Nutrition, the visceral immune system, and the evolutionary origins of pathogenic obesity

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The global obesity epidemic is the subject of an immense, diversely specialized research effort. An evolutionary analysis reveals connections among disparate findings, starting with two well-documented facts: Obesity-associated illnesses (e.g., type-2 diabetes and cardiovascular disease), are especially common in: (*i*) adults with abdominal obesity, especially enlargement of visceral adipose tissue (VAT), a tissue with important immune functions; and (*ii*) individuals with poor fetal nutrition whose nutritional input increases later in life. I hypothesize that selection favored the evolution of increased lifelong investment in VAT in individuals likely to suffer lifelong malnutrition because of its importance in fighting intraabdominal infections. Then, when increased nutrition violates the adaptive fetal prediction of lifelong nutritional deficit, preferential VAT investment could contribute to abdominal obesity and chronic inflammatory disease. VAT prioritization may help explain several patterns of nutrition-related disease: the paradoxical increase of chronic disease with increased food availability in recently urbanized and migrant populations; correlations between poor fetal nutrition, improved childhood (catch-up) growth, and adult metabolic syndrome; and survival differences between children with marasmus and kwashiorkor malnutrition. Fats and sugars can aggravate chronic inflammation via effects on intestinal bacteria regulating gut permeability to visceral pathogens. The extremes in a nutrition-sensitive trade-off between visceral (immune-function) vs. subcutaneous (body shape) adiposity may have been favored by selection in highly stratified premedicine societies. Altered adipose allocation in populations with long histories of social stratification and malnutrition may be the result of genetic accommodation of developmental responses to poor maternal/fetal conditions, increasing their vulnerability to inflammatory disease.

inflammation | type-2 diabetes | metabolic syndrome | developmental plasticity | social selection

Obesity is a global epidemic directly associated with serious chronic diseases: type-2 diabetes mellitus (T2DM) and cardiovascular disease (CVD). Obesity-associated diabetes now affects more than 300,000,000 people worldwide (1), with the "staggering" costs to health and public-health budgets greatest in low- and middle-income countries (2). The devastating health consequences of obesity pose an evolutionary puzzle: What adaptive purpose could be served by a metabolic physiology so disastrous for so many? Clearly, pathogenic obesity is not selectively advantageous so it must arise from some advantageous process gone awry.

The explosion of literature on obesity and related disease now greatly exceeds 600,000 articles and books (3), a literature so fragmented and divergently specialized that its study is a challenge as daunting as the obesity epidemic itself. But two well-documented facts stand out. First, not all obesity is the same. Adipose tissue occurs in numerous locations or "depots" in the human body. But it is the exaggerated development of visceral adipose tissue (VAT), located within the abdominal body cavity, that is most strongly associated with the so called "metabolic syndrome," including the chronic inflammatory diseases of the obesity epidemic: T2DM and CVD (4, 5). Second, poor fetal nutrition correlates with occurrence of adult chronic inflammatory disease, especially in individuals whose food input is later increased. This effect, famously described by Barker and colleagues (6) in adult offspring of mothers pregnant during the Dutch Hunger Winter, is now supported by a very large number of studies (*SI Appendix*, *Appendix 1*).

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Based on these two salient facts, I propose the following "VAT prioritization" hypothesis regarding the evolutionary and developmental nature of pathogenic (visceral) obesity: Investment in VAT is prioritized relative to subcutaneous tissue (SAT) and sometimes other tissues in poorly nourished and therefore infection-prone individuals because of the immune advantage of maintaining VAT. Augmented nutrition then leads to visceral obesity and associated chronic disease, whose inflammatory nature may reflect the inflammatory immune responses of VAT.

This perspective differs from previous discussions of obesity in attempting a coherent view of the relationships between the immune functions of VAT, its connection with inflammatory chronic disease, population differences in disease incidence, the role played by modern mass-marketed foods, and the evolutionary setting that may have favored adaptive fetal effects on patterns of fat allocation.

The Immune Functions of Visceral Fat

The strong link between visceral obesity and chronic disease compels a close look at the functions of visceral fat, especially the omental and the mesenteric VAT. (A less-studied intraabdominal depot, the retroperitoneal, is discussed in *SI Appendix, Appendix 2*.) Trying to analyze the diseases of obesity without understanding the biological functions of these key structures is like trying to analyze circulatory disease without understanding the biological functions of the heart.

