Assiut University

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"Experimental Induction of Local and Systemic Food Allergy Using Ovalbumin in Rats: Pathology and Treatment by Glucocorticoids and Omega-3 Fatty Acids"

Thesis

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2011

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Introduction

Immunologically mediated **enteropathies** consist of a group of different disease that is characterized by varying degree of villous destruction in the small intestine. Examples of these diseases are celiac disease and food allergy (Marsh, 1996 and Westerholm -Ormio, 2004).

Cow milk, egg, soybeans, wheat, peanut and fish contain protein antigens that responsible for the most dietary protein induced allergic reactions (Sampson, 1999). The ingested proteins are either protein allergens or protein immunogens (Kimber et al., 2003). Protein allergens are proteins or peptides that can induce IgE antibody immune response when injected, eaten or inhaled by atopic patients (Ferguson, 1997). Protein immunogens are capable of provoking T-helper-1(Th-1) immune response with the secretion of interferon- γ (IFN-γ) that antagonizes IgE response ((Kimber et al., 2003). These **reactions** are a sequential immune response involving the processing and presentation of the allergen, activation of allergen-specific T cells and B cells, production of IgE antibodies, excessive eosinophil and mast cell recruitment against the allergen and expression of adhesion molecules with the resultant mucosal lymphocytes recruitments (Kweon, et al., 2000 and Hogan et al., 2001 and Kamingawa and Nanno, 2004).Th-1 cells are more strongly activated in intestinal food allergy than Th-2 cells; regulatory Th-3 may be deficient at the site of antigen entry and allow uncontrolled immune reaction to food antigens to take place (Savilahti and Wester holm-Ormio, 2004).

Hypersensitivity can result when there is a break in the intestinal barrier function and an abnormal immune response to the presented antigen. This can occur in young animals whose intestinal mucosal barrier is not fully developed, in old animals whose intestinal mucosal barrier has begun to degenerate and in animals with gastrointestinal illness that damaged the intestinal barrier (Logas, 2009).

Food allergy is treated in human and experimental animals by using either omega-3 (Ishihara et al., 1998; Nagafuchi, et al., 2000; Nagura, et al., 2002; and Takano et al., 2004) or dexamethasone (Soda et al., 1993; Das et al., 1997; Krishnaswamy, et al., 2001; Sampson, 2003 and Kamingawa and Nanno, 2004).

In rat administration of **ovalbumin** produce anaphylactic reactions (Scudamore et al., 1995) and cell mediated enteropathy (Ogawa et al., 2002 and Ogawa et al., 2004). Rat is a good model of experimental animal.

The goal of the study is to evaluate the effects of **dexamethasone and omega-3** treatments in experimentally induced **ovalbumin allergic enteritis** in the three intestinal segments of the small intestine of rats. By using the morphological indices of the intestinal inflammation as alteration, exudation and proliferation and the measurement of villi heights and crypts depths and intraepithelial lymphocytes (IELs) count.

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REVIEW OF LITERATURE

Food hypersensitivity reactions include the allergic food hypersensitivities and the non allergic food hypersensitivities (Bruijnzeel-Koomen et al., 1995 and Ortolani et al., 1999). In non allergic food hypersensitivities, the symptoms can be induced or accelerated by non immunological factors such as emotions or exercise (Johansson et al., 2004). The **allergic** reactions to food are mediated by the dietary antigens with involvement of the immune system. These reactions are classified into 4 types which lead to tissue damage as described by Coombs and Gell, (1968). Both type I, II and III hypersensitivity reactions are antibody mediated while type IV cell mediated reaction.

