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Revisiting D'Adamo's Blood Type Diet: The Critical Role of Secreted Antigens in Digestive Health - An Evolutionary Perspective

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ABSTRACT

The theoretical construct of a 'Blood Specific Diet' advocated by Peter D'Adamo, on the premise that food lectins react differently with each blood type, has met with criticism from different quarters for different reasons.The approach followed in this paper is a paradigm shift from 'blood types' to 'secreted antigens', as the key factor, in the relationship between diet and disease (gastric / duodenal ulceration). The problem is analyzed from an evolutionary perspective, relying essentially on a built-in-set of biological mechanism in the form of secreted blood group substances, which confer a selective advantage in an environment of lectin-rich-diet. It is an evolutionary legacy that has been retained, to this day, in hunting-gathering societies. Lectins have been implicated as the trigger factor for peptic ulceration. Decreased susceptibility of secretors to peptic ulceration is closely related to the presence of glycoprotein form of blood group substances in large quantity In the brush border cells, which act as a defense against the mucous stripping effect of lectins in food. Due to their lectin binding affinity, secreted antigens also prevent the lectins from attaching to and damaging the cell membrane lining of the gut. Three primary factors namely, quantum of lectin intake, secretor status along with ABO phenotype and preferential affinity of H. pylori key-adhesins for competing H type 2 and Lewis-a and Lewis-b antigenic receptors, seem to play a pivotal role in determining the bacterial load, inflammatory response and severity of H. pylori infection leading to gastric / duodenal ulceration. Propensity for gastric ulceration is a bane of modern societies which are not so well adapted to withstand the onslaught of lectin-rich-diet.

HYPOTHESIS

The ability to secrete A-B-H substances in saliva and other glandular secretions was, perhaps, of paramount adaptive significance at a stage in the early history of man when human ancestors subsisted on raw food like other animals. Dietary habits shifted profoundly with the invention of fire making techniques, which greatly increased consumption of cooked food, The cultural revolution in food habits of early man resulted in relaxation of selection pressure on the dominant secretor gene (Se) necessary for survival in a lectin-rich dietary environment. With the abatement of selection pressure, conditions were set for the recessive mutant gene 'se', to accumulate over a long period of time, leading to the establishment of ABH polymorphism in man. Evidence lending support to 'selection-relaxation' hypothesis is derived from the distribution of secretor types (which is purportedly related to history of dependence on raw food) in man and non-human primates. Serological investigations carried out on hundreds of apes and monkeys reveal that they are invariably secretors. The non-

human primates have a diversified diet, but they are primarily vegetarian and feed on ripe fruits, leaves, blades, and a plethora of wild plants available in their forage area. Their diet is most stressful in terms of its un-tempered lectin activity, which explains the absence of non-secretors in monkeys and anthropoid apes. The hunter-gatherers obtain a bulk of their food from hunting, fishing and gathering insects and wild plants. Both in size and level of their economy, the hunting-gathering societies present the closest approximation, one can find, to the conditions under which early ancestors of man lived. The content of raw food is high in their diet. A very low incidence, bordering on virtual absence, of non-secretors (zero to 3%) in hunter-gatherers can be attributed to a surfeit of dietary lectins present in the food consumed by them. Population surveys across the world show a frequent occurrence of non-secretors (over 20%) in modern human societies. A significant increase in the incidence of non-secretors in modern human societies is, in all likelihood, the consequence of subdued lectin activity in cooked food (lectins being sensitive to heat), which forms a major component of their daily diet. The selection-relaxation hypothesis perceives the observed differences in the incidence of non-secretors in man and non-human primates as an adaptive adjustment to environmental stress exerted by lectins in food on gastric mucosa. A piquant situation arises, more so in developed countries, due to abundance of food and a tendency among the affluents to consume lectin-rich food in excess, which makes them prone not only to ulceration but also to diseases of affluence viz., obesity, diabetes type 2 and cardiovascular diseases.

