# THE EFFECT OF DIETARY COTTONSEED PROTEIN ON SERUM AND SECRETORY IgA LEVELS IN INDIVIDUALS WITH DOWN'S SYNDROME

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CAROL BARNHART FRANKMANN, B.S.

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# INTRODUCTION

Down's syndrome is one of the most common of the clinically classifiable categories of mental retardation. It is a genetic disorder involving an abnormality in chromosome No. 21, and virtually every tissue in the body is abnormal. Down's syndrome individuals exhibit disordered growth of the skeletal system with an abnormal development of the skull which is responsible for the characteristic facies. Cardiac abnormalities and duodenal atresia occur more frequently than in the general population. Chronic inflammatory changes involving the conjunctivae and lid margins, skin infections, and acute and chronic infections of the upper respiratory tract are common. There are frequently abnormalities of the white blood cells, and the incidence of leukemia in Down's syndrome is 10-20 times greater than in the general population. An increase in some of the gamma globulin fractions also has been observed. There have been reported decreased levels of serotonin in serum. The mental status is usually in the moderately to severely retarded range. In the absence of serious associated congenital defects, and when the child is given good medical care, the life span can be expected to approach normal (1).

Reports in the popular press have claimed that a Down's syndrome individual whose diet was supplemented with cottonseed protein exhibited physical and behavioral improvement (2). Although there have been no controlled clinical trials to assess the effects of cottonseed protein in the diet of these individuals, it does appear feasible that a change in the nature of the dietary protein could have an impact on physical and behavioral parameters. Synthesis of cellular protein is the basis of life itself, and a change in the amino acid

patterns provided by dietary protein could be expected to have a physiological impact.

## PROBLEM STATEMENT

With this in mind, the research question addressed by this study was: What are the effects of a diet in which 50 percent of the protein is from cottonseed on the serum and secretory levels of IgA in Down's syndrome individuals?

## REVIEW OF THE LITERATURE

The frequency of upper respiratory tract infections and chronic inflammatory changes in the conjunctivae and lid margins of persons with Down's syndrome is well known, and it is possible that this phenomenon could be related to the function of secretory immunoglobulin A (IgA). Secretory IgA is the major antibody of the external secretions, e.g., milk, saliva, tears, and bile as well as in nasal, bronchial, intestinal and genitourinary secretions. It differs structurally from serum IgA. Whereas serum IgA exists as a monomer, the structure of secretory IgA has been shown to be an IgA dimer with an additional polypeptide chain, the secretory component (3). The two IgA monomers are bound together by a joining (J) chain. The compact structure of secretory IgA is more resistant to enzymatic attack than is serum IgA. The IgA dimers and J chain are produced by specialized lymphoid cells found close to the submucosal exocrine glands. The secretory component is synthesized by the epithelial cells and added to the IgA dimer-J chain complex during its passage through these cells on its way to the glandular secretion (4).

It has been suggested that about half the number of lymphocytes in the body of humans are found in association with mucous membrances and exocrine glands (4). Most of these cells are IgA producers. It has also been noted that the IgA producing cells in the mucous membranes of the intestinal wall, as well as the respiratory tract, can be substituted with cells from the Peyer's patches in the intestine or the bronchus-associated-lymphoid-tissue, BALT, in the lungs. Antigenic stimulation in the gut is followed by migration of specialized lymphoid cells from the Peyer's patches via the mesenteric lymph nodes to other parts of

the gut mucosa where they produce secretory IgA antibodies which are released into the intestinal secretions. There is some evidence to indicate that IgA-producing cells from the BALT and the Peyer's patches are sent to various exocrine glands in the body (4).

Human milk has been reported to contain antibodies of the secretory IgA type which act against antigens of a large number of Escherichia present in the intestine of the lactating mother (4). However, as outlined above, there does not appear to be a direct transport of IgA from serum to breast milk or saliva. Stiehm et al. determined the IgA content of saliva obtained from two normal subjects and of breast milk from two lactating women after injection of $I^{131}$ labeled serum IgA and was unable to demonstrate transport of IgA from serum to these secretions (5).

