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Infant mouthing behavior: the immunocalibration hypothesis

Daniel M.T. Fessler*, Elizabeth T. Abrams

Department of Anthropology, 341 Haines Hall, University of California, Los Angeles, CA 90095-1553, USA

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Summary Avid mouthing, the propensity of infants to suck objects and put them in their mouths, is a pattern characteristic of the first 2–3 years of life, with its most intensive manifestation occurring during the first year. Although traditional accounts explain infant mouthing as a source of sensual gratification and/or environmental exploration, these proximate hypotheses are inconsistent with the high costs of mouthing, including choking, poisoning, and exposure to pathogens. We propose that mouthing serves to proactively expose the naive gastrointestinal tract to environmental antigens and commensal bacteria while under the sheltering umbrella of breastfeeding. Mouthing functions to accurately calibrate the developing immune system, including antibody production and mucosal immunity, to the local disease ecology. The critical exposure period is not open-ended, as failure to expose the gut to an adequate number of antigens early in life is associated with an increased risk of allergies, asthma, and atopy. Weaning initiates a number of immune changes that may program the neonatal immune system into certain life-long responses.

Introduction

A marked feature of the early phases of human life is the propensity to mouth or suck on a wide variety of objects. Infants and toddlers (hereafter simply 'infants' for brevity) avidly pursue opportunities to engage in this behavior, engaging in clearly goal-directed efforts to grasp small objects and bring them to the mouth or, in the case of larger items, to bring the mouth into contact with them. Importantly, infants are relatively indiscriminate in this regard, displaying few or none of the criteria employed by adults in discerning which objects merit oral contact (see [1]). From an evolutionary perspective, such behavior is puzzling, as avid and indiscriminate mouthing places the infant at substantial risk of ingesting pathogens, parasites, and toxins, as well as choking on foreign objects. In the United States, between 1 and 18 out of every 100,000 infants die each year due to accidental poisoning (from data reviewed in [2]), while ≈4 out of 100,000 lose their lives choking on foreign objects [3]. Granted, in ancestral populations, the incidence of such events might have been lower due to a combination of the more extensive oversight of infants afforded by the distribution of child care duties among a network of extended kin and the greater rarity of poisons as potent as the

* Corresponding author. Tel.: +1 310 794 9252; fax: +1 310 206 7833.
E-mail address: dfessler@ssc.ucla.edu (D.M.T. Fessler).

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synthetic toxins present in modern societies. However, the absence of modern medical care in ancestral populations would likely outweigh such differences, added to which the more intimate contact that infants would have had with the natural environment would have placed them at considerably greater risk of ingesting pathogens and parasites (cf. [4]). In fact, mucosal pathogens, particularly those that target the intestine, are a major cause of death of children under 5 years old, killing 5 million children per year in developing countries [5]. In short, there are good reasons to believe that infant mouthing behavior is dangerous, and always has been.

Given the substantial fitness costs of this behavior, existing attempts to explain infant mouthing are surprisingly inadequate. Freud [6] argued that sensual gratification is initially focused on the mouth because nursing is the infant's sole source of nourishment. However, given the unique sensory properties of the human breast, it is difficult to see why infant mouthing behavior should be so indiscriminate — shortly after birth infants orient to the scent of the mother's breast [7], hence they are clearly capable of differentiating this source of food from other objects in their environment. A quasi-Freudian account common in the contemporary literature is that mouthing and sucking provides a sense of well-being. However, while unquestionably accurate (witness the aptly-named 'pacifier'), this is merely a description of the proximate workings of the phenomenon at issue rather than an ultimate explanation of the behavior.

An explanation enjoying near-universal popularity in textbooks and scholarly publications is that infants mouth objects as a means of exploring their environment. Adults and older children rely on sight, sound, and touch to explore their environment, and employ the mouth only in a highly selective manner when seeking to learn about objects. Infants are obviously capable of employing these same sensory modalities to gather information about the environment — indeed, they use sight and touch in detecting and manipulating objects with the goal of mouthing them, thus raising the question as to why infant exploration should differ so greatly from that of adults. Moreover, because young infants' ability to transfer information across sensory modalities is limited [8,9], infant mouthing may confer few of the information-gathering benefits that, on those rare occasions when they employ it, adults reap from oral exploration. Consistent with these objections, direct tests of the exploration hypothesis reveal that, at best, it explains only a limited proportion of all mouthing behavior. First, overall mouthing does not decline with familiarization with an object, and tends to occur after, not before, visual examination of the object [10,11]. Second, when active and passive mouthing are differentiated, observations of 5-month olds reveal that, while the former is associated with subsequent visual examination, suggesting an exploratory function, this accounts for slightly less than half of all mouthing behavior, leaving much activity unexplained [12]. Similarly, a cross-sectional study of infants aged 5–11 months [12] reveals that only mouthing behavior associated with manipulation of the object declines with familiarization and, again, such behavior accounts for only some mouthing. These findings indicate that exploration can only account for a specific subset of mouthing, and hence cannot explain the overall avidity with which this behavior is pursued.

