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Summary

Recent research on Anorexia Nervosa (AN) and Bulimia Nervosa (BN) has shown an increasing understanding of the biological and physiological abnormalities that underlie the development of an eating disorder. Cultural pressures, individual and family experiences, along with physiological and genetic systems all appear to contribute to the onset of these disorders. There is significant evidence for genetic factors in the susceptibility of AN/BN, however current research has focused on the possibly of characterizing eating disorders as being an autoimmune disease. Autoantibodies have recently been discovered in patients with eating disorders and could be affecting the biological pathway of many hormones, specifically α-melanocyte-stimulating hormone, by various mechanisms. Also these autoAbs have been associated with physiological traits which also have been proven to be symptoms of eating disorders. The origin of these autoAbs remains to be established. Yet childhood viral infections and gut microflora may provide two explanations for the creation of autoAbs. Future research needs to examine the direction of causation, the underlying mechanism of the immune response, and if this could be contributed to the development of AN/BN. Although there have been substantially advances in the knowledge of eating disorders, the goal of offering effective treatment to all patients remains elusive.

Background on Anorexia Nervosa and Bulimia Nervosa

History and Prevalence of Eating Disorders

Over the past 25 years Anorexia Nervosa (AN) and Bulimia Nervosa (BN) have been recognized as eating disorders and have received major attention among both the general public and the research community (1). AN and BN have both been characterized by clinically significant disturbances in body image and eating behavior (2). AN can be defined as a disorder in which adolescents or young adults, mostly females, become engaged in a relentless and successful pursuit of thinness that usually results in serious weight loss (1). The core features of AN are cognitive and disturbances in body image. These can include: feeling fat even when emaciated, denial of seriousness of one's low weight, morbid fear of weight gain. AN also has many physical consequences which can include: failure to maintain a minimum adequate body weight less than 85% expected, and in girls and women, amenorrhea, and can be engaged in the misuse of laxatives, diuretics or enemas (2,3). BN is defined by an overvaluation of weight and shapes in one's sense of self worth and behavioral symptoms of recurrent binge eating, accompanied by inappropriate compensatory behaviors (e.g. purging, fasting, excessive exercise, use of drugs). AN was first recognized as a mental disorder in the late 19th century; BN, after briefly being considered a variant of AN in 1970, it was considered a disorder by 1980. Therefore, given this short history, it is not surprising that eating disorders are far less researched than any other mental disorder (2).

Together both illnesses affect about 3% of women over their lifetime. However, BN, the more common disorder, appears to be increasing in incidence (1). Estimates of the prevalence of BN behaviors have ranged from as low a 5% in family practice adult samples to 20% in a population of college females. BN in males has been reported as ranging from 0% to 5% in college males (4). More importantly, eating disorders all together have a prevalence of 10% among any given population (1). Research has shown that the average age of onset can range from 10 years of age to 20, however 86% have reported the onset of the illness by age 20. The duration of this illness can also vary, yet 77% report the duration of the illness from 1 to 15 years. Nevertheless, what is important to note is that only about 50% of people with an eating disorder report ever being cured.

The Development and Treatment of Eating Disorders

So the question remains how do people develop AN or BN and why is it hard to stop? Many AN/BN patients report that their eating habits regain in the contest of or immediately following a diet, and many continue to restrict their caloric intake. Psychological factors also seem to be critical in that patients frequently suffer from depression, which has been linked to disturbances in eating behavior. In addition, a variety of nonspecific individual and familiar risk factor for psychiatric disorders, such as a history of sexual abuse, seem to increase an individuals chances of developing AN or BN (1). More importantly, cultural influences play an important role in the development of eating disorders. Reports of AN and BN stem predominantly from the industrialized world, where food is plentiful and thinness (particularly for women) is equated with attractiveness (2).

