The History of the Hygiene Hypothesis

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Since the beginning of the nineteenth century, the prevalence of immunoregulatory problems has rised.[1] For example, in 1998 about one in five children in industrialized countries suffered from allergic diseases such as asthma, allergic rhinitis or atopic dermatitis.[2] One attempt to explain the correlation between the rise in autoimmune diseases and allergies occurring during the urbanization period of the United States and parts of Europe is the Hygiene Hypothesis. The actual phrase, "Hygiene Hypothesis", was first used by Strachan in 1989 in his discussion of hay fever and family size;[2] but to fully appreciate the predictive value of this epidemiological hypothesis one must travel back to the Paleolithic period which dates to >10,000 BCE.

Prior to the Neolithic period, humans existed in small groups and occupied the roles of hunter, gatherer and scavenger. Because of the exposure to wild game, botanicals and carrion, the gut of early man contained a plethora of parasites, viruses, bacteria and various microbiota. This early cornucopia of microorganisms was primarily commensalistic; therefore the immune system of paleolithic man did not mount a response against them. This co-existence as well as co-evolution between microbes and man explains another phrase commonly used to further explain the Hygiene Hypothesis: Old Friends.[3] The different strains of heirloom bacteria or "Old Friends" are critical for shaping the immune system and preserving the intestinal barrier, protecting against leakage.

As man moved from the Paleolithic to the Neolithic period, social groups expanded, and permanent communities were formed. Humans abandoned the hunter-gatherer lifestyle for one of raising domesticated livestock and farming which provided stabilization in dietary intake. Along with the stabilization of the food supply, Neolithic communities had greater exposure to untreated fecal matter from livestock which often ran off from the animal pens into the drinking water. This exposure to a variety of new animal viruses caused major microbial changes in the gut and has been labeled the "First Epidemiological Transition". This change promoted the development of epidemic diseases. Cholera, plague and typhus spread rapidly through the communities and were directly related to untreated sewage in the water supply.[3]

The "Second Epidemiological Transition" occurred in the 1800s as developed countries transitioned from the pre-industrial to the industrial era. More people lived in cities, and with the urbanization of Europe and the United States, streets were paved, animals were tended outside of the city, reducing contamination of the water supply and personal hygiene improved as did the safety of the food supply. The microbes of the gut responded to this change in hygiene by decreasing the variety of microbiota. One of the microorganisms lost during the 19th century were worm-like parasites collectively referred to as helminths. These worms (roundworms or flatworms) were endemic to the intestinal tract up to the early 20th century. In less developed countries over one billion people still have colonies of helminths in their intestines. These worms appear to reduce the response of the immune system in order to form colonies. They appear to control effector pathways of the immune response and prevent inflammation.[4]

While no one would advocate for a return to the days of massive cholera epidemics, the improvement in hygiene, vaccines and antibiotics led to a gene-environment crises as "Old Friends" over time were removed from the modern environment.[5] The development of active artificial immunity resulting from wide-spread immunizations triggers the immune system to produce antibodies against infectious antigens and could actually inhibit responses to weaker antigens such as auto- antigens and allergens.[6]

Importance of "Old Friends" in Allergic and Autoimmune Diseases

Hypotheses are generated through observation. With the concept of the Hygiene Hypothesis, Strachan attempted to correlate the occurrence of hay fever with family size. In his research he noted that hay fever was inversely related to the number of children in the household. It appeared that younger siblings were less likely to develop hay fever or allergic rhinitis because of early exposure to the antigens brought into the household by older siblings. This finding also led Strachan to comment that a "window of exposure" existed and was critical to the development of a healthy immune system.[3]

Strachan's research was foundational to a number of other studies which tested the Hygiene Hypothesis as a possible explanation for allergic and

autoimmune diseases. Kramer et al. (2008) conducted an observational study of asthma occurrence in Belarusian children as a follow-up to a Breastfeeding Intervention Trial.[1] Their findings supported the Hygiene Hypothesis in that pet ownership, contact with farm animals, the presence of younger and especially older siblings living in rural areas decreased the incidence of asthma. In this study of almost 14,000 children, breastfeeding was not found to be protective against allergic reactions.

In 2010, Okada, Kuhn, Feillet and Bach published an interesting article correlating the rise of asthma to the decrease of infectious disease.[6] Hygiene as a result of increased socio- economic level may explain why asthma, Type 1 diabetes and multiple sclerosis were increased in well developed, high income countries. While other risk factors such as diet and genes may explain the rise in allergies and autoimmune disease, Okada et al provide a strong international case for the Hygiene Hypothesis.

Using the Hygiene Hypothesis in Future Medicine

While epidemiological studies support the Hygiene Hypothesis, laboratory studies with rodents also support the "Old Friends" theory. Elliott, Summers and Weinstock (2007)[7] list several animal studies in which helminths appeared to provide immunological protection from conditions like multiple sclerosis, asthma, Graves' hyperthyroidism, food allergies, Type 1 Diabetes and rheumatoid arthritis.[7] The researchers conclude their article with cautious hope that the porcine whipworm may have great promise in human trials.

Elliott et al (2007)[7] leave the reader with the strong impression that the development of a safe "Old Friend" may tame the rising incidence of allergic and autoimmune diseases; however, Bager et al (2012)[8] leave the reader with exactly the opposite impression.

Bager et al (2012)[8] reviewed records relating to prescriptions filled for Mebendazole which is used against a helminth: Enterbius vermicularis (pinworm). Using data from the Civil Registration System in Denmark, a cohort of more than 900,000 children was screened for Mebendazole prescriptions. The results of the study indicated that "enterobiasis did not reduce the risk for asthma, type 1 diabetes, arthritis, or inflammatory bowel disease".[8] The size of the cohort and the fact that the study was completed in a high-income country does little to advance the Hygiene Hypothesis.

Before we rule out the use of a refined helminth treatment in the future, it is important to remember that Bager et al. (2012)[8] looked at just one species of worms while many more genus and species have been identified as "Old Friends". It will be interesting to watch for further application of the Hygiene Hypothesis in treatment protocols for allergic and autoimmune disease.

References

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