Infants consistently spontaneously expend energy, time, and attention engaging in an activity that entails obvious costs. Natural selection maintains costly species-typical behavior patterns under only two circumstances. First, costly behaviors are preserved when the given action is an inevitable consequence of some other, highly adaptive, feature. However, as noted in regard to Freud's orality hypothesis, given that infants are capable of appropriate discrimination, it is unclear why the motivational systems underlying nursing behavior or similar ingestive activity should produce indiscriminate mouthing as a costly side-effect. Second, costly behaviors are preserved when they entail a benefit, often not readily apparent, that outweighs the evident costs. Although advocates of the exploration hypothesis contend that mouthing is an important form of information gathering, they provide no explanation as to why infantile exploratory behavior should differ so much, and in such a costly fashion, from that employed by older individuals. In contrast to existing explanations, we suggest that infant mouthing behavior is best understood in light of the need to rapidly expose the developing digestive and immune systems to locally-prevalent antigens and microflora during the period when the infant is protected by the sheltering umbrella of maternal breast milk. Because this immunocalibration hypothesis hinges on coordination between the avidity of mouthing, the timing of breastfeeding, and the development of the digestive and immune systems, we begin by reviewing evidence regarding the ontogeny of infant mouthing behavior.

The ontogeny of infant mouthing

Based on the thesis that mouthing behavior is a form of exploration, a number of psychologists

interested in play and cognitive development have examined mouthing. Employing a cross-sectional design, Uzgiris [13] conducted in-home observations of 84 infants, aged 1—23 months, interacting with a standardized set of objects. Mouthing behavior climbed from 1 month of age, reached a peak at 6 months, declined slightly between 6 and 8 months, then declined steeply to 23 months. In a cross-sectional design, Belsky and Most [14] employed in-home naturalistic observation to study 40 infants ranging in age from 7.5 to 21 months. Results show a peak at 7.5 months, steady decline to 12 months, then a steep decline, reaching a relatively constant low level by 16.5 months. McCall [15] conducted a longitudinal study of play in 32 infants between the ages of 8.5 and 11.5 months, finding that mouthing behavior decreased throughout this period. Ruff [10] conducted two structured in-home investigations of reactions to novel objects by 60 infants aged either 6, 9, or 12 months. The first study, using a simple method of presenting each stimulus object once, showed a slight (14%) increase from 6 to 9 months, then a significant (73%) decline between 9 and 12 months. The second study, employing a more complex presentation consisting of three familiarization trials followed by a test trial, failed to find significant age differences. Ruff et al. [12] presented 32 infants, aged 5, 7, 9, or 11 months, with objects in a standardized format. Mouthing time more than doubled between the 5- and 7-month olds, then declined (as a proportion of time in contact with the object, mouthing was 11%, 28%, 18%, and 17% for the 5- to 11-month-olds, respectively). Palmer [16] conducted two studies ($N = 48$, 60) of infants aged 6, 9, and 12 months, using structured observations to examine the effects of object type, composition, and weight on various interactive behaviors. For most objects examined, there was a slight decline in mouthing time between the 6- and 9-month olds, then a much more significant decline at 12 months; for a minority of objects, the direction of the change between 6 and 9 months was reversed, but the decline at 12 months was unchanged.

