

The Frog in Taffeta Pants

KENNETH WEISS

What is the magic that makes dead flesh fly?

Where does a new life come from? Before there were microscopes, and before the cell theory, this was not a trivial question. Centuries of answers were pure guesswork by today's standards, but they had deep implications for the understanding of life. The phrase *spontaneous generation* has gone out of our vocabulary except as an historical relic, reflecting a total success of two centuries of biological research.¹ The realization that a new organism is always generated from one or more cells shed by parents explained how something could arise where nothing could be seen.

However, if this solved one question about the origin of organisms, it left a related problem that is still with us, that of explaining autonomous generation—development—which has become a core question in modern biology and genetics, and is relevant to the physical and behavioral traits that are at the heart of anthropology. Where do they come from each generation?

OMNE VIVUM EX VIVO?

The ancients knew about parents producing offspring of their own kind, but also that there isn't a chicken inside an egg when it is freshly laid.^{1,2} It was not just a lack of microscopes that made this latter fact one that de-

manded explanation. There was no compelling reason to think that what one needed to find was too small to see. Aristotle hypothesized *epigenesis*, a kind of spontaneous generation of life from the required materials (provided in the egg), that systematic observation suggested coalesced into a chick. Such notions persisted for centuries into what we will see was the critical 17th century, when the following alchemist's recipe was offered for the production of mice:^{3,4} mix sweaty underwear and wheat husks; store in open-mouthed jar for 21 days; the sweat will penetrate the wheat, changing it into mice.

There was an equally persistent alternative view. In 50 BC, Lucretius (*de Rerum Natura*) wrote that "The first bodies of each thing must be inside the seed; because of this all things can not arise from anything. For each particular seed has, in itself, hidden inside its own distinctive powers." It seemed reasonable to assume continuity in nature, so that what we see reflects what happens before we can see it, making it logical to infer that either the sperm or egg contained a future organism in miniature, an issue long and hotly debated between the "ovist" and "spermist" schools of thought. The imagery of *preformation* has been made famous by countless reprinting of Nicolaas Hartsoeker's 1694 AD drawing (Figure 1). An implication was that an organism's gonads contain, in ever more miniaturized and nested form, the preformed embryos of all its potential future descendants. Biblical scholars related this to a preordained course of human beings from Adam to Armageddon (though after later work, Hartsoeker

himself gave up on the preformation view).

These various intuitions arise naturally, if sometimes fancifully. The naturalist Henry Bates observed that the natives in the village of Aveyros, up the Tapajos tributary to the Amazon, believed the fire ants, that plagued them horribly, sprang up from the blood of slaughtered victims of the rebellion of 1835–1836 in Brazil.⁵ In fact, Greek mythology is full of beings spontaneously arising—snakes from Medusa's blood, Aphrodite from sea-foam, and others. Even when the truth is known, we can be similarly impressed with the phenomena of generation. John Muir observed, "The bluebottle is abundant in these Yosemite woods, ever ready with his marvelous store of eggs to make all dead flesh fly."⁶

TWO CENTURIES AT THE HEART OF BIOLOGY

The scientific assault on the question began in earnest in the 17th century,^{2,7} but took two centuries to complete. The most famous example of spontaneous generation was the appearance of maggots in dead meat. In 1668 Francesco Redi (Figure 2) performed a classic study⁸ that some consider to have been the first controlled experiments in the history of science. He put dead flesh in an open dish, in which maggots soon appeared as expected. I never realized until I repeated the experiment for this column (Figure 3) that if you were not aware of the tiny fly eggs, the maggots make their appearance, dramatically, burrowing out *from the inside*, the whole piece of flesh subsequently throbbing like a heart before being transformed almost entirely into maggot. No wonder the explanation that had been

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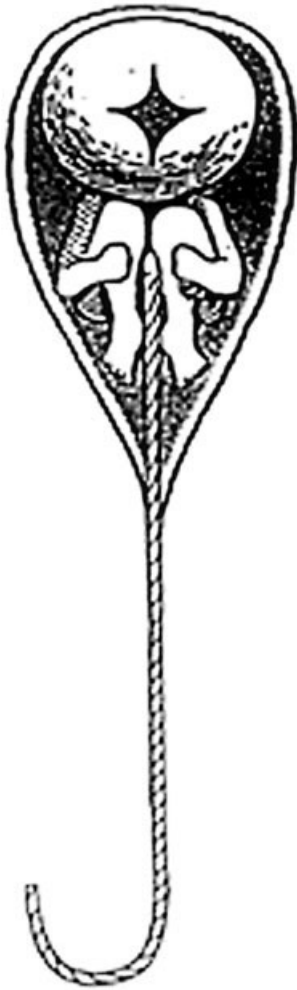