Nevertheless, the dissociation between serum and secretory IgA is not absolute. Minor amounts of secretory IgA may appear in the blood. Thompson et al. found secretory IgA in the sera of 31 of 113 patients with gastointestinal disease and in 9 of 101 healthy individuals (6). However, among the patients studied, not all of those with high serum IgA levels had evidence of secretory IgA in the serum, and some who had secretory IgA in the serum had normal serum levels. Thompson postulated that the finding of secretory IgA in the sera of the patients with gastointestinal disease may represent the reabsorption of intraluminal IgA through a damaged epithelium. Work in animals also indicates that, in some instances, serum IgA levels may be related to the presence of secretory IgA in the blood. Vaerman et al. studied the concentration of IgA in serum versus mesenteric lymph in guinea pigs and rats and concluded that the intestinal mucosa is the major source of serum IgA in guinea pigs and rats (7). Lemaitre-

Coelho et al. have shown that ligation of the bile duct in the rat induces a rapid and progressive elevation of secretory IgA levels in the serum, which is totally reversible if the bile duct is reopened one day after ligation. Lemaitre-Coelho suggest this may be relevant to the elevated serum IgA levels detected in patients with liver disease, particularly in those with primary biliary cirrhosis and obstructive jaundice (8). Elevated levels of serum IgA are seen in patients with myeloma; however, it is primarily the monomer form (9).

Although the structure of serum IgA is well known, the function remains largely obscure. Russell et al. suggest from their studies with rats and mice that serum IgA antibody mediates the transport of a foreign protein antigen from the circulation into the bile by a mechanism that may be found to circumvent the inflammatory consequences of the activation of complement and phagocytosis (10). It is generally accepted that IgA does not fix complement and is poorly opsonic, whereas the protective functions of IgG and IgM antibodies in complement and phagocytosis mediated processes are well understood. Thus, one might expect that if elevated serum IgAs were associated with an infectious state, serum levels of IgG and IgM would also be elevated.

Several authors have reported elevated serum levels of IgA in Down's syndrome individuals (11,12,13,14,15,16), others have observed depressed levels (17,18,19), and others have found normal levels (20,21). However, levels of secretory IgA were not determined by any of these investigators. Secretory IgA is of major importance in creating an immune barrier against micro-organisms at exposed mucous surfaces (22). If this IgA level and/or function also is disturbed in individuals with Down's syndrome, it could serve as a contributing factor to the high incidence of chronic inflammatory changes involving the conjunctivae

and lid margins and the acute and chronic infections of the upper respiratory tract observed in this population.

Chandra reports that secretory IgA is low in protein-calorie malnutrition and that secretory antibody response following immunization with live attenuated virus vaccines is reduced. Moreover, he reports that the decrease in secretory IgA is out of proportion with the slight reduction in levels of other proteins in mucosal secretions, perhaps indicating that secretory IgA is more sensitive to nutritional status (23). Although the subjects in this study were not overtly malnourished, it would seem possible, that dietary cottonseed protein could have an impact on serum and/or secretory IgA levels in persons with Down's syndrome, thereby affecting the incidence of infections related to mucosal defense.

Cottonseed protein has been processed and marketed in this country as a food additive since the 1930's. However, its initial use was primarily for its functional qualities, such as to improve the browning of bakery goods or to reduce fat absorption during frying, rather than for its nutritional qualities (24).

Cottonseed protein became widely known as a source of nutrients for humans during the late 1950's and 1960's as a result of Scrimshaw's work at the Institute of Nutrition of Central America and Panama in the development of low-cost vegetable protein mixtures for the supplementary and mixed feeding of infants and young children (25). The generic name "Incaparina" was given to these cereal mixtures which in dry form contained over 25 percent protein of a quality comparable to that of some proteins of animal origin. Mixture 9B, which was successfully marketed, included 29 percent each of uncooked ground corn and sorghum, 38 percent cottonseed flour, 3 percent Torula yeast, 1 percent

$CaCO_3$, and 4500 I.U. Vitamin A acetate. It supplied desirable amounts of essential nutrients except ascorbic acid. When compared with milk in the treatment of children with kwashiorkor, the protein of "Incaparina" was of relatively good quality. When the level of protein intake was adequate for the needs of the child, the body retained as much nitrogen from the vegetable mixture as from an equivalent amount of protein in milk. However, during inadequate intakes of protein, proportionally more nitrogen was retained from the protein in the milk. Nevertheless, Scrimshaw et al. did demonstrate that a vegetable mixture in sufficient quantity can provide protein adequate for preventing protein malnutrition.