Yet how can we help people who develop these eating disorders? Current treatments for AN are aimed at normalizing body weight and correcting the pre-occupation with weight loss. This intervention can be achieved through admission to a hospital or a day-treatment program where meals and exercise are closely supervised and psychological counseling is provided (1). Two approaches have been developed as treatment for people with BN. The first approach is a short term (4 to 6 month) form of physiological therapy referred to as cognitive behavioral therapy. In this

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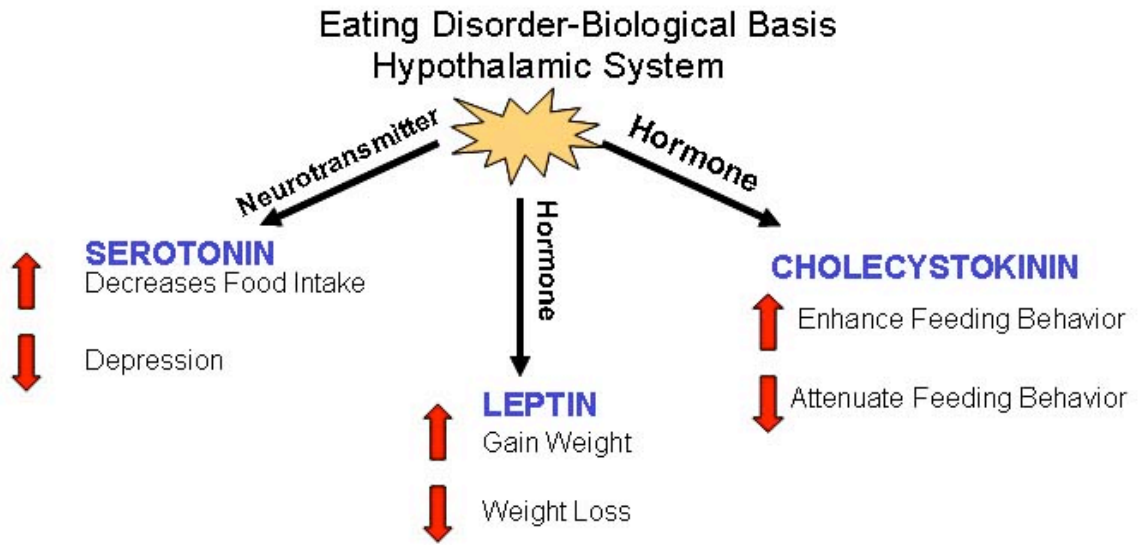

Figure 1: Biological Basis of Eating Disorders
AN and BN have been known to be sustained by physiological and biological processes. Serotonin, Leptin, and Cholecystokinin have been recognized as three primary neurotransmitters and hormones involved in the regulation of food intake, fat storage, and eating behavior. Changes in the concentrations of these can lead to the symptoms seen in eating disorders.

therapy, patients monitor their thoughts, feelings, and help to cease binge-purge episodes and promote regular eating. The second approach is the use of antidepressant medications, such as Norpramin and Prozac. These medications were initially demonstrated as helping patients reduce binge frequency by helping mood disturbances; however, only a minority of patients have achieved full remission, and it is not known if there will be a relapse in patients if medication is discontinued (1, 2). Despite these advances in the current treatments of AN and BN, the results are often short term and do not focus on the long term psychological disturbances and relapse is common. Therefore, new interventions are needed.

Biological Basis of Eating Disorders

Due to the fact that AN and BN have prominent psychological disturbances, many researchers have questioned whether eating disorders have a biological or genetic basis. Recent studies have shown abnormalities in serotonin and leptin function (2). The neurotransmitter serotonin is involved in physiological systems, specifically mood disturbances, relevant of AN. Increases in brain serotonin function lead to reductions in food intake, and decreases in brain serotonin function are associated with depression (3). Additionally, leptin is a hormone secreted by fat cells that appears to play an important part in the relation of body fat stores. Consistent with the low body weight of individuals with AN, research has shown at patients with AN have low serum levels of leptin and these increase with weight gain (1). Furthermore, cerebrospinal fluid (CSF) levels have also been proven to be low in underweight individuals, but appear to also rise to normal levels if patients have long recoveries (4). BN patients have also been linked to abnormal serotonin function and this may contribute to the persistence of binge eating. In addition, in some patients with BN, may have an enlarged stomach and have an excess amount of the satiety hormone cholecystokinin (CCK) following a meal (Refer to Figure 1 for a more detailed description). These changes may impede normal eating behavior (5). On the other hand, familial factors also play a role in the development of eating disorders. With regard to AN, a number of twin studies have been performed in an attempt to determine its heritability. Recent research has shown that monozygotic (MZ) twins have 56% concordance rate for developing AN whereas dizygotic (DZ) twins have had 7% (6), however the statistics decrease if these twins are reared apart. Therefore, it is predictable that a substantial proportion of the predisposition to AN could be genetic.