Fat tissue is sometimes called an "endocrine organ" because its products affect systemic metabolism and immune responses (7, 8). But this does not distinguish between subcutaneous and visceral fat tissue. VAT has been seen as a storage- and command-center that influences energy redistribution during nutritional emergencies, arguably to protect the brain (9). Without denying the importance of this and other possible functions, the visceral fat depots can also be seen as intraabdominal adipo-immune organs (10). VAT adipocytes (fat cells), like those of lymph nodes (11), are specialized to sequester the particular diet-derived polyunsaturated fatty acids required for immune activities (12), helping to free VAT immune cells from the vagaries of dietary availability that could compromise a rapid and energetically costly immune response (8). They are also specialized to respond to immune-related signals (e.g., inflammation-associated TNF-α, IL-6, IL-4) and when activated they facultatively increase numbers of receptors for these and perhaps other cytokines (12).

The omentum has been called "the abdominal policeman" [see ref. 13, after Morison (14)] for its multiple lines of defense against intraperitoneal pathogens and foreign matter (*SI Appendix, Appendix 3* discusses types of infection subject to omental defenses). In a nonobese individual, the greater omentum is a loosely hanging fold of the peritoneum that is moved within the peritoneal cavity by respiratory movements, intestinal peristalsis, and general body activity (13, 15). It adheres (through the rapid production of fibrin) to foreign bodies, wounds, and other sites of inflammation and infection, acting like a bandage laden with antibiotic and healing agents. Phagocytes (macrophages and others) ingest bacteria and particulate foreign matter and transport them to the omentum. The omentum itself encapsulates larger foci of infection and seals microperforations with collagen, thus limiting the spread of infection while stimulating revascularization and tissue regeneration (reviewed in ref. 13).

Within the omentum immune activities are centered in lymph node-like "milky spots." When activated by the presence of bacteria, the bacterial endotoxin lipopolysaccharide (LPS), or the inflammation-associated cytokine TNF-α, neutrophils (white blood cells of the innate immune system) rapidly move from the blood to milky spots, where they kill accumulated bacteria (16, 17). Unlike lymph nodes, milky spots are unencapsulated, and they enlarge and become more numerous during pathogen-induced endotoxemia, sepsis, and chronic inflammation (18).

The remarkable immune and healing powers of the omentum are dramatized by the surgical practice, more than 100-years-old and still used, of placing surgically devised omental flaps on sites within the abdomen, and even (via a small incision in the diaphragm) on the heart when recovery is threatened by severe postoperative infection (13, 15, 19). A possible role in the dissemination phase of abdominal cancer metastasis, especially of ovarian cancer, is proposed in *SI Appendix, Appendix 4*.

Mesenteric VAT, which surrounds the small intestine, is "the first line of defense" against pathogens and endotoxins translocated from the intestine to the circulation (11). Mesenteric immune activities occur in small fat-associated lymphoid clusters (FALCs), which resemble milky spots in being unencapsulated, in becoming more numerous in response to inflammation (20), and in having extensive lymphatic, arterial, and venous capillaries. Unlike the milky spots, FALCs are not open to the peritoneal cavity. Instead, they process pathogens and bacterial endotoxins that have entered the blood after crossing the semipermeable mucous and endothelial barrier between the lumen of the small intestine and the blood vessels. Endopathogenic diarrheal bacteria, such as wild-type *Escherichia coli*, can damage the intestinal barrier (21); and intestinal parasites sometimes pass, along with LPS, into the blood exposed to mesenteric FALCs (22–24). Hyperpermeability of the gut barrier ("leaky gut"), which can occur with high-fat and high-fructose diets and in extreme childhood malnutrition (see below), can lead to pathogen-induced endotoxemia, (typified by presence of LPS in the blood), which activates immune responses of the mesenteric FALCs (25), as well as stimulating an inflammatory response in the omentum (26).

The portal-vein connection to the liver of these two VAT structures is an anatomical indicator of their immune importance. The blood from both mesenteric and omental VAT, joined by other abdominal tributaries, is met at the entry point to the liver by an array of immunologically important cells: specialized fat cells (stellate cells) and macrophages (Kupffer cells) that parallel and complement the immune functions of those found in VAT (*SI Appendix, Appendix 5*). Only after processing by this double filter of immune defenses in liver and VAT does the viscerally exposed blood enter the general circulation.