The concept of 'Blood Type Diet' advocated by Dr. Peter J. D'Adamo [1] is a contentious issue that has met with criticisms from different quarters for many different reasons [2,3,4,5]. Central to D'Adamo's theory of Blood Type Diet is his assertion that lectins in food react differently with each ABO blood type. According to him, lectins which interact with different blood types are 'incompatible and harmful', and that selection of different foods for A, B, AB and O blood types is important to minimize reactions with the lectins. D'Adamo's claim that there are many ABO specific lectins is not substantiated by findings of biochemical research. Investigations carried out on a wide variety of foods show that, "Most lectins in plant species are not ABO blood type specific. Even fewer Edible plants have lectins that are ABO type specific" [6]. Lectins found in commonly consumed foods are mostly nonspecific in their reactivity with red cells of different blood types [6,7]. The theoretical construct of a blood group specific diet, on the ground that food lectins react differently with each blood type, therefore, remains unsubstantiated.

Addressing to the role of secretor factor, D'Adamo [1] writes on page 20 of 'Eat Right 4 your Type' "at this point you might be wondering about other blood type identifiers, such as positive / negative, or secretor / non-secretor ... These variations or subgroups within blood types play relatively insignificant roles".

Contrary to D'Adamo's assertion, there is ample evidence available in the published literature to support the critical importance of secreted ABH antigens, due to their ability to inhibit both specific as well as non-specific lectins [8,9,10].

Early indications of a protective role of secreted antigens appeared soon after Clarke et al., [11,12] reported that duodenal ulceration is likely to develop 50% more often in non-secretors of A-B-H substances than in secretors. Taking the likelihood of group least susceptible to duodenal ulcers (Secretors not O) as 1, the relative liability of O secretors was estimated as 1.35, of A and AB non-secretors as 1.6 and of O non-secretors as 2.5. It can be deduced from these statistics that O non-secretors are two and a half times more likely to have duodenal ulcers compared with A, B and AB secretors. These early findings have been largely upheld by subsequent researches. While some of the data are open to criticism, a large body of observations made in hundreds of studies from many different countries show close association

between non-secretion and both duodenal and gastric ulceration [13,14,15]. Researches, in more recent years, have linked the incidence of ulcers to the presence of Helicobacter pylori, a Gram-negative bacterium [16,17,18,19], which colonizes the stomach and induces chronic gastritis, a long lasting inflammation of the stomach. About 10-20% of those colonized by H. pylori will ultimately develop gastric and duodenal ulcers [19]. Chronic gastritis can harm the stomach and duodenal lining by several mechanisms. One such mechanism involves the adherence of H. pylori to the epithelial cells by producing adhesins which bind to lipids and carbohydrates in the epithelial cell membrane [20]. In order to survive in the harsh acidic environment of the stomach, H. Pylori uses chemotaxis to avoid areas of low pH. It burrows into the mucus lining of the stomach to reach the epithelial cells beneath, where the pH is more neutral [21,22]. Colonization with H. pylori is not a disease in and of itself but a condition associated with a number of disorders of the upper gastrointestinal tract [19]. While both secretors as well as non-secretors may harbor H. pylori in their digestive tract, the inflammatory response, which is mediated in whole or in part, by host expression of secreted A-B-H and Lewis antigens in gastric mucosa, and the consequent severity of infection leading to duodenal / gastric ulceration, is more likely to occur in Group-O non-secretors than in A, B and AB secretors. Consistent with these observations, Mentis et al., [23] found persistent infection by H. pylori in 80% of non-secretors compared with 37% of secretors following attempted eradication therapy.