Figure 1. Homunculus (Hartsoecker, 1694, *Essay de Dioptrique*).

given! But if Redi covered an identical container with fine gauze, no maggots appeared. Instead, he observed flies

swarming around the gauze and laying eggs on it that quickly hatched as maggots. Dead flesh does not fly of its own accord.

This was not entirely the end of a story whose importance even to late 19th century science was reflected in the famous 1870 Presidential address by Thomas Huxley (Figure 4) to the British Association for the Advancement of Science.⁹ If Redi had shown that complex animals like insects did not arise spontaneously, this did not account for the appearance of tiny “animalcules” when substances like beef broth, infusions of grain or hay, grapes, and many other things decayed or fermented. These had been observed since the early days of microscopy. Could this *simple* form of life arise spontaneously? Attempts to repeat Redi’s experiments in regard to the origin of this primitive life-form were notoriously inconsistent, explaining why the issue could remain for so long a central question in biology. The problem (we now know) was the incomplete elimination of boiling-resistant spores, cells too small to filter by the means that were tried, and the ubiquity of microbial life in the air around us.

The fermentation question was finally put to rest by the vigorous energies of another of the century’s great science entrepreneurs, Louis Pasteur (Figure 5), in promoting his microbial view of the world. In an 1864 address to the Sorbonne Scientific Soirée he noted that “the most striking errors

count their persistence in centuries,”⁴ but that did not make them right. A fighter like Huxley, he was determined to prove the errors of rivals like the famous Comte de Buffon and his own peer Felix Pouchet, who advocated molecular vitalistic versions of epigenesis. In experiments beginning in Darwin’s year, 1859, that essentially refined Redi’s logic, Pasteur placed fresh, boiled broth in a flask constructed with an S-shaped neck that kept microorganisms from settling from the air onto the broth, and no fermentation occurred. With this proof that microbes, too, arise only from parents of like type, Pasteur provided another instance of what Huxley called “the great tragedy of Science—the slaying of a beautiful hypothesis by an ugly fact.” Not even tiny microbes arise by themselves.

I’m omitting many details of a long history,^{1,2,7} but Pasteur and Huxley were both clear about the importance of a proper understanding of microbial generation. That had enormous implications for agricultural pest control and manufacturing (e.g., wine, baking, beer, silk), and for public health. Huxley raised the additional and unanswered question of *xenogenesis*, the appearance of animal tumors and plant galls: what form of new life were these, that sprung up within an organism?

If even complex organisms come from other life, what is the contribution of male and female and why are both needed? Was the fly contained in



Figure 2. Pioneers (A) Francesco Redi. (B) Title page (5th ed., 1688). (C) Lazzaro Spallanzani. Portrait sources: Spallanzani www.chemheritage.org/EducationalServices/pharm/antibiot/activity/spapas.htm Redi: www.francescoredi.it/