Increased Investment in VAT Relative to SAT Following Poor Fetal–Maternal Nutrition

The VAT-prioritization hypothesis proposes that poor fetal nutrition should lead to prioritization of investment in the immune function of VAT. Individuals subject to fetal nutritional stress, as indicated by low birth weight (LBW), are especially susceptible to infection as infants and children (27, 28). So they should show relatively great investment in VAT due to its importance in fighting intraabdominal infections. Well-nourished individuals, better able to resist infections (28), should invest relatively more in SAT (for reasons given below). Possible mechanisms of VAT prioritization in fetally poorly nourished individuals include a raised level of VAT insulin sensitivity by omentin, glucocorticoids, and (in adults) sex hormones (*SI Appendix, Appendix 6*), factors that would regulate glucose allocation to VAT relative to SAT and other insulin-responsive tissues.

Catch-up growth—accelerated growth when increased nutrition follows an underweight state—permits measurement of energy allocation to different fat depots in formerly undernourished individuals. Catch-up growth is of special interest as a way of assessing VAT prioritization because it has long been recognized as a better predictor of adult obesity-associated disease than is LBW itself (29; see refs. 30 and 31 for reviews). This suggests that childhood catch-up growth can be regarded as an early phase of the developmental mismatch, in the sense of Gluckman and Hanson (32), that connects fetal malnutrition with inflammatory adult disease.

Data on catch-up growth indicate that VAT prioritization, relative to SAT allocation, occurs early in LBW and small for gestational age children compared with those of adequate birth weight or adequate size for gestational age (33, 34) (details in *SI Appendix, Appendix 7*). Such children often show systemic insulin resistance (*SI Appendix, Appendix 8*), which, combined with the effects of omentin and other factors that raise the insulin sensitivity of VAT (*SI Appendix, Appendix 6*), would channel glucose preferentially to the VAT immune structures. In newborns with LBW due to maternal preeclampsia VAT was maintained while SAT was reduced (35).

MRI studies in rural India of "thin–fat" babies, a distinctive phenotype with LBW, low muscle mass, and high-fat content per unit weight (*SI Appendix, Appendix 9*) have, at birth (within 2 weeks of age): greater abdominal fat [including VAT and superficial and deep abdominal SAT (ASAT)] and less superficial nonabdominal SAT compared with counterparts born to white Caucasian mothers in London (36). Fall (37) reviews data on variable correlations between birth weight and abdominal adiposity (ASAT + VAT) in other populations.

VAT-prioritization following poor fetal nutrition evidently continues into adulthood: among overweight adults (in the United Kingdom), LBW individuals had relatively high VAT but not high abdominal SAT (38). In contrast, "white" nonhispanic adults (in the United States) that were fetally well nourished (adequate for gestational age at birth) and underwent rapid childhood growth (between 0 to 2 years) showed increased abdominal fat as adults but no preferential investment in VAT vs. abdominal SAT (39).

These studies indicate that investment favoring VAT over SAT is present early in life following poor fetal nutrition, and continues into adulthood, whereas adequate fetal nutrition is not associated with preferential investment in VAT over SAT. (A purportedly contradictory study is discussed in *SI Appendix, Appendix 10*.)

Are LBW children better protected against infection as expected if VAT-prioritization occurs? LBW children more often develop marasmus (nonedematous wasting) than kwashiorkor (edematous wasting) in extreme malnutrition (40); and marasmics show a stronger acute response to infection and more often survive extreme malnutrition than do kwashiorkor children (41), a difference consistent with a greater ability to fight abdominal infections and fetally mediated VAT prioritization. The "tissue paper" small intestine of severe malnutrition, with weakened mucosa and increased gut permeability (leaky gut) (42) is especially marked in patients with kwashiorkor, at least in some populations (42, 43), further increasing their exposure to the pathogens and endotoxins that are subject to VAT defenses, and further augmenting (by the present hypothesis) the advantage that VAT-prioritized LBW marasmus children would have relative to those suffering from kwashiorkor (see also *SI Appendix, Appendix 11* on hepatic steatosis). Also consistent with the VAT prioritization hypothesis is the greater level, in adults who suffered marasmus vs. kwashiorkor as children, of insulin resistance and other factors predisposing to T2DM (44), conditions associated with relatively high investment in VAT.

