychobiology research can contribute to psychoanalysts’ understanding of the early formation of object relations, mental representations, the devastating effects of early separation or loss, and the long-term effects of early experience on adult development. The new field of cognitive developmental neuroscience, and its psychoanalytic counterpart, neuropsychanalysis, are already creating new links between measures of brain function and intrapsychic processes within the psychoanalytic situation, such as transference, unconscious conflict, empathy, mental representation, and the emerging sense of self.

Likewise, psychoanalysts can benefit from the implications of the Evo-Devo synthesis for three major components of psychoanalytic developmental theory (as defined in Gilmore, 2008): (1) the psychogenetic view of the adult patient in treatment, (2) the growing field of infant research by psychoanalysts, and (3) the several different schools of psychoanalytic developmental theory. Analysts representing one or another of these three components are currently pursuing more or less separate courses, with the legitimacy of each being challenged by proponents of the others (Gilmore, 2008). The conceptual ground on which evolutionary developmental biology and psychoanalytic thinking are closest to meeting each other in the future is at the level of the unconscious mental processes that have evolved, and appear to develop similarly in humans and many other mammals.

I have given several examples earlier in this paper, but there are many more such meeting points to be found in the increasingly mature field of sociobiology. Here, unconscious conflict between numerous evolved motivational systems is also a central concept that has been increasingly well established and understood across species: for example, parent-offspring conflict, sexual and parental conflict, kin selection, symbiosis, and psychosexual maturation (Alcock, 2001). In sociobiology,

the evolutionary history of conflict between competing selection pressures in the evolution of many behaviors is being worked out and confirmed by predicted outcomes across species (including humans) and within different ecological conditions.

Most recently, in a startling new departure, E. O. Wilson, arguably the founder of sociobiology, has made a major change of course in his new book, *The Social Conquest of Earth* (Wilson, 2012) by re-evaluating the gene-based kin-selection theory (Hamilton, 1996) he formerly embraced, and replacing it with a modern-day version of Darwinian group selection. The original scientific paper first proposing this new view (Nowak, Tamita, & Wilson, 2010) and the lively arguments that have been raised, both for and against it by others, have been elegantly presented and analyzed (Bourke, 2011), without any clear outcome in sight. Wilson, Nowak, and colleagues’ new theory has the remarkable potential for bringing our understanding of cultural evolution, based on groups with competing traditions, technology, arts, and language (Fitch, 2009), closer to evolutionary biology (Smaldino, 2013) on the one hand, and to psychoanalysis on the other.

In closing, I’d like to speculate about the future relevance of Evo-Devo for psychoanalysis by imagining a young psychoanalyst in training with a college degree in evolutionary developmental biology and a Ph.D. in neuroscience, who decides to derive a set of psychoanalytic principles from their biological roots, just as Freud did; except he could use, in addition, his clinical training and early experience as a psychoanalyst. Could he use his knowledge of how the study of evolution is necessarily approached retrospectively through the study of the fossil and genetic records, as a parallel and a framework for the “psychogenetic” view which sees development retrospectively through the memories of the patient, along with the patients’ reenactment of their development in the transference? Could our young psychoanalyst find ways to use infant observation research as well as developmental psychobiology in animal models, to build a stronger and more useful psychoanalytic theory of development? Would she be able to find a way to use new techniques of brain imaging and neural-circuit analysis to gain a picture of how human capacities for inner experience and for art, music, and language, might have evolved from earlier primates and how they develop in each individual? Or perhaps this person is already at work somewhere, and readying her first paper for publication ...

Clearly, we are in the very early stages of our attempts to understand the evolution and development of mind. Biologists are just beginning to ask questions at the level on which psychoanalysts have been working for more than a century. But progress in psychoanalytic investigation has been less rapid than in biology over the

last two generations, and it seems possible that with increasing communication between the two fields, we are on the brink of a new era of discovery in psychoanalysis as well as in biology. It is too early to know how far this new synthesis in our views of development and evolution will take us in our thinking, but it seems to me that it has brought us much closer to being able to think about psychological and biological development in the same frame of reference. And it is hard to believe that this will not eventually be valuable for both psychoanalysts and neuroscientists.

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