Subsequently, the nutritive value of cottonseed as the major source of protein in the diet has been studied in children, adults, and the elderly (24,26,27,28,29,20,31). In all cases, it has been shown to support growth and development and to maintain nutritional status when the protein level is sufficient to maintain nitrogen equilibrium. Alford (28) and Thomas (29) found that when cottonseed flour was the sole source of protein in the diet of young college women, 0.106 grams of nitrogen per kilogram of body weight were required to maintain nitrogen equilibrium. Alford observed that this level was between the reported values in men for soybean and wheat protein.

It is important to note that the nitrogen balance requirements in the two studies were the same, although Alford utilized a purified formula diet and Thomas used baked food products containing glandless cottonseed flour. This difference is of interest in that cooked cottonseed food products were used in this study and several authors have stated that heat in processing and/or baking renders the lysine in cottonseed unavailable via linkage of the free amide groups

with carbonyl groups (29,30,32,33). This bond is not broken by digestive enzymes, and thus, the lysine unit is nutritionally unavailable. Some authors, thus, report lysine to be the limiting amino acid in cottonseed (29,30).

Acid hydrolysis gives about a 50 percent release of the lysine, so the usual method of amino acid analysis may obscure the nutritional damage to lysine and overvalue the protein quality (33). For that reason, the chemical scores determined in comparing the levels of amino acids in the cottonseed flours in Table 1 with those in whole egg may be misleading. Such a comparison shows the limiting amino acids in cottonseed flour to be histidine for the Bowes and Church analysis (34) and methionine for Lawhon's analyses (35,36). Although Lawhon reports two values for lysine, acid hydrolysis was used for all sample preparation and an assay determination for available lysine was not indicated.

The difference in amino acid value of the formula used by Alford (7) and the baked products used by Thomas (29) may have been obscured by the body's ability to adapt to some degree to amino acid deficiencies by decreasing the rates of catabolism of the appropriate amino acid and conserving it for reutilization. Hegsted reports that this adaptive response appears to be maximal for lysine, less so for most other amino acids, and practically nonexistent for threonine (37). Thus, the minimum nitrogen requirements from cottonseed protein appeared to be the same, even though it is probable that the amino acid values of the formula used by Alford were different than those in the baked products used by Thomas.

TABLE 1

CHEMICAL SCORE OF GLANDLESS COTTONSEED FLOURS VS. WHOLE EGG

| Amino Acid | Data Source: Bowes & Church | Lawhon '72 | Lawhon '74 |
|---|---|---|---|
| Lysine | 78% | 63% | 66% |
| Histidine | 0% | 113% | 112% |
| Tryptophan | 93% | 100% | 100% |
| Cystine | 0% | 104% | 109% |
| Threonine | 89% | 68% | 68% |
| Valine | 85% | 66% | 65% |
| Methionine | 52% | 45% | 52% |
| Isoleucine | 75% | 53% | 53% |
| Leucine | 84% | 72% | 69% |
| Tyrosine | 0% | 85% | 77% |
| Phenylalanine | 115% | 111% | 98% |
| Available lysine | -- | 59% | 55% |
| Methionine + cystine | 29% | 69% | 75% |
| Phenylalanine + tyrosine | 67% | 100% | 81% |

## HYPOTHESES

It was the purpose of this study to test the following hypotheses:

1. A diet in which 50 percent of the protein is from glandless cottonseed will have no significant effect on the levels of serum IgA in individuals with Down's syndrome.

2. A diet in which 50 percent of the protein is from glandless cottonseed will have no significant effect on the levels of secretory IgA in individuals with Down's syndrome.

## METHODS AND PROCEDURES

The population studied consisted of eight Down's syndrome females residing at the Center for the Retarded, Inc. in Houston, Texas. All were over 18 years of age, and each along with the parent/guardian consented to participation in the study in compliance with the requirements of the TWU Human Research Review Committee and the Board of Directors of the Center for the Retarded, Inc.

During the first week of the study, all subjects received a diet controlled in calories and protein, consisting of usual menu items. The subjects had participated in a weight control program during the previous year and had received a calculated 1400-1800-calorie reduction diet during that time. A similar calculated diet in which 50 percent of the 60 grams of protein was provided by glandless cottonseed flour and nuts was given during the second through the fourth weeks of the study. The subjects resumed their normal diet during the fifth week of the study.