Molecular Basis of Eating Disorders

At a molecular standpoint, researchers have been trying to link various genes to AB and BN. Many have been identified including: 1) serotonin 2A receptor- involved in regulation of food intake, 2) tryptpophan hydroxlase- the rate limiting enzyme in serotonin

synthesis, lack of this gene is found in patients with AN, 3) dopamine and estrogen receptors- play a role in amenorrhea, distortion of body image, and hyperactivity seen in AN patients, 4) UCP 2ad UCP 3 proteins- involved in control of energy expenditure and metabolic adaptation during fasting, and 5) melanocortin 4 receptor gene, which has been involved in energy balance, food intake, body weight regulation, and has recently been involved in autoantibody research (7). A few other genes such as leptin, agouti-related protein, ESR1 and ESR2 genes (8), and neruopeptide Y have also been studied for association with eating disorders (9). Yet with all of this previous knowledge, genetic research on eating disorders still remains in its first steps. Many gaps still remain in our understanding of

eating disorders such as what each gene does specifically and does it interrupt the biological pathway? More importantly can AN and BN be predicted genetically or it is only a physiological disorder? These questions still remain unknown as researchers are trying to figure out how these genes influence the development of an eating disorder. Current research has been examining the possibility of characterizing AN or BN as autoimmune diseases. In the following review I would like to introduce the background regarding autoimmunity by introducing the viral theory and question where the origin of antibodies in AN or BN patients.

Research Progress: Autoimmunity

What is an Autoimmune Disease?

Autoimmune disease can be defined as a disorder caused by an autoimmune response, i.e., an immune response directed to something in the body of the patient. Since autoimmunity can affect any organ in the body (including brain, skin, kidney, lungs, liver, heart, and thyroid), the clinical appearance of the disease depends upon the site affected. For many years, medical professionals and researchers were skeptical of the existence of autoimmunity since it seemed to defy common sense. Why would a person develop an immune response to himself or herself rather than to an invading germ? Yet, once a person realizes that the immune response is a powerful and complex biological reaction, then one can assume, on occasion, the reaction can misfire. These misfirings of the immune system are the reason that autoimmune diseases occur. Sometimes autoimmunity can be the initiating cause of a disease. In other cases, autoimmunity can contribute to, or exaggerate, a disease caused by another factor. The presence of an autoimmune response is signaled by the appearance of autoantibodies (autoAbs) in a patient's circulatory system. Therefore, the demonstration of a particular autoAbs usually constitutes the path to recognize an autoimmune disease (10).

There are a few autoimmune diseases that have already been identified by reasechers. For example, Lupus is an autoimmune disease in which B cells make autoAbs against histones and DNA. Additionally, Insulin-Dependant Diabetes also has white blood cells (T cells) of the body's immune system attack and destroys the pancreatic beta cells, halting the production of insulin. Furthermore, extensive research has been conducted regarding the autoimmune disease Multiple Sclerosis (MS). In MS, the body produces T cells that react against the myelin sheath, the "coating" that covers and protects the nerve fibers in our CNS, causing inflammation and scarring. Once this occurs, the nervous system, which is the known "control center" is unable to send messages, and that in turn has a direct affect on brain signaling and movement all over the body (11).

Based on previous knowledge in which eating disorders have been characterized by having changes in the concentrations of neuropeptides, researchers have been examining possible underlying mechanism causing this change. Currently, researchers have identified autoAbs in patients that have eating disorders and more importantly they have recognized the target of these autoAbs.