Corroborative evidence lending support to a protective role of secreted A-B-H substances against lectins in diet has also been derived from comparative study of secretor types in man and nonhuman primates [24]. Among hundreds of apes and monkeys tested by Wiener, Moor-Jankowski and coworkers [25], all were found to be secretors. In striking contrast, the human population groups show wide variations in the incidence of non-secretors. The advanced (modern) human societies, by and large, exhibit a high incidence of non-secretors (over 20%). The primitive human societies (Eskimo, Australian aborigines, Bush-men of South Africa, Natives of New Guinea, Onges of Andaman Islands and a number of North and South American tribes), on the other hand, show strikingly low incidence of non-secretors, diminishing to zero in some of the samples drawn from these human isolates [26]. Both in size and level of their economy, the hunting-gathering societies present the closest approximation, one can find, to the conditions under which early ancestors of man lived. A complete absence of non-secretors in non-human primates, an exceedingly low incidence in hunting-gathering societies and a sustained high frequency in advanced human societies, clearly indicate that non-secretors are at a selective disadvantage in populations exposed to an environment of lectin-rich-diet.(24). The ability to secrete A-B-H substances in saliva and other glandular secretions was, perhaps, of paramount adaptive significance at a stage, in the early history of man, when human ancestors subsisted on raw food, like other animals (24). With the invention of fire making techniques, food habits of early man witnessed a radical change from raw to cooked food. The cultural revolution in food habits, which greatly increased the consumption of cooked food, resulted in a reversal of negative selection pressure bearing upon non-secretor alleles (se), leading to it's establishment and maintenance in human populations, at frequencies much above the level of it's mutation rate [24].

Humans have lived by hunting and gathering for more than 99% of our evolutionary history [27]. The hunting-gathering economy, (which is essentially non-agrarian in nature), represents the original mean of subsistence common to all prehistoric humans during the old Stone Age [27]. Agriculture was introduced by some populations about 10,000 years ago, and their descendants possibly have some genetic adaptation to an agrarian diet [28,29]. However, many of the human populations shifted to an agrarian (cereal based)

diet more recently (< 100 generations ago) which, from an evolutionary point of view, is very short time for any measurable signs of adaptation [30]. Thus, when examining human diet from an evolutionary perspective, it makes sense that humans with an evolutionary novel agrarian diet consisting of cereals (wheat, rice, maze etc.), could suffer from diseases of affluence (obesity, cardiovascular diseases and diabetes type), due to insufficient adaptation [31]. The cereal based diet specific to agrarian societies could be an important environmental factor to initiate these diseases through lectins as cereal constituents with sufficient properties to cause leptin resistance [32]. Many metabolic factors are important in the onset and development of diseases of affluence. Considering the close connect between ABH secretion and dietary lectins, it will be of interest to study the role of secretor status as a susceptibility factor to leptin resistance and predisposition to diseases of affluence.

The example of ABH secretion does serve to explain how modern civilization has led to relaxation of selection pressure on secretor gene (Se) necessary for survival in lectin-rich-environment. However, there still remains the need to understand biochemical basis of quantitative and qualitative variability in blood group active substances in saliva and other glandular secretions, and their interaction with lectins in food. Lectins differ widely in their hem-agglutinating reactions and in the susceptibility of these reactions to inhibition by saccharides. Most lectins agglutinate human erythrocytes of all groups and are usually referred to as nonspecific lectins or panagglutinins [33]. The group specific lectins, on the other hand agglutinate preferenti-ally the human erythrocytes of a given blood type and form precipitates with corresponding soluble blood group substance [33]. It has been shown that among the large group of so called nonspecific lectins, there are many which react selectively with human and animal red cells [34], indicating that the nonspecific lectins too have a measure of specificity. The interaction of nonspecific lectins with cells can, in many cases, be inhibited specifically by human saliva [8,35,36] and simple sugars [33,37,38,39]. It is clear from the results of hemagglutination and inhibition studies that the nonspecific lectins differ markedly in their reactivity and sugar binding specificity. While some of them are highly specific in their binding affinity for saccharides, others fail to be inhibited by any of the sugars or other chemical compounds. The sugar specificity of nonspecific lectins is not necessarily related to that of blood group determinants. Even so, some of these could be converted into blood group specific agglutinins in the presence of inhibiting sugar(s) [8,33,40,41]. Lectins often do not occur singly but exist as groups of closely related proteins or isolectins. Identification of sugar specificity of lectins in food and their inhibition reaction with human saliva can be expected to provide useful insight into the clinical significance of differences between secretors and non-secretors and their adaptive response to agrarian and non-agrarian foods.