Chronic Inflammatory Disease as an Immune Disorder of VAT Obesity

One might suppose that VAT obesity—adipo-immune organs supercharged with excess fat—would lead to supereffective protection against intraabdominal infections. Instead, obese VAT is diseased VAT; it turns against the organism with what appears to be a prolonged and low-level immune response characterized by chronic inflammation and increasing insulin resistance, signal characteristics of CVD (45) and T2DM (46). In the chronic systemic inflammation of obesity VAT responds with adipocyte multiplication and (permanent) fat-depot enlargement (12).

The immune nature of chronic inflammatory disease has often been documented without being connected with VAT obesity (*SI Appendix, Appendix 12*). But it is in visceral obesity that the aberrant immune phenomena of obesity occur, not (with the exception of deep abdominal SAT) (*SI Appendix, Appendix 13*) in subcutaneous obesity. This has led some to regard SAT as "healthy" or "protective" fat (e.g., see refs. 47 and 48); and obese individuals without visceral obesity are sometimes called the "metabolically healthy obese" (49, 50).

Obese VAT is marked by chronic elevated expression of immune responses (10). In the obese omentum macrophage cells (or their progenitor monocytes, from bone marrow) accumulate to an abnormal degree (46, 51), and increased cell death (46, 52)—promoted by increased production of the cytokine TNF-α (53)—leads to the formation of "crown-like structures": dead adipocytes surrounded by macrophages that engulf them (52). Several authors have enumerated immune-system cytokines and cell types involved in both the short-term inflammation of a healthy VAT response to infection and the chronic "metaflammation" (54, 55) of the metabolic syndrome (10, 18, 46, 56–58).

To the degree that prioritized VAT, as in VAT overweight and obesity, contributes to increased systemic/peripheral insulin resistance while VAT itself remains sensitive to insulin, and therefore to preferential allocation of excess energy (see above, and *SI Appendix, Appendix 6*), there is the potential for a self-reinforcing feedback loop (59): increased VAT leads to increased chronic inflammation, and this leads to further peripheral insulin resistance and further increased VAT enlargement and increased susceptibility to disease.

Several factors might sustain immune-like responses of the obese VAT in the absence of infection: (*i*) obesity itself, with increased fat-cell size (hypertrophy) can lead to cell death, macrophage recruitment, and inflammation (46); (*ii*) sheer fat mass places clusters of fat cells distant from vasculature, stimulating inflammation (60) and increased hypoxia (61), which can contribute to insulin resistance (50, 62); and (*iii*) nutritional factors, especially diets high in saturated fats and fructose (see next section).

Disease Aggravation by Saturated Fats and High-Fructose Sugars

The chronic diseases of obesity, and modern diets of saturated and transfats and high-fructose foods and beverages, are associated phenomena (63). That association takes on new significance when seen in relation to the pathological immune responses of visceral obesity: evidence indicates that saturated fats and high-fructose sugars stimulate VAT inflammatory responses via their

effects on symbiotic bacteria that regulate the permeability of intestinal membrane. Increased intestinal permeability, or leaky gut, then exposes the VAT immune system to LPS and pathogenic bacteria, producing "metabolic endotoxemia" (64), which like pathogen-induced endotoxemia (see above), stimulates VAT immune responses.

Dietary fats have been shown to affect intestinal permeability in mice (64, 65) and in humans (66, 67). And fructose effects on gut permeability have been studied in humans (68–70; for reviews, see refs. 71 and 72). Particular gut bacteria may be implicated, such as a deficiency of the symbiotic mucosal bacterium *Akkermansia muciniphila* (73–76), and proliferation of *Bifidobacterium* spp. (64, 77, 78). Several authors (79–81) review further evidence for the causal relation between high-fat diet, LPS, endotoxemia, immune responses, and both T2DM and CVD. Alcock et al. (82) describe other dietary effects on immune responses via the intestinal microbiome, citing evidence that diet-derived saturated (but not unsaturated) fatty acids lead to inflammation and proliferation of harmful gut microbes, activating immune responses, including activation of phagocytic monocytes and macrophages (the omentum is a major source of both).

In support of the idea that dietary alterations of the intestinal microbiome affect intestinal permeability and endotoxemia, adverse effects of pathogen-induced endotoxemia can be controlled by antibiotics that alter specific permeability-affecting intestinal bacteria (83); and one effect of metformin, a drug commonly used to control T2DM, is to decrease intestinal permeability (leaky gut) (*SI Appendix, Appendix 14*). It has also been suggested that fats may "trick" the immune system into responding due to their structural resemblances to LPS (84). These findings indicate that high-fructose sugars, saturated and trans-fats, and perhaps other processed-food additives (85) may be literally toxic for vulnerable (e.g., abdominally obese, VAT-prioritized) individuals.