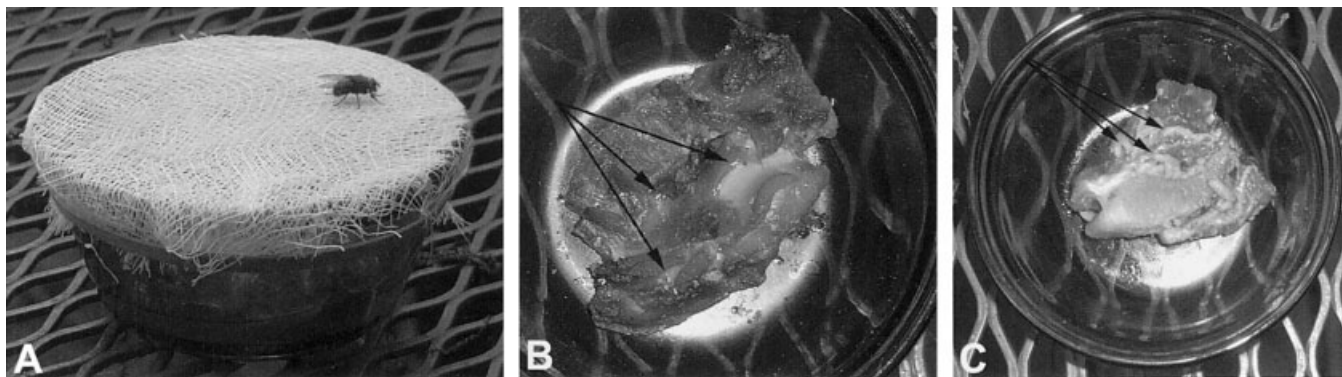


Figure 3. Redi redux triptych (2003 AD). (A) Fly desirous. (B) Fly eggs after 24 hours (arrows show a few). (C) Riddled with maggots and pulsating after 48 more hours (arrows show a few).

the egg, or sperm? We think of ovis versus spermists as quaint naivety, but when microscopists demonstrated parthenogenesis in aphids, it seemed an important issue. To address it, Lazzaro Spallanzani (Figure 2) performed a series of clever experiments in the 1760s. Semen was known from microscopy to contain wormified beings in a thicker component, and a thinner liquid. Spallanzani dressed male frogs in tight-fitting taffeta pants and let them “seek the female with equal eagerness, and perform, as well as they can, the act of generation.”¹⁰ (cited in Moore¹). All jokes about amorous frog Princes aside, the males’ modest attire prevented the denser fraction from reaching the eggs, and this prevented fertilization: the egg was not the ovis’s self-contained en-

tity needing only chemical stimulation by the seminal fluid.^{1,7} Actually, in the end Spallanzani concluded that something in the thicker fraction of semen was responsible, because he could not accept that it was its wriggly contaminants.

THE MODERN VIEW: AUTONOMOUS GENERATION

Hartsoeker’s homunculus and frogs wearing taffeta condoms draw smiles, because we are now completely convinced not just that all life comes from other life, but of Virchow’s additional dictum that all cells come from other cells. But we should think a little more carefully, because showing *that* a new life only comes from other life forces the question *how* it happens. The answer is as remarkable as the notion of spontaneous generation could ever have been, and ties together elements of preformation and epigenesis as well.

After all, what is a new human life? A fertilized egg has no limbs, sense of humor, or hair. Yet, this single cell is in many ways an *autonomous* entity that really does develop spontaneously from raw materials. In the modern view the key is DNA. The notion of the genome as an information-storage unit may be an overworked metaphor of our computer age,^{11,12} but fertilized eggs do, after all, turn into people.

Perhaps even more profound is that the same few basic processes transform raw materials into people and oak trees. These include 1) complementary base-pairing of DNA and RNA (A with T, C with G); 2) the specificity of interactions between pro-

teins and other compounds; 3) ligand-receptor binding involved in the receipt of extracellular signals that change gene expression within cells; 4) protein-DNA binding that allows transcription factor proteins to express or repress specific genes based on regulatory sequences in DNA located near the genes;¹³ and 5) the sensing of extra-cellular conditions (such as pH or salt concentrations) to which cells can actively adjust (e.g., ion channels, neurotransmission).

It is not just its genome but the relative timing and use of context-specific subsets of a species’ genes that produces all complex organisms. Figure 6 is a schematic representation of the way this works. S number represents signaling factors released by cells (not shown) and received by target-cell receptors indicated by arrows entering the latter, and G number indicates specific genes expressed within each cell. The hierarchy of signaling switches leads to hierarchically differentiated combinatorial gene expression among the cells in an organism. Since the cells are otherwise *sequestered* from each other, local tissues can develop independently—autonomously. For this reason, local gene combinations that include some overlapping genes can specify unrelated structures (e.g., G1 and G4 in the figure).^{14,15–17}

Internal conditions start a cell off by controlling the expression of an initial set of genes. Those conditions are not “spontaneous” in that they include parental mRNA as well as the right assemblage of nutrients and other



Figure 4. Thomas Huxley as President of the BAAS (from *The Period*, Nov 26, 1870).