Many infants die every year from ingestion of concentrated synthetic toxins such as cleansers and pharmaceuticals. However, a more insidious hazard posed by modern life is the presence of substances routinely used in manufacturing or disbursed throughout the home environment. Mouthing behavior brings infants into repeated contact with low doses of materials such as phthalates (used to soften plastics) and pesticides. In order to provide a baseline for estimations of the risks posed by such contact, a number of investigators have sought to quantify naturally-occurring mouthing behavior in infants and children. Sugita et al. [17] studied 25 Japanese infants age 6—10 months, finding a substantial peak in mouthing time (154 min per day) at 8 months. Groot et al. [18] used structured naturalistic observation to study 42 Dutch children age 3—36 months. Mouthing time was high in the 3—6 month category, rose slightly in the 6—12 month category, and then declined steadily. Initially, the fingers were the object mouthed most often, but, by 6 months, with increases in mobility, foreign objects predominated. The U.S. Consumer Product Safety Commission [19] conducted an ethological study of 169 children age 3—36 months. Excluding pacifiers, estimated total daily mouthing times for objects were 70 min for the 3—12 month age group, 48 min for the 12—24 month-olds, and 37 min for the 24—36 month-olds. In three studies encompassing 385 U.S. children age 3—22 months, Juberg et al. [20] used a standardized diary method in which parents recorded timed observations. Although results are presented in a manner that makes the delineation of marked changes in frequency difficult to discern, there is a decline in mouthing time across the entire age range surveyed. Through naturalistic observation using trained observers, Tulve et al. [21] studied 72 U.S. children, age 11—60 months. Although there is some decline across the entire age range, the only statistically significant break occurs at 24 months, with children younger than this averaging 73 mouthing events per hour, and children older than this averaging 31 events per hour. Freeman et al. [22] surveyed parents of 168 U.S. children age 3—12 years regarding oral behaviors. Parents reported that 71% of those age 3 often placed non-food items in the mouth, dropping to 31% by age 4, a figure which did not change appreciably until age 12. In a subsequent ethological study capturing the same age range, the authors found that 3 year-olds placed objects in the mouth significantly more frequently than older children.

Records of medical care provide an indirect index of mouthing behavior, since the likelihood of a medical emergency is a combination of the avidity of mouthing and the degree of mobility, a factor affecting access to dangerous objects. In a study of 1085 Australian hospital admissions of children under 15, Altmann and Ozanne-Smith [23] found that medical emergencies due to foreign body incorporation were most frequent at 2 years, decreased somewhat during the next year, and thereafter declined steadily with advancing age. Given the substantial increases in mobility between ages 1 and 2, this pattern is consistent with the conclusions

derived from direct measures of mouthing behavior.

Taken together, the preponderance of existing evidence indicates that there is an initial peak in mouthing behavior in the latter half of the first year of life. Some time during the next two years, mouthing behavior drops off precipitously. In order to underline the potential strength of the selection pressures operating against infant mouthing behavior, before turning to the possible benefits of this developmental pattern, consider the following: the risk of choking is in part a function of both the size of the throat and the extent of coordination of the muscles used in swallowing. Food-related asphyxiation provides a useful index of maturational progress in this regard, as, unlike many non-food objects, food is usually provided to the infant, hence issues of mobility are less relevant. The Altmann and Ozanne-Smith [23] study reveals that hospitalization for food-related asphyxiation peaked during the first year of life, then declined to low levels by age 3, whereafter there was little change. Infant mouthing behavior is thus most avid during precisely the phase of life when it entails the greatest risk of death by choking. Even holding aside the costs of ingesting pathogens, parasites, and toxins, this fact alone suggests that natural selection would likely have eliminated avid and indiscriminate infant mouthing long ago were it not for some significant benefit provided by this behavior.

A critical period of immune development

All material ingested in the process of mouthing passes through the gastrointestinal (GI) tract. The intestine is an important gateway regulating the passage of most pathogens, allergens, and carcinogens [5], yet must also function in its primary role in the digestive system. At birth, the GI tract is immunocompetent but naive [24], hence the development of an immune system capable of extracting nutrients, differentiating food from non-food items, and combating pathogens is of paramount importance for a newborn. However, both the development and the maintenance of the immune system are calorically expensive, as illustrated by weight loss and muscle wasting in HIV and cancer patients (e.g. [25,26]). McDade and Worthman [27] describe the ''informational'' model of the development of the immune system in which calorically expensive thymic tissue and T and B cell numbers are largest in infancy and decrease thereafter as the individual adapts to the local disease ecology. The neonatal immune system thus exhibits a plasticity of development that reflects the local pathogen environment.