New Research on Eating Disorders as a Possible Autoimmune Disease

Fetissov and colleagues in 2002 were able to identify antibodies against α-melanocyte-stimulating hormone (α-MSH) and adrenocorticotropic hormone (ACTH) in patients with AN and BN. In this study, they hypothesized that because people with eating disorders have trouble with the regulation of food intake and the hypothalamic system is involved in energy intake and expenditure, then it may be the target by autoAbs in AN/BN patients, as shown in other neurological disorders. After testing the sera of 57 patients with eating disorders, they found that a significant subpopulation of AN/BN patients have autoAbs that bind to α-MSH or ACTH hormone. Another major finding pointed to the involvement of stress (12). α-MSH is a peptide found in the anterior pituitary gland that is involved in appetite control and the stress response (13), and ACTH is a hormone extracted from the pituitary gland involved in stimulating the adrenal glands to release glucocorticoids, which in turn affect metabolism (14). Nevertheless, if these hormones are being attacked by autoAbs, with what biological pathway could this interfere? First of all, these autoAbs could interrupt signaling with food intake regulatory neurons such as neuropeptide Y, which was already recognized in AN/BN patients (15, 16). Second, they could interfere with receptors, like MC4, which is involved in the regulation of body weight (16). Lastly, these autoAbs may block the overall function of α-MSH/ACTH thereby affecting a person's appetite and metabolism. Therefore, all these explanations suggest that if autoAbs react with neuropeptides responsible for the central control of appetite and this further characterizes the pathogenesis of eating disorders. Yet, some researchers still view AN/BN as a mental disorder, so can these autoAbs have an affect on psychological traits?

In October 2005, Fetissov and colleagues further studied the occurrence of autoAbs in AN and BN patients using a sample from Estonia. In this population, they found more autoAbs reacting with two more neurohormones—Oxytocin (OT) and Vasopressin (VP)—which are involved in the regulation of water balance as well as in several motivated behaviors (17). Therefore, they hypothesized that the levels of these autoAbs many correlate with some psychological problems found in AN and BN patients. Using the Eating Disorder Inventory-test that is widely used to assess the cognitive and behavioral characteristics commonly found in individuals with AN and BN (18), along with autoAbs levels measured by immunohistochemistry of human sera, they found significant correlations between α-MSH autoAbs levels and the total Eating Disorder Inventory 2-score. Some of these physiological traits that were correlated include: drive for thinness, bulimia, ineffectiveness, interpersonal distrust, ascetism, impulse regulation, and social insecurity. The first three traits seem to be consistent with the symptoms of both AN and BN patients. Hence, autoAbs against α-MSH seem to be interfering with the body through the melanocortin system and could lead to the development of an eating disorder (17).