VAT Prioritization and the Epidemiology of Pathogenic Obesity

The global epidemic of pathogenic obesity is a product of a nutritional transition in populations with a recent history of poverty, famine, or traditionally poor nutrition that undergo migration, urbanization, or food-product marketing that brings increased caloric intake (*SI Appendix, Appendix 15*). In terms of the VAT-prioritization hypothesis, the nutrition transition represents a developmental mismatch on a massive scale: poor fetal nutrition favors VAT prioritization; then increased caloric input would contribute to the likelihood of developing (pathogenic) VAT obesity, exacerbated by the fat and sugar content of available foods (see above, and *SI Appendix, Appendix 14*). Individuals without such a fetal–adult nutritional mismatch (e.g., nonmigrants from source populations, with poor nutrition throughout life) do not have such a high incidence of abdominal obesity and diabetes (reviewed in ref. 86; see also refs. 87–90).

The prevalence of abdominal obesity and associated disease in migrant or rural–urban transition populations sometimes gives the impression of an "ethnic" or genetic predisposition (e.g., ref. 91), when in fact the underlying cause so often involves developmental dietary mismatch (92–94). Of course, genetic influence on the propensity for obesity and disease can be assumed: genetic variation in complex developmentally plastic traits (e.g., fetal responses to maternal nutrition) is virtually inevitable (see ref. 95 on familial variants) and, under regional and cultural differences in natural selection, could lead to evolutionary change (see ref. 96 and next section). But the extensively documented correlations with intrauterine nutritional variation indicate that variation in nutritional factors usually overwhelms the influence of genetic variation within the populations involved. Fetal nutritional differences are associated with differences in occurrence of T2DM even between genetically identical (monozygotic) twins (for an insightful discussion see ref. 97).

The evidence that pathogenic obesity is usually a product of developmental flexibility offers hope that individual and epidemic VAT obesity can be reversed. Reversal of metabolic syndrome, early T2DM, and even consequences of gestational diabetes have occurred due to exercise and dietary change (*SI Appendix, Appendix 16*). But many factors can impede reversal, maintaining pathogenic VAT obesity beyond the single-generation fetal effects discussed here. They include maternal obesity and gestational diabetes, learned food preferences, aggressive marketing of palatable damaging foods, genomic imprinting (epigenetic effects), and genetic accommodation of a high degree of VAT (immune) prioritization in some populations (documentation for each factor in *SI Appendix, Appendix 17*).

Evolutionary Considerations

The VAT-prioritization hypothesis involves a predictive adaptive response [in the sense of Gluckman and Hanson (32)] initiated by maternal/fetal conditions. But rather than proposing a thrifty storage function for body-fat depots, it envisions a fetally cued energy-investment trade-off between VAT and SAT. A VAT–SAT trade-off is suggested by distinctive adult body shapes in overweight adults (98, 99): even though variable, there is an "apple" or android (male) shape, in which upper body adiposity (VAT as well as deep ASAT) is exaggerated relative to lower-body adiposity; and "gynoid" or "pear" (gluteo-femoral), "hourglass," and "steatopygial" (gluteal) shapes (most notable in females), where the reverse is true. Under the present hypothesis, nutrition-sensitive development enables investment in VAT vs. SAT to be adaptively shifted, such that each is subject to heightened expression, selection, and evolution in the context where it is important.

The immune-related VAT–SAT trade-off may be involved, among other factors that could affect fat depots, in certain severe immune diseases: VAT is enlarged while SAT is reduced when HIV fails to progress to AIDS and becomes a chronic infection (8); and in Crohn's disease, an inflammation of the intestine in which there is excessive "fat wrapping" by enlarged mesenteric VAT, with reduced SAT elsewhere (100). In malnutrition, a VAT–SAT trade-off is a general phenomenon: immune-associated adiposity is maintained whatever the underlying cause (e.g., illness, starvation, anorexia nervosa), while lower body SAT depots and even muscle tissues are depleted (100). In well-nourished healthy individuals, with lesser demand on VAT, large SAT depots are maintained, including the breast, gluteal, and femoral depots of adult females, and the superficial ASAT of the male paunch: fat areas that among their other functions reflect fertility, beauty, social stature, and power (11, 31). As such these SAT depots are subject to sexual and social selection (101–103), selection that favors traits (including signals of health and strength that become elements of attractiveness) that augment success in social competition for resources. So the VAT–SAT trade-off can be seen, in evolutionary terms, as involving to some degree a trade-off between the immune functions of VAT and the social (body shape) functions of SAT.