Neonatal gastrointestinal tracts are sterile at birth, but begin to be colonized by organisms in the birth canal and external environment within a few hours [28]. Bacteria appear in feces within hours after birth, and increase progressively in the first week of life; by the end of the second year, the composition and metabolism of infants' fecal flora resembles that of adults [28,29]. Commensal gut microbes play an important role in intestinal defense, adding a non-immunological barrier protection, and stimulating and directing the development of the gut immune system [30]. Normal flora in the gut appears to prevent transfer of pathogenic bacteria across the intestine, as live bacteria in germ-free animals readily cross the intestinal barrier and reach the lymph nodes, blood stream, and other organs (reviewed in [31]).

The mucosal immune system in the gastrointestinal tract includes lymphocytes in villi, Peyer's patches, and lymph nodes, as well as accessory cells like dendritic cells, mucosal mast cells, and eosinophils [24]. Peyer's patches in the small intestine collect and present antigens from the epithelial surfaces of the GI tract [32]. Post-natal exposure of the neonatal GI tract to bacterial antigens is associated with increased numbers of B cells and the antibodies they produce, and increased number, size, and germinal centers of Peyer's patches, emphasizing the interactive requirements of appropriate mucosal immune development [24].

In addition to the immature nature of immune structures in the neonate, T cell cytokine production also does not encompass the full range of functionality at birth. T helper 1 (T_H1) and T helper 2 (T_H2) cells are polarized forms of the highly variable CD4+ T_H cell-mediated immune response [33]. T_H1 cells, which generally defend against bacterial, fungal, and parasitic infections, are characterized by production of Interferon-γ (IFN-γ), Tumor necrosis factor-α (TNF-α), Interleukin-1β (IL-1β) and IL-2, and T_H2 cells, which defend against extracellular pathogens, by IL-4, IL-5, IL-6, IL-9, and IL-13 production [33,34]. The early environment influences the development of T_H1 or T_H2 cells from naive T_H cells, which are not preprogrammed, but once a certain cell has been fated for a particular developmental path, its phenotype is fixed [34]. Normal immune function is thought to require a T_H1-T_H2 cytokine balance; however, at birth, the neonatal immune system is biased toward T_H2 cytokine expression, which mediates the formation of allergic inflammation [30]. Intestinal bacterial flora are critical for counterbalancing T_H2 activity and regu-

lating the Immunoglobulin E (IgE) response [30]. In particular, exposure to bacterial antigens induces secretion of T_H1 cytokines including TNF-α, IL-6, and IFN-γ [30].

In sum, exposure of the naive GI tract to commensal bacteria within the first two years of life, the period in which the gut flora comes to resemble that of an adult, is critical in aiding maturation of the immune structures of the mucosal immune system and achieving a healthy cytokine balance. In addition, commensal intestinal bacteria provide a measure of immune defense in their own right, blocking access of non-commensal pathogens to the intestinal wall and beyond. While this period of immune development might seem to render the neonate vulnerable, as reviewed in the next section, several key features of breast milk protect the nursing infant during this phase.

The sheltering umbrella of breast milk

Avid mouthing is a pattern characteristic of the first 2—3 years of life, with its most intensive manifestation occurring during the first year. Importantly, this coincides with the probable period of breastfeeding characteristic of that vast majority of human history during which members of our species lived in relatively small semi-nomadic groups of hunter-gatherers. Analysis of the ethnographic record reveals that, while there is substantial variation in the duration of breastfeeding in preindustrial populations, the average is $\approx$2.5 years, a period that coincides with many contemporary medical recommendations [35]; the same figure applies when the sample is limited to extractive foragers, societies that are often employed as approximate models of human ancestral conditions [36].

The protective role of breastfeeding was first identified in the early 20th century, and has since been shown to reduce the incidence of both common childhood illnesses such as diarrhea, pneumonia, and ear infections, and uncommon ones, such as childhood lymphoma, necrotizing enterocolitis, and botulism (reviewed in [37]). Historically, orphans without access to a wet nurse have experienced mortality rates as high as 90% [38].

At birth, the neonatal immune system is functional yet still developing. Due to passive transport of non-specific maternal IgG across the placenta, the neonate has 90% of maternal serum IgG levels at delivery [39]. While the tissue defense provided by transplacentally-transported IgG is important, most of the infectious threats to the newborn are intestinal, requiring IgA, the main defense immunoglobulin of mucosal surfaces. The infant produces very little IgA, but the high content of secretory IgA (SIgA) in breast milk provides as much surface IgA coverage on neonatal mucosal membranes as those of an adult [31].