An important issue that needs to be addressed is the role of dietary lectins in the pathogenesis of disease. Humans consume a significant amount of lectins as part of their daily diet. Although many of the dietary lectins are inactivated by proper heat treatment, some lectins found in wheat bran, wheat flour, wheat germ, peanuts, dry cereals, carrot, maize, apple, pumpkin, banana etc., survive cooking [7,39,42]. Grant and coworkers [43] demonstrated that the kidney beens that have been heated for several hours in slow cookers are likely to retain enough lectins to cause gastroenteritis, especially, if not pre soaked before cooking. Having survived many lectins are destroyed by digestion. However, enough remain to cause enteric signs and symptoms in man and animals. They bind to the surface epithelium of the digestive tract and lead to anti-nutritional, mild allergic or other subclinical effects in humans and animals [44,45]. The nutritional toxicity of the lectins is dependent on whether significant amount of lectins are systemically absorbed or not

[46]. Lectins which are not bound by the mucosa usually induce little or no harmful effects [47]. Lectins have been implicated as the causative factor in several diseases. White flour consumed excessively by humans contains a high proportion of gluten and has agglutinating activity suggestive of lectins [48,49]. Peptides behaving in a lectin-like manner have been obtained form cleavage of gliadin in gluten [50] which bind to human intestinal mucosa and cause coeliac disease in people sensitive to gliadin in diet [51]. Sour dough lactic acid bacteria hydrolysegliadin peptides and inhibit their lectin like behaviour [52] which, perhaps, explains some of the unexplained health effects of probiotics [53]. Some other suspect lectin diseases triggered by foods are insulin dependent diabetes (trigger factor: tomato lectin and probably also wheat potato and peanuts) [54,55], rheumatoid arthritis (trigger factor: wheat lectin) [56], coeliac disease (trigger factor: wheat gliadin) [57], IgA nephropathy (trigger factor wheat lectin) [58], food poisoning from raw and under cooked kidney beans [59,60] etc.

Of particular interest is the implication of lectins for peptic ulcer disease. There is mounting evidence indicating that peptic ulceration is a lectin induced disease [61]. The toxicity of lectins has been linked with consumption of food with high lectin content. Foods such as beans, cereal grains, potatoes, nuts etc., which contain lectins in high concentration, if consumed in excess can interact with mucosa to cause acute gastrointestinal symptoms in experimental animals [39,51,62]. One of the effects observed in the small intestine of lectin-fed rodents is stripping away of mucous coat to expose naked mucosa, and overgrowth of the mucosa by abnormal bacteria and Protozoa [63]. Lectins also cause discharge of histamine from gastric mast cells, which stimulate acid secretion [64]. Freed [61] sums up these observations to conclude that, "the three main pathogenic factors for peptic ulcer - acid stimulation, failure of the mucous *defense* and abnormal bacterial proliferation (Helicobacter pylori) are all theoretically linked to lectins. If true, blocking of these effects by oligosaccharides would represent an attractive and more physiological treatment for peptic ulcers than suppressing stomach acid". An obvious question that arises is that if we all eat lectins as a part of our daily diet, why only some people develop ulcers and not others. One plausible explanation would be the presence of glycoprotein form of blood group substances in large amounts in brush border cells of the secretors which, by virtue of their binding affinity for lectins, mitigate their mucus stripping effect and protect the epithelium from heavy colonization of infecting bacteria.