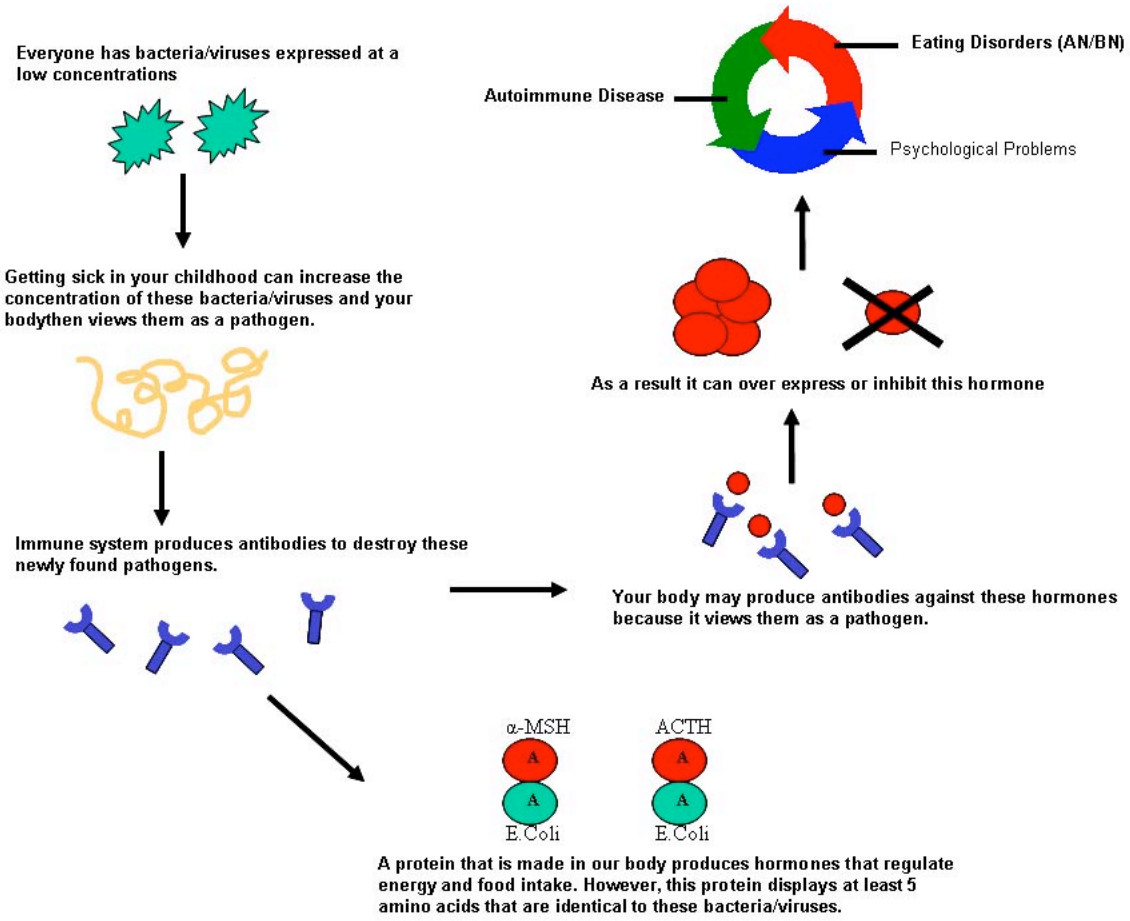

Figure 2: The Viral Theory
Recently AN/BN have been correlated to autoimmune disease. One possible explanation for the appearance of autoantibodies could be due to a childhood infection. This can lead to the expression of autoantibodies that have been found in AN and BN patients.

Research as It Stands Today
Viral Theory Proposal: Why do Autoantibodies Originate?

If autoAbs could be correlated to physiological traits, then it is important to question where these antibodies come from. Yet researchers are only finding some possible answers to this question by looking at childhood diseases (i.e. The Viral Theory as seen in Figure 2 could be a possible mechanism to why we are seeing these new findings). Therefore one explanation for the origination for these autoAbs could be their recognition of certain hormones as foreign such as the flu or some other form of bacteria. Another explanation could be intestinal microflora found in the gut. Estonian and Swedish populations seem to have significant differences in the intestinal microflora compared to other populations, which could trigger the development of autoAbs in response to a foreign pathogen (19). The intestinal route could be a main source of autoAbs reacting with neuropeptides. However, a direct comparison of autoAbs levels and gut microflora has yet to be conducted. The viral theory does not have enough support and needs to be examined further. More importantly, the direction of causation still remains to be established, as does the mechanism underlying the exact immune response for each hormone. There have been substantial advances in the underlying knowledge of eating disorders in the last couple of decades. However the goal of offering effecting treatment to all individuals with eating disorders remains elusive. Finding the underlying cause that affects so many women everyday will be another step forward in the finding a cure. With AN and BN being among the most disabling and lethal of psychiatric disorder (20), along with many physical attributes, it is not hard to understand why researchers are having such a difficult time finding the biological basis of the origin of eating disorders. By further examining of autoAbs and other genes it should provide important insights into the genetic susceptibility to Anorexia Nervorsa and Bulimia Nervosa

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References

1. Walsh, T. & Devlin M. Eating Disorders: Progress and Problems. *Science*. 1998, 280: 1387-1390.

2. Sterigel-Moore, R., & Smolak, L. *Eating Disorders: Innovative Directions in Research and Practice.* Washington D.C: American Psychological Association, 2001.