IgA from breast milk provides protection against all microbes the mother has or has had in her intestinal tract, as the mother's intestinal Peyer's patches send SIgA against current antigens to the mammary glands, and memory lymphocytes able to target past antigens congregate there as well during lactation [39]. These passively transmitted antibodies are highly targeted to the maternal environment, encompassing those antigens most likely to be encountered by the infant during its first few weeks of life [5]. IgA functions by coating non-commensal intestinal bacteria, effectively blocking their interaction with the gut epithelium [31]. Because the protection afforded by IgA is both specific to mucosal surfaces, like the intestine, and much less energetically costly than that of IgG (which induces complement activation, neutrophil influx, and proinflammatory cytokine production [39]), breastfeeding is particularly critical in protecting neonates from exogenous pathogens before they are able to produce specific antibodies.

In addition to its high concentration of IgA, breast milk also contains hormones and growth factors that promote GI maturation, immunomodulating agents, anti-inflammatory agents, direct-acting antimicrobial agents, and living leukocytes [37,41]. Maternal immune cells in breast milk, including neutrophils, macrophages, and lymphocytes, can phagocytose and kill bacteria and fungi [37]. Lactoferrin, which comprises 30% of the protein in mature milk, acts directly in responding to pathogens, killing bacteria, viruses, and yeast, and indirectly, preventing energetically costly cytokine induction [40]. Other antimicrobial agents in breast milk include lysozyme and oligosaccharides, which can act as receptors for pathogenic bacteria, including *Vibrio cholerae*, the agent that causes cholera, and thus block the access of these pathogens to the gut epithelium [31]. Of key importance in immunomodulation are cytokines, in particular IFN-γ, which is present in breast milk in a fourfold higher concentration than in peripheral blood, and Transforming growth factor-β (TGF-β), which is present in very high concentrations in breast milk, but is usually not present in blood [24]. TGF-β is critical in modifying neonatal immune responses, as it inhibits the production of T_H1 cytokines like IL-1, IL-6, and TNF-α, reduces the expression of human leukocyte antigen (HLA)-DR on antigen-presenting cells, and inhibits the synthesis of nitric oxide by IFN-γ-activated macrophages [42].

TGF-β and other cytokines are also likely of particular importance in mediating oral tolerance, immune unresponsiveness to the ingestion of common proteins [24]. The gastrointestinal tract must concurrently tolerate food and commensal bacteria and allow immune responses to pathogens. In the 1890s, Paul Ehrlich was the first to demonstrate that maternal immunity to a toxin (ricin) could be passively transferred via breastfeeding and protect the neonate against a secondary lethal challenge [43]. Exposure to cow's milk proteins via human breast milk has been shown to decrease antibody levels in the infant, suggesting a role of passively transferred breast milk antigens in the development of oral tolerance [44] or the selective colonization of maternal mammary gland with memory T cells reflective of previous maternal antigen exposure [37]. In rats, oral priming with an antigen before one week of age induced priming instead of tolerance [45], whereas neonatal colonization with commensal intestinal bacteria via both exogenous and maternal exposure led to greater tolerance than did exogenous exposure alone in the maternal generation [46].

Although the protection afforded by breastfeeding lasts for several years after cessation [40], several key immunological changes occur at weaning, changes which Cummins and Thompson [24] suggest may lock the infant's immune system into certain life-long responses. In particular, in the respiratory mucosa, expansion of dendritic cells, which present antigens for immune responses, is delayed until after weaning [24]. In the GI tract, weaning is associated with expansion and granulation of mast cells, expansion of intraepithelial lymphocytes, and increase in T cell activity (reviewed in [24]). In the pig, weaning is associated with a transient upregulation of T_H1 cytokine mRNA, including IL-1β, TNF-α, and IL-6 [47].