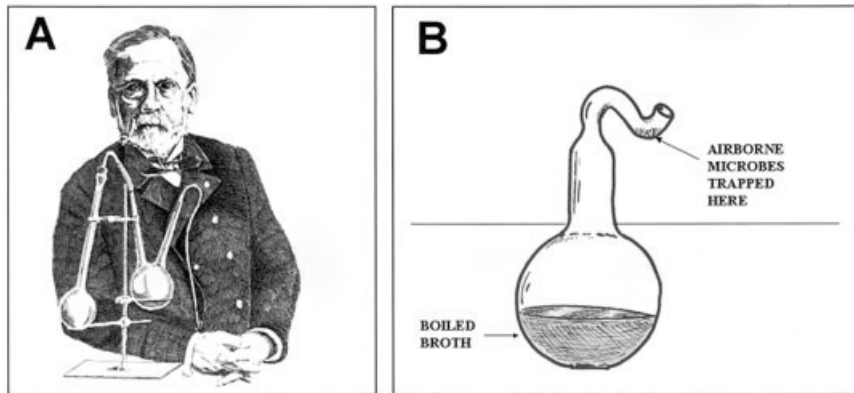


Figure 5. Louis Pasteur. (A) Portrait. (B) S-shaped experimental flask. Pasteur: www.accessexcellence.org/AB/BC/Louis_Pasteur.html.

chemicals. But once this begins, cells produced by subsequent mitosis retain their expression profiles until signaled to change. Thus, the genes that set up the anterior-posterior body axis lead to the expression of genes related to the formation of vertebrae, but because the latter occurs later in the embryo, the genes expressed in different parts of the vertebral column are different, and so are the resulting vertebrae. This is a temporally forward, *conditional* (context-specific) process of differential, combinatorial gene expression that does not look backward, either within the organism or from the organism to its parents. Subsets of the tree of developmental descent are themselves as autonomous as the original egg was (thus, tooth germs can be cultured and develop *in vitro*). It is this developmental unfolding (the original use and meaning of the term “evolution”) of what is already there that makes a complex organism.

DNA settled the ovist-spermist debate, and also accounts for xenogenesis. Viruses and somatic mutation, unknown to Huxley, can cause tumors by introducing new or modified DNA into a cell. This directly affects the cell in which it occurs, not the whole organism, but the affected cell can then proliferate, generating a new, partially autonomous tree of descent within, but not part of, the organism, one of the major killers of our time. We don't consider a tumor to be a new kind of organism or species, but it is easy to see that it blurs the distinction between notions of spontaneous generation and parental transmission.

The difference between you and an oak tree is due to DNA sequence differences. It is this “information” that allows the cell to develop autonomously without instruction imposed from the outside and without the need for an organism-in-miniature. This is also why the system is universal from microbe to macro-organism.

So, in meaningful ways, by starting out life as a single cell you really were preformed in your genome, and you really were generated by epigenesis out of non-living materials. But far from spontaneous assembly out of unformed raw materials, and far from containing the preformed miniatures of all *future* generations, the genetic

components have built into them the legacy of 3+ billion years of *prior* ancestry.

KICKING THE PRIMAL SOUP UP TO NOTCHES UNKNOWN

The modern denial of spontaneous generation is not quite as total as it may seem, because we are merely deferring the question of the origin of life itself back to a sufficiently remote time when, in what Huxley called “an act of philosophical faith,” we can safely assume that spontaneous generation *did* occur. In fact, given that assumption, it is not surprising that there are efforts to develop a recipe by which we, too, can create new life from scratch.¹⁸

The goal is to synthesize a functional organism, not just fire up self-sustaining biochemical reactions. Craig Venter, the Dark Force who challenged NIH to a race to sequence the human genome, and several other groups, are attempting to identify the minimal set of genes that would suffice. A combination of approaches is being taken, using simple single-celled organisms. The approaches include comparing the gene sets of very distantly related bacteria, the systematic experimental inactivation of genes, one by one, to see which are needed and which dispensable, and even the stepwise assembly of artifi-