All cottonseed-containing products were prepared by the investigators and provided by Texas Woman's University. All cottonseed containing products were heated in the preparation process. An amino acid profile was obtained on an aliquot of the cottonseed flour and the Tamu nuts (a cottonseed nut distributed by Texas A & M University). Other foods were prepared by personnel at the Center for the Retarded and were portioned and served by the investigators who also observed and recorded the intake of each subject.

At the end of the first, fourth, and fifth weeks, determinations were made for serum immunoglobulins A, G, and M, and saliva samples were obtained to determine the presence of secretory IgA. Serum determinations were again

repeated fourteen weeks after the cottonseed protein was discontinued.

Serum immunoglobulin levels were determined on the Technicon Auto-Analyzer II continuous-flow analytical instrument using an automated immuno precipitin method by the Department of Laboratory Medicine at the University of Texas M. D. Anderson Hospital and Tumor Institute at Houston (38). Salivary secretory IgA levels were determined by radial immunodiffusion and were done by Smith Kline Laboratories of St. Louis, Missouri (38).

Data from the study was analyzed using a T-Test and Friedman's two-way ANOVA, available in the Statistical Package for the Social Sciences. Statistics were done on the DEC-20 Computer at Texas Woman's University.

## RESULTS AND DISCUSSION

Elevated serum IgA levels in individuals with Down's syndrome have been reported by a number of investigators (25,26,27,28,29,30), although others have observed normal or depressed levels (31,32,33,34,35). A number of factors appear to influence these findings. Most investigators found elevated serum IgA levels to be associated with age, with elevated levels appearing in mid to late adolescence (25,26,28,35,39). Griffiths et al. studied 48 Down's syndrome individuals matched for age, sex, and length of institutionalization and found only males to have higher levels of serum IgA than their controls (29). In retrospect, those males had had a higher incidence of pyrexial illnesses during the preceding five years, and Griffiths suggested that the elevations in serum IgA were due to chronic infections.

The findings of this study differ from those of Griffiths in that all of the subjects were females over 18 years of age, and serum IgA levels were elevated in six of eight subjects prior to and 14 weeks after the diet. Moreover, there was no evidence of infection at the time the determinations were made, and serum IgG and IgM levels were within the normal range for all subjects except one. That one subject had an elevated serum IgG level throughout the study, although the serum IgA levels changed during that same period. Since there was no indication of a chronic infection or other abnormality, it would appear that the subject with the elevated serum IgG levels is in that five percent of the population for whom a higher level than the normal range is typical.

Many authors attribute elevated immunoglobulin levels in Down's syndrome to institutionalization. In a well-controlled study, Sutnick et al. studied serum

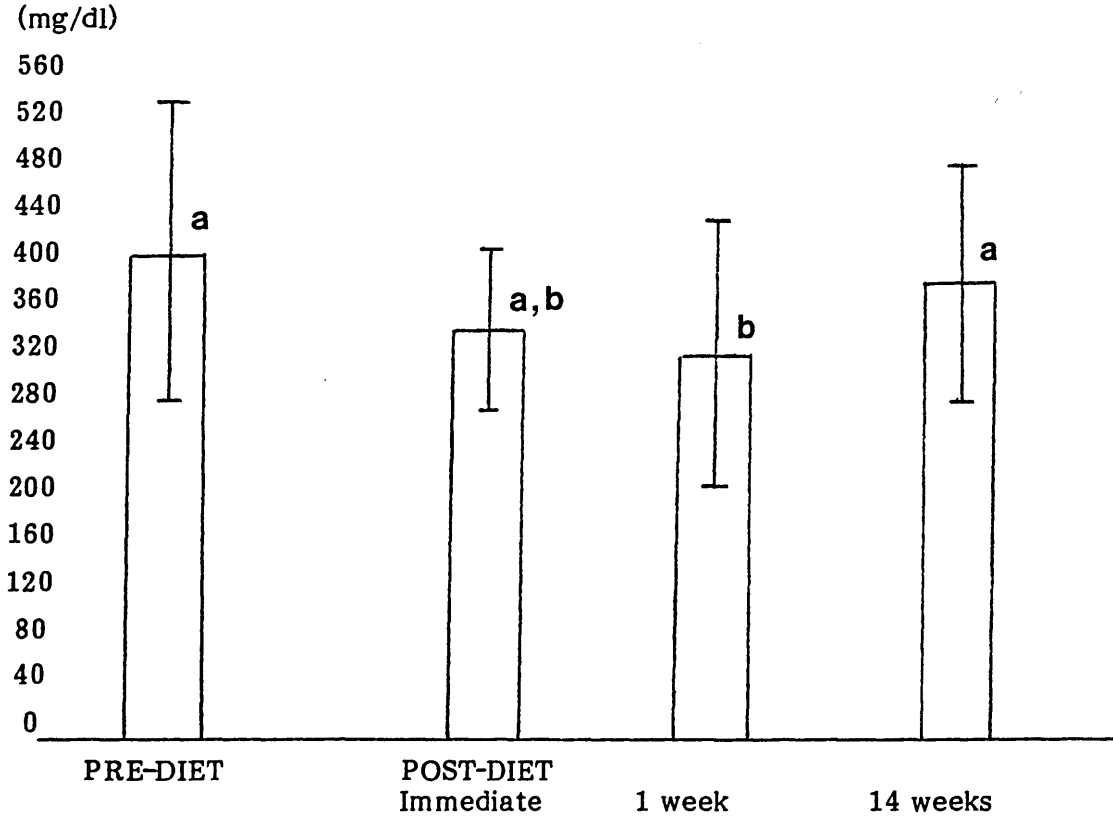
immunoglobulin levels in Down's syndrome versus other mentally retarded and examined the effects of living in an institution versus living at home and attending a day school (34). He found no significant difference in serum IgA levels in Down's syndrome and other mentally retarded, regardless of living arrangements. However, he did find serum IgG levels to be higher in the institution versus at home for Down's syndrome, but not for other mentally retarded. In contrast, serum IgM was higher in Down's syndrome in institutions versus at home, but it was not as high in Down's syndrome as in other mentally retarded. In another study, Kaldor et al. observed elevated serum IgG levels in institutionalized Down's syndrome individuals (33).