The disease-prone, nutrition-sensitive visceral adipo-immune system is evidently an ancient human trait (*SI Appendix, Appendix 18*). Adaptive extremes in the human VAT vs. SAT trade-off may have evolved during the age of agriculture, when changes occurred that would have increased selection on the immune functions of VAT as well as the social functions of SAT. Despite wide variation in the nature of human societies, there is widespread agreement regarding the general importance of certain changes: the spread of agriculture brought a decline in overall nutrition, and increased exposure to intestinal infections due to life in sedentary groups with poor sanitary conditions (31, 104–106). Then, with the origin of the great civilizations starting about 5000 years BP, there was greatly increased socioeconomic stratification, creating divergent extremes in access to resources including food (31, 104, 105), events that coincided with increased health inequalities in the archaeological record (105). The VAT-prioritization hypothesis implies that VAT investment would have been most highly favored in low-resource individuals who suffered a disproportionate burden of hunger, disease, and physical labor in ancient stratified societies (e.g., see refs. 31, 32, 104, and 107–109), while the social advantages of SAT would have skewed investment toward SAT in the high-resource elites, who were more involved in high-stakes social competition and less exposed to hunger and infection.

It is difficult to ignore the likely power of social factors in recent (Neolithic) human evolution. Socially mediated differences in access to resources (food, mates, and others) can lead to enormous fitness and phenotypic differences in highly social species (110–113). Individuals under social (including sexual) selection (102) invest in socially important morphology and behavior even when useless or costly in terms of survival (101). And socially subordinate individuals are under selection to adjust to the consequences of limited resources, investing in alternative traits that salvage elements of their compromised survival and reproduction (111, 114). In humans rank-related differences in survival and reproductive success begin at birth (115, 116). High-ranking individuals and families in ancient civilizations were often engaged in ruthless as well as subtle social competition for resources, competition where physical attractiveness (like SAT-influenced body shape) can matter (11) (*SI Appendix, Appendix 19*). Body shapes molded by SAT show patterns of variation like those of socially and sexually selected traits in other organisms (102): adult human body shape is influenced by sex hormones (117) and is sexually dimorphic (118, 119). And female body shape varies geographically (racially) (5, 120–123), suggestive of genetic diversification evolved under Darwinian social selection and the rapid evolution that characterizes such traits for reasons discussed in West-Eberhard (102). As expected, there are also differences of geographic origin in social preferences for SAT-mediated body shape (122, 123) (*SI Appendix, Appendix 19*). The social stigma of body shapes altered by obesity (124) invites serious attention to social selection on SAT as a factor in Neolithic human body-shape evolution. So does a history of premodern costume that, to give some easily documented examples, has included waist-narrowing corsets, gluteal-augmenting bustles, artificial paunches (125), and hip enlargements in dresses, one of them so extreme that women were obliged to walk sideways through doorways (126).

Doubts regarding the predictive power of fetal nutritional cues (e.g., refs. 127 and 128) commonly refer to selection in hunter-gatherers during the Paleolithic, and the fact that short-term (e.g., seasonal) scarcities and even famines, usually shorter than the human lifespan, would likely have undermined the predictive value of fetal cues. But human evolution did not end with the Paleolithic. Numerous human traits were established under selection during the 10,000 years of the Neolithic period, including lactase persistence in adults (129) and many others (130) (*SI Appendix, Appendix 20*), some of them immune-related (131) and protective against T2DM (132). The lifelong predictive value of fetal nutritional cues would have increased in stratified societies, where inheritance of resources (133) greatly increases the probability that maternal/fetal nutritional conditions would persist across generations (134).

It is important to realize that nutrition-sensitive adipose investment patterns are subject to selection and evolution, like all genetically variable traits, including those that are condition-sensitive or sex-limited in their expression (96). Genetic isolation between stratified groups is not necessary to produce contrasting phenotypes. Instead, the evolution of condition-sensitivity (e.g., to nutritional cues) in gene expression can adjust the expression of traits and the underlying genes to fit the circumstances where they are likely to be advantageous (96, 135) (for quantitative models of predictive adaptive plasticity, see refs. 134, 136, and 137).