The role of Lewis-b antigen, which is biochemically related to ABO blood groups and secretor factor, and has been implicated as a putative receptor for Helicobacter pylori in the gastric mucosa, is debatable. Several studies have reported an increase of Lewis-b phenotype in H. pylori infected patients [65,66]. It has been suggested that H. pylori bacteria adhere to the epithelial cells by producing adhesins such as BabA, which bind to the Lewis-b antigen displayed on the surface of stomach epithelial cells [20]. Another adhesin, SabA binds to sialyl Lewis-x antigen expressed on gastric mucosa [67]. Clyne and Drumm [68], using flow cytometry to investigate the binding of H. pylori to Kato III cells and the primary gastric epithelial cells, found that adherence of the bacterium occurred in a manner independent of Lewis-a and Lewis-b expression. Alkout and coworkers [69] identified an H. pylori adhesin 61-kDa that binds H type 2, Lewis-a and Lewis-b antigens. They argued that if a key adhesin of H. pylori binds to H type 2 of epithelial cells, the presence of Lewis-b in the mucus of secretors will compete with greater effect for the 61-kDa adhesin and reduce colonisation of H. pylori. Alternatively, non-secretors expressing Lewis-a in their gastric mucosa will compete less effectively with the adhesin and, as a result, will be more densely colonised by the bacterium. Probing the relationship between host Lewis and ABO blood group phenotypes and prevalence of H. pylori

infection, Heneghan et al., [70] reported that, "although no in vivo relationship exists between H. pylori and preferential adhesion to the putative Lewis-b receptor, bacterial colonisation and ensuing inflammatory response may be influenced at least in part by host expression of ABO and Lewis-a blood group antigens". They found greater bacterial density among patients whose red cells expressed Lewis-a antigen (non-secretor phenotype). Consistent with these results, Heneghan et al., [68] observed that both acute and chronic inflammatory cells were present in greater quantity in the antral mucosa of non-secretors and that there was a positive correlation between density of H. pylori infection and the degree of lymphocyte and neutrophil infiltration in both secretors and non-secretors.

Conclusion

Understanding the clinical significance of ABH secretor status, Lewis subtypes and lectins in diet affords a valuable insight into the pathogenesis of peptic ulceration. It is hypothesized that ability to secrete A,B and H substances in saliva, mucus and other glandular secretions was, perhaps, of paramount adaptive significance at a stage in the early history of man when human ancestors subsisted on raw food [24]. Dietary lectins exert a strong selection pressure favoring secretors. Evolutionary trends in the establishment of ABH polymorphism strongly suggest an inverse relationship between the incidence of non-secretors and the component of raw food rich-in-lectins in diet. The non-human primates who feed mostly on wild plants (fruits, leaves, tubers etc.), and consume untempered lectins in bulk, are invariably secretors [25]. The hunter-gatherers, with a high content of lectin-rich raw food in their diet, likewise, are mostly secretors. The non-secretors are rare (zero to 3%) in these human isolates [26]. The modern human societies, on the other hand, show a sustained high frequency of non-secretors (over 20%) [26]. As many of the dietary lectins are heat sensitive, they get inactivated, partly or fully, in the cooked food which forms a major component of their daily diet. A frequent occurrence of non-secretors in modern human societies is perceived as the consequence of relaxation of selection pressure on the secretor gene (Se) which has a selective advantage in a lectin-rich dietary environment [24]. Plants are a rich source of lectins. Foods with high lectin content (legume seeds, cereal grains, nuts etc.), if consumed in excess, in uncooked or partially cooked form, can cause gastrointestinal distress [39,51,62]. There is mounting evidence implicating lectins as the trigger factor for peptic ulceration[61]. Decreased susceptibility of secretors to ulceration can be attributed to the presence of water soluble blood group substances (glycoproteins) in large amount in brush border cells lining the gut, which act as a defense against the mucus stripping effect of lectins in food, and protect the epithelium from heavy colonization of Helicobacter pylori. Some other factors influencing the onset and development of peptic ulcer disease are, a lectin rich diet [24,39,51,62], ABO phenotype [11,12] and preferential affinity of H. pylori key-adhesins for competing H type 2, Lewis-a and Lewis-b antigenic receptors in gastric mucosa [69,70]. Proactive role of some seemingly unrelated factors such as leptin resistance, trypsin inhibitor types, passage into blood plasma of intestinal alkaline phosphatase, PTC tasting ability etc., which have a bearing on the etiology of peptic ulcers also need to be investigated. Propensity for ulceration is a bane of modern human societies which are not so well adapted to withstand the onslaught of a lectin-rich-diet (raw, unprocessed and partly cooked foods).

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