This study does not substantiate the premise that elevated serum IgG levels are prevalent in institutionalized Down's syndrome individuals. Unlike Sutnick and Kaldor's work, the only significant abnormality in this study was the elevated serum IgA levels. Moreover, in this study, changes in serum IgA levels were associated with changes in diet. Table 2 demonstrates the changes in mean levels of serum IgA during the study. The normal range was 75-330 mg/dl (38). Note that prior to the diet, the mean level was above the normal range. After three weeks on a diet in which 50 percent of the protein was provided by glandless cottonseed, serum IgA levels dropped, and the difference approached statistical significance ($p=.06$) when compared to pre-diet levels. Serum IgA levels continued to fall during the first week after the cottonseed diet was finished, and the difference in values from pre-diet to one week after diet was statistically significant ($p<.03$). Fourteen weeks after the cottonseed diet was terminated, serum IgA levels approached the pre-diet levels. Again, the difference in serum IgA levels from immediate post-diet to 14 weeks after the

diet was statistically significant ($p<.04$).

TABLE 2

MEAN SERUM IgA LEVELS IN INDIVIDUALS WITH DOWN'S SYNDROME: PRE- AND POST-DIET WITH 50 PERCENT PROTEIN FROM GLANDLESS COTTONSEED




NOTE: Different subscripts are significantly different at the $p<.03$ level.

In this study, changes in levels of serum IgG and IgM did not reach statistical significance at any time, as shown in Table 3. Moreover, as discussed earlier, except for one subject, all levels were within the normal range, so it is unlikely these subjects had an acute or chronic infection at the time the determinations were made.

TABLE 3

MEAN SERUM IMMUNOGLOBULIN LEVELS: PRE- AND POST-DIET WITH 50 PERCENT PROTEIN FROM GLANDLESS COTTONSEED

| | IgA (mg/dl) | IgG (mg/dl) | IgM (mg/dl) |
|---|---|---|---|
| PRE-DIET | 398±131 | 1416±324 | 108±47 |
| POST-DIET | | | |
| Immediate | 340±69 | 1456±332 | 108±49 |
| 1 Week | 318±110 | 1348±408 | 111±40 |
| 14 Weeks | 373±99 | 1398±373 | 106±45 |
| NORMAL RANGE | 75-330 | 650-1750 | 30-225 |

Since the function of serum IgA is not well understood, the basis of the elevation of the serum IgA levels in these subjects is a matter of speculation. One area to consider relates to possible allergies to food proteins. Chandra reported finding antibodies to several food proteins in the serum of 13 of 20 malnourished children (40). Antibody activity was found mainly in the IgG and IgA classes, and he suggested that the food antibodies in these malnourished children result from atrophied gut mucosa and reduced secretory immune response which permit passage of intact or incompletely digested protein

molecules and impaired phagocytic function of hepatic reticuloendothelial system. While it is unlikely that the subjects in this study had atrophied or damaged gut mucosa, the function of the secretory immune response was not fully assessed since only the presence of secretory IgA in saliva was confirmed. However, the relevance of Chandra's findings to these adult subjects would have to be considered in light of the report by Hanson et al. that proteins from cow's milk, as well as antibodies to such proteins, are often found in the serum of formula-fed babies in contrast to findings in adults in whom no antigenic material could be detected in serum after peroral exposure (41).