Condition-sensitive adaptation, rather than a genetically fixed phenotype as in the thrifty-gene hypothesis (138), would have been favored in stratified societies by occasional changes in familial rank, for example, due to social upheavals (e.g., war, conquest, or disease) (139, 140), and social mobility (e.g., due to migration, individual social attributes, and marriage patterns) (141–143). The chronic diseases of VAT obesity, even though sometimes postreproductive, may have been a cost of nutritional mismatch helping to maintain plasticity in the fetal response. [In humans the socially important lifespan can persist into postreproductive adulthood (144–146) (*SI Appendix, Appendix 21*)].

The "thin–fat" infant and diabetes-prone adult phenotype in South Asia (India) (*SI Appendix, Appendix 9*) may reflect an extremely VAT-shifted tissue-investment pattern due to genetic accommodation in a population with a long history of extreme malnutrition and high infection rates [see Wells et al. (147) for a 10,000-year history of relevant socio-ecological conditions and recent genetic change]. Genetic accommodation can shift the frequency, intensity, or form of a trait without leading to its fixation (96). Epigenetic effects (increased methylation-sensitivity of relevant genes) may be involved (148). Reasons why complex developmentally plastic metabolic traits are predisposed to undergo especially rapid evolution are discussed by Nijhout and Reed (149).

Conclusions and Predictions

Of the two major kinds of obesity, one primarily subcutaneous and the other primarily visceral (intraabdominal), it is visceral abdominal obesity that is the main culprit in the inflammatory diseases of obesity. Visceral fat is part of the immune system. This fact illuminates both the nature of the chronic diseases of obesity and the evolutionary background that links them to fetal development and nutritional conditions. Type 2 insulin-resistant diabetes and the circulatory problems of abdominally obese people are not just metabolic disorders, they are disorders that involve inflammation rooted in the intraabdominal immune system. They probably owe their origin to the advantage, in poorly nourished individuals, of prioritized investment in fat tissue that fuels defenses against abdominal bacterial and parasitic infections, beginning with a fetal allocation decision that reflects maternal nutritional state. When betrayed by later increased food input, especially of modern mass-marketed foods high in fats and high-fructose

sugars, the insulin resistance and inflammation associated with a healthy immune response becomes chronic and ultimately damaging to health.

While the details of these connections are still under investigation, they suggest some potentially fruitful areas for future research and public health efforts. A key area is to investigate the fetal cues that affect variation in the development of the visceral immune system, because of their potential role in the etiology of the chronic inflammatory diseases of visceral obesity. Epigenetic genomic effects may be involved, as they appear to connect some effects of nutrition with the metabolic syndrome (150, 151).

Similarly, the role of omentin, suggested here to be involved in VAT-prioritization via its effect on VAT insulin sensitivity, invites further research: Does omentin respond to infection and thereby raise insulin sensitivity and glucose input in support of a VAT immune response? The possible role of omentin in immunity and inflammation is discussed by Yu (152).

If VAT-prioritization supports immune function as proposed here, then healthy, lean VAT-prioritized individuals should have relatively high resistance to intraabdominal infections. And if the prevalence of visceral obesity and associated disease in some populations, as in India, is due to relatively high investment in visceral immune organs, then resistance to intraperitoneal infections in those populations may be relatively high as well. Future genomic studies may reveal further evidence that recent human evolution (during the last 10,000 years) has involved loci related to dietary change and the abdominal immune system, including its malfunction during chronic disease. Genomic studies of different ethnic populations (of different geographic/racial origin)—especially those, like Asian Indians, with distinctive metabolic-immunological phenotypes—may illuminate the genetic nature of those phenotypes.

The findings summarized in this Perspective suggest that even more attention needs to be paid to abdominal obesity than has been in the past (see also ref. 153). Even though abdominal obesity is well known to be associated with chronic disease, it is still surprisingly common for "obesity" to be represented by body mass index (based only on weight and height) and then verbally linked to diseases like T2DM and CVD, without pointing out that subcutaneous obesity is not usually associated with those diseases: it is a different illness that requires different treatment.

There can be no doubt that visceral fat depots have important immune functions. The possibility that they are related to immune aspects of the chronic inflammatory diseases of abdominal obesity at least merits increased attention, given the currently incomplete understanding of the causes of pathogenic obesity and its globally increasing human costs.

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