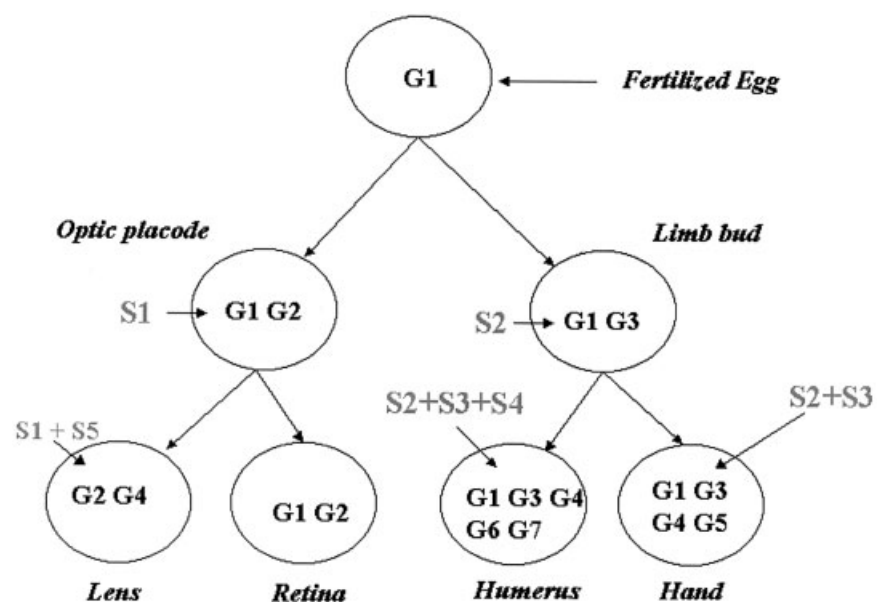


Figure 6. Schematic of hierarchical gene regulatory cascade by which hierarchically autonomous development is controlled (see text).

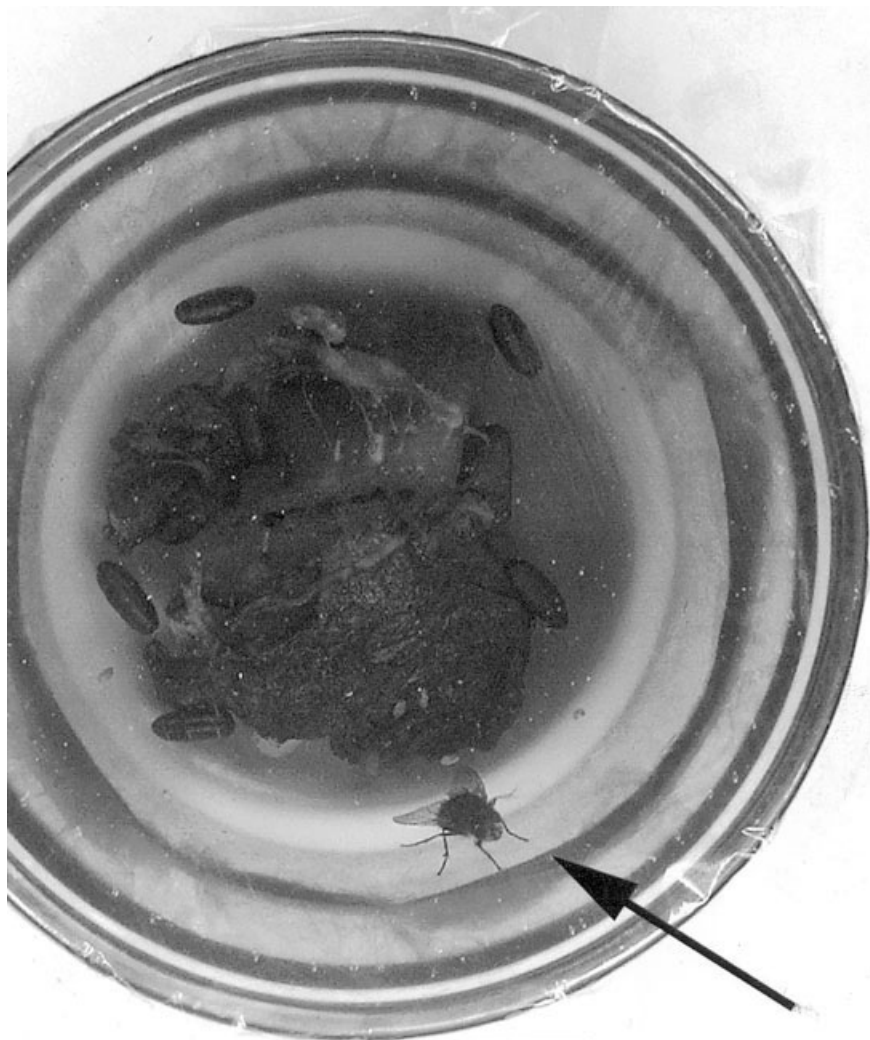


Figure 7. "Evolution" Emerging: dead flesh flies with pupae waiting in the wing.