The cost of inadequate antigen exposure

Failure to expose the infant to a disease ecology reflective of the local environment within the appropriate time frame carries a long-term cost. In particular, because the neonatal immune system is biased towards T_H2 cytokines, exposure to a paucity of exogenous antigens and/or delay in exposure past the critical window are thought to be key risk factors for T_H2-biased disorders such as allergy, atopy, and asthma, presumably stemming from the lack of induction of T_H1 cytokine expression stimulated by contact with bacterial antigens. This ''hygiene hypothesis'' draws its principal support from the reduced risk of allergies associated with the presence of older siblings and day care attendance (reviewed in [48]). Exposure to endotoxin and lipopolysaccharides, which form an intrinsic part of the outer membrane (and thus the antigenic portion) of gram-negative bacteria, also decrease risk of allergy and atopy. Endotoxin is a component of house dust, and indoor endotoxin levels are increased when pets are kept inside, and when poultry and livestock are kept near homes, factors associated with reduced risk of allergy and atopy (reviewed in [48]). Endotoxin exposure induces IL-12 production, a signal for naive T cells to mature into T_H1-type cells (reviewed in [48]).

T_H1-associated infectious diseases, like measles, have also been implicated in reducing allergy and atopy in children. In Guinea-Bissau, researchers found that contracting measles before age 6, as opposed to being vaccinated against it, was associated with a decreased risk of atopy ([49], but see also [53]).

The maintenance of a healthy T_H1—T_H2 balance may require opportunistic exposure to pathogens requiring a T_H1 or T_H2 response at appropriate time intervals. Thus, in an ideal immunological environment, either both sides would be present or both would be eliminated. In the West, pathogens requiring a T_H2 response, primarily extracellular helminths, have largely been eradicated, while many diseases requiring a T_H1 response, like chicken pox, croup, and even the common cold, are still relatively prevalent. As discussed above, incidence of allergy may increase in response to lack of appropriate T_H1-biased stimulation. In addition, lack of exposure to inflammation-regulating helminths, which generate a balancing T_H2 immune response, may lead to T_H1-biased autoimmune disorders, like Crohn's disease and ulcerative colitis [51]. Helminths also induce production of immunoregulating cytokines like IL-10 and TGF-β, and thus may also protect hosts from aberrant T_H2-biased disorders like asthma, atopy, and allergy [51]. In rural Ethiopia, for example, hookworm infection was inversely associated with asthmatic wheezing [52]. In non-Western environments, children may be able to facultatively adjust their T_H1—T_H2 cytokine balance via mouthing-related consumption of helminths in soil. In Guinea, 53% of children ages 1—18 years were found to harbor at least one orally-acquired soil-transmitted intestinal worm, and parentally-reported geophagia was noted in 57% of 1—5 year olds, a proportion that declined slightly with increasing age [4].

Oral ingestion of pathogens associated with mild infection appears to play a critical role in

GI tract immune maturation. Orofecally-transmitted organisms that do not disrupt the normal flora, such as *Toxoplasmosis gondii*, *Helicobacter pylori*, and the Hepatitis A virus are associated with a decrease in the risk of allergy and asthma, in stark contrast to the effects of serious intestinal pathogens like *Clostridium difficile, Campylobacter jejuni*, and *Yersinia enterocolitica*, which are associated with an increased risk of atopy [50,54].

Mouthing: a proactive immune strategy

The immune system is the body's principal defense against a complex world of rapidly evolving pathogens. Calorically expensive, an efficient immune response adequately and accurately reflects the degree of immunological insult, much as an economically efficient military would maintain a large army only in wartime, and shrink considerably in times of peace. Unlike an army, however, we propose here that the immune system has a critical period of calibration, in which the neonate adjusts its investment in the immune system to reflect the environment into which it has been born. Despite the clear risks of toxin and pathogen exposure and choking, the infant proactively introduces antigens and commensal microflora into its intestinal system in order to stimulate gut maturation within the parameters required by the local disease ecology. Exposure to diverse antigens and healthy flora is critical for gut maturation and cytokine balance. Timing of gut maturation, however, is limited to the period of breast-feeding, as breast milk provides strong immunological defenses specifically targeted to the maternal, and thus the neonatal, environment. The onset of weaning is accompanied by immunological changes that may lock the infant into life-long patterns of immune response. In particular, the failure to accurately expose the immune system to sufficient antigens and colonize it with commensal microbes within the critical time period may entail significant costs, including increased risk of allergy, asthma, and autoimmune disorders. Although allergy, asthma, and autoimmune diseases are mostly disorders of Western and urban settings, changing ideals of cleanliness in developing countries may yet greatly increase their prevalence. Likewise, the immunocalibration hypothesis presented here predicts that immune dysfunction of this type can be expected when, due to either handicap or caretaker intervention, infants are prevented from active and extensive oral interaction with the environment.

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