Secretory IgA levels were determined from saliva samples taken prior to the diet, at the end of the diet, and one week after the diet. Secretory IgA was present in all suitable samples. However, since quantitative values were not available, it was not possible to assess whether or not changes in levels were associated with changes in diet. For this reason, determinations were not repeated 14 weeks after the diet was completed. Nevertheless, in view of changes in the serum IgA levels asociated with diet, it would be desirable to have had quantitative values for secretory IgA. It was interesting to observe, subjectively, that the saliva of the subjects prior to the diet was sparse and viscous and that it appeared to be less so following the diet. Functional quality of the secretory IgA system also would be of interest, since the mucosal defense system of Down's syndrome individuals may be related to the high incidence of infections in the conjunctivae and the respiratory tract reported in this population. Other reports have indicated specific defects in host immune responses in patients with Down's syndrome. Defective white cell chemotaxis has been found by two investigators (42,43), and a third study reported correcting defects in

white cell chemotaxis, skin-test reactivity, and lymphoblast transformation in Down's syndrome subjects with zinc supplementation (44).

## CONCLUSIONS

In conclusion, the null hypothesis which stated that a diet in which 50 percent of the protein is from glandless cottonseed would have no significant effect on the levels of serum IgA in individuals with Down's syndrome was rejected. Elevation of serum levels of IgA was prevalent in these adult females with Down's syndrome while residing in an institution, free of infection, and consuming a mixed, normal diet for an extended period. Consumption of a diet in which 50 percent of the protein was from glandless cottonseed was associated with a decrease in serum IgA levels to near normal in these individuals. The decrease continued one week after the cottonseed diet was terminated; however, serum IgA levels rose to pre-cottonseed diet levels 14 weeks after the normal, mixed diet was resumed. It was not possible to determine whether the elevated levels of serum IgA were primarily the monomer form or whether the presence of secretory IgA in the serum contributed to the elevated levels.

The hypothesis that a diet in which 50 percent of the protein is from glandless cottonseed will have no significant effect on levels of secrtory IgA in individuals with Down's syndrome was not rejected. Secretory IgA was present in all suitable saliva samples, regardless of diet. Nevertheless, it is not possible to fully assess the impact of diet on secretory IgA in these individuals since no quantitative or functional information was available.

## IMPLICATIONS FOR FUTURE RESEARCH

This study has shown that elevations of serum IgA exist in this population. The reason for the elevation in unclear, but it does not appear to be related to an infection in that serum IgG and IgM levels were essentially normal. In an effort to elucidate the reason for the elevation of IgA, it would be helpful to identify the form of IgA present, e.g., monomer versus dimer. Presence of greater two percent dimer form would not be expected, since this is the highest value reported for persons free of disease (22).

Since serum IgA levels did move toward normal levels with a change in diet, it would be of interest to know what nutrients were primarily involved in effecting this change. Glandless cottonseed flour contains nutrients and substances other than protein, and these components may have contributed to the changes observed. For example, when compared to enriched wheat flour, cottonseed flour is high in iron, protein, fiber, fat, calcium, magnesium, phosphorus, and potassium and contains gossypol, a pigment located in the gland of the cottonseed. A future study might utilize a cottonseed protein isolate, preferably in a formula diet with 100 percent of the protein from the isolate. It also would be interesting to study Down's syndrome individuals who have consumed a diet high in cottonseed for an extended period to determine if the effect is temporary and whether serum levels become elevated again after a period of time.

Better assessment of secretory IgA levels and function would be of special interest in this population with a known high incidence of mucosal infections. Since there are reports of defective function in specific components of the

humoral immune system in Down's syndrome individuals, it is possible that the secretory IgA component also is defective. It also would seem reasonable that, if diet impacts serum IgA, secretory IgA also could be effected.

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