cially synthesized known candidate genes (polio virus has already been generated this way¹⁹) to see what is needed. Because the work is in progress and may have commercial value, public details are hard to come by, but results so far suggest that only a few hundreds of genes are needed.^{20,21} These are involved in energy metabolism, DNA replication, and protein translation. Making a Minimal Being with these abilities would demonstrate that *some* minimal functional set of genes is viable. But the achievement would be tempered by the fact that we already know these basic functions are needed and have worked out their genetics. The Minimal Being would be so crippled of natural function that it could only

survive in the loving care of a lab technician in a highly controlled environment. It would not be an organism in the usual sense; what it takes to be a real minimal being and how the existing ones got that way are subtle.²²

Attempts like these are relevant to the issue of spontaneous generation. The Minimal Being will resemble neither the first life nor any existing life. When successfully created, it will *not* be spontaneously or probably not even autonomously generated. The cell was evolution's Great Leap Forward from the biochemistry of Primal Soup. But so far we know of no way other than nature's way to make the membranes that are fundamental to all cells. To mimic real life we need to set up a tubeful of chemicals that first

self-assemble into a cell with new membranes and then replicate—and do it without any pre-existing RNA (like the maternal mRNA that got each of us going). And all indications so far are that even after this neoalchemy, we will have to supply a spark of existing life of some kind—to "shake well before using."

Even when this is done it will in no way be spontaneous generation of life congealing in an artificial NeoPrimal Soup. Life generated *in vitro* will be based on assembling *pre-existing* genes that we *discover*, and they will be genes with 3+ billion years' evolutionary maturity. At best, a test-tube cellular baby might be viewed as spontaneous (and artificial) *speciation*.

We already can engineer genes into existing species, like herbicide resistant genes in corn or soy beans. This and more extensive genetic engineering will undoubtedly occur in the foreseeable future. Such changes are the spontaneous introduction, not generation, of new traits. They may have widespread effects on the organism, but even this would be neither the spontaneous generation of an organism or even of a gene, because we would be simply modifying or transferring an existing evolutionary product (the gene).

However, we can dream. It is possible to synthesize random amino acid sequences, and screen them *in vitro* to find ones that served some prespecified function like resistance to microbial attack or speeding up some metabolic process, then back-translating the winner into corresponding DNA sequence and introducing the resulting gene into a species. That would be a new, in a sense, spontaneous, product that will be highly touted as having got us much closer to Genesis. It is likely to happen, perhaps soon (pharmaceutical firms are working in directions of this sort). But a gene is not an organism, and it will be some time before we can synthesize those anywhere outside of Hollywood.

Truly spontaneous generation in nature would play havoc with evolutionary biology, which is based entirely on the concept of all life having diverged from essentially a single and ancient common origin. But if life

could arise all by itself once, why doesn't spontaneous generation, at least of the primeval kind, still occur? Perhaps it does. The raw ingredients are everywhere. In fact a recent experiment showed that random short strings of amino acids could rather easily generate fundamental biological properties.²³ But whether or not rudimentary biochemistry is taking place in the soil, sea, or air around us is basically irrelevant to evolutionary biology.

Any such activity would be based on primitive molecular interactions that cannot compete with organized life (which would probably just eat it up at every encounter). There is no evidence whatever of brand new life evolving clades of differentiation, autonomy, or complexity. There is only one of *that* kind of life, and the truly spontaneous generation we assume once did occur was only of the simplest of biochemical processes, not bluebottle flies or fire ants. Today, only a fly can make dead flesh fly. This was what Pasteur showed "with experiments so gripping that you cannot fail to remember them."⁴

NOTES

I welcome comments on this column: kenweiss@psu.edu. I maintain *Crotchety Comments* on my web page: www.anthro.psu.edu/rsrch/weiss lab.htm. I thank Anne Buchanan, Nancy

Tuana, and John Fleagle for critically reading this manuscript.

ERRATUM

A typo that neither Word nor I spotted in my installment "Dinner at Baby's" (Vol. 12, p. 247) compares brutish brutes to "advanced and gentle" humans. No compliment to any religion was intended, as all are (hopefully) "gentle."

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Many things discussed here can be profitably explored by web searching.

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