3. Garner, D., & Garfinkel, P. *Handbook of Psychotherapy for Anorexia Nervosa and Bulimia.* New York: Guilford Press, 1985.

4. Bulik, C., Reba, C., Siega-Riz, A., & Reichborn-Kjennerud, T. Anorexia Nervosa: Definition, Epidemiologist, and Cycle of Risk. Psychopathology. 2005, 37: S2-S9.

5. Johnson, C., & Connors, M. *The Etiology and Treatment of Bulimia Nervosa*. New York: Basic Book Publishers, 1987.

6. Pieri, L., & Campbell, D. Understanding the Genetic Predisposition to Anorexia Nervosa. *European Eating Disorders Review.*1999, 7: 84-95.

7. Klump, K., & Gobrogge, K. A Review and Primer of Molecular Genetic Studies of Anorexia and Nervosa. *International Journal of Eating Disorders.* 2005, 37: S43-S48, 2005.

8. Eastwood, H. Brown, K., & Pieri L. Variation in the ESR1 And ESR2 genes and genetic susceptibly to anorexia nervosa. *Molecular Psychiatry*, 2002, 7: 86-89.

9. Tozzi, F., & Bulik, C. Candidate Genes in Eating Disorders. *Current Drug Targets-CNS & Neurological Disorders.* 2003, 2: 31-39.

10. Rose, N. The Autoimmune Diseases. *American Autoimmune Related Diseases Association.* 2001, 9, 1-4.

11. Campbell, N., Reece, J., Taylor, M., & Simpson, E. *Biology Concepts and Connection*. 5th ed. San Francisco: Pearson & Benjamin Cummings, 2006.

12. Fetissov, S., Hallman, J., Oreland, L., Klinteberg, B., Hulting, A. & Hokfelt, T. Autoantibodies against α-MSH, ACTH, and LHRH in anorexia and bulimia nervosa patients. *PNAS*, 2002, 99: 17155-17160.

13. Fan, W., Boston, B., Kesterson, R., Hruby, V., & Cone, R. Role of melanocortinergic neurons in feeding and the agouti obesity syndrome. Nature. 1997, 385 :165-168.

14. Ollmann, M., Wilson, B., Yang, Y., Kerns, J., Chen, Y., Gantz, I., & Barsh, G. Antagonism of Central Melanocortin Receptors in Vitro and in Vivo by Agouti-Related Protein. Science. 1997, 278:135-137.

15. Bagnol, D., Lu, X., Kaelin, C., Day H., Ollmann, M. Ganta, I., Akil, H., Barsh, G., & Watson, S. Anatomy of an Endogenous Antagonist: Relationship between Agouti-Related Protein and Proopiomelanocortin in Brain. *The Journal of Neuroscience*, 1999, 19: 1-7.

16. Huzar, D., Lynch, C., Fairchild-Huntree, V. Dunmore, J., Fang, O., Berkemeier, L., Gu, W., Kesterson, R., Boston, B., & Cone, R. Targeted Disruption of the Melanocortin-4 Receptor Results in Obesity in Mice *Cell*, 1997, 88: 131-141.

17. Fetissov, S., Harro, J., Jaanisk, M., Jarv, A., Podar, I., Nilsson, I., Sakthivel, P., Lefvert, A., & Hokfelt, T. Autoantibodies against neuropeptides are associated with psychological traits in eating disorders. PNAS, 102: 14865-14870.

18. Garner, D., Olmsted, M., & Polivy. Development and Validation of a Multidimensional Eating Disorder Inventory for Anorexia Nervosa and Builmia. *The International Journal of Eating Disorders.* 1983, 2: 15-34.

19. Oona, M., Rago T & Massroos, H. Long-term recurrence rate after treatment of Helicobactor pylori infection in children and adolescents in Estonia. *Scandinavian Journal of Gastroenterology.* 2004, 39: 1186-1191.

20. Godfrey, J. Toward Optimal Health: The Experts Discuss Eating Disorders. Journal of Women's Health, 2004, 13: 662-667.