1- Type I, immediate anaphylactic hypersensitivity

This reaction is characterized by the production of IgE antibodies against foreign proteins (Platts-Mills, 2002). These antibodies bind to high-affinity FCεRI receptors on mast cells and basophils causing degranulation of a mast cell /basophil, with subsequent release of histamine , vasoactive amines , eosinophil chemotacting factor (ECF), neutrophil chemotacting factor (NCF), leucotriens, prostaglandins and thromboxane (Janeway et al.,1997 and Romagnanine, 2000). The IgE allergic immune response can be divided into 3 phases: the sensitization phase, a facultative late-phase reaction and a chronic phase (Bischoff and Crowe, 2005).The sensitization phase is dependent on the uptake and processing of the antigen by antigen-presenting cells such as dendritic cells, macrophages or B cells and the subsequent presentation of antigenic peptides to naïve $CD4^+$ T cells. Under the influence of particular cytokines such as IL4 and IL-13, the naïve T-helper cells are transformed to T-helper 2 lymphocytes required for B-cell switch plasma cells producing larger amounts of specific IgE directed against particular food antigens. Once mast cells and basophils expressing the high-affinity IgE receptor, they bound with sufficient specific IgE, recurrent antigen exposure may induce an effector acute-

phase by cross-linking of surface IgE molecules. This acute phase causes activation and degranulation of mast cells and basophils and occurs within seconds to minutes and may be followed by a late-phase reaction. The late-phase reaction starts within 2-24 hours after allergen challenge and characterized by a cellular infiltration of the tissue with granulocytes and lymphocytes. The chronic phase that may be the result of repetitive late phase-reactions (Macfarlane et al., 2000).

2-TypeII, antibody-dependentcytotoxic hypersensitivity:

IgG or IgM antibodies can identify foreign antigens binding to cell surface then activate the complement system and damage the cell. Killer cells, platelets, neutrophils, eosinophils, and monouclear phagocyte cells have receptors for IgG and the activated C_3b components of the complement system and can therefore cause type II lytic damage to the target cells (Male, 2002).

3-Type III, immune-complex-mediated hypersensitivity

Soluble food antigens are often absorbed from the gut in small amounts and may form immune complexes with specific antibodies (Suen and Gordan, 2003).These immune complexes are not removed by mononuclear phagocytes system but persist, get trapped in small blood vessels and establish themselves in tissues and organs. The complexes fix complement system to release the anaphylatoxin products C3a and C5a. These induce the release of vasoactive amines and chemotactic factors that attract platelets and other inflammatory cells (Thomas, 2001). These cells may exocytose their granule contents and release reactive oxygen and nitrogen intermediates to cause vasculitis and tissue damage.

4-Type IV, delayed cell-mediated hypersensitivity:

These reactions take more than 12 hours to develop (Britton, 2002). T cells identify antigens and the antigen-sensitized T cells produce cytokines and other soluble factors which mediate the hypersensitivity reaction, or else they

develop cytotoxicity. Tissue damage occurs as a result of persistent antigenic stimulation. Type IV hypersensitivity has been classified into:

A-Contact hypersensitivity.

This reaction occurs within 3 days of challenge.

B- Granulomatous hypersensitivity reactions.

Which develop over a period of 21-28 days and are clinically the most serious type IV response. More than one type of delayed hypersensitivity follow a single antigenic challenge and reactions may over lap.

More than one mechanism may be involved in any allergic reaction, but the most plausible mechanisms are IgE-mediated (Type I) and the cell-mediated (Type V) as allergies may be exclusively IgE-mediated, partially IgE mediated or exclusively cell mediated (Sampson, 2001).

Factors that promote the developing of food allergy:

1-gut permeability

In food allergy, the alteration of the permeability of the mucosal barrier is the most proximate cause of the disease (Tatsuno, 1989).

2-IgA level in the intestine

IgA-low level or IgA–deficient individuals are predisposed for the development of food allergy (Savilahti et al., 1991; Burrows and Cooper, 1997 and Frossard et al., 2004).

3-Digestion and absorbed function of the gut

A reduction in the proteolytic activity may be contributed to the poor digestibility of soybeans proteins in calves (Nitzan et al., 1972) and leads to soybeans induced enteropathy .Gut motility and absorptive function of the gut as well as digestibility of the food may be crucial factors influencing the occurrence of food allergic reactions (Ferguson, 1996). Anti-acid medications

inhibited the digestion of dietary proteins causing fish allergy in mice (Untersmayr et al., 2003).

The allergenicity of food antigens may be determined by a combination of factors such as solubility and resistance to PH as well as proteolysis by digestive enzymes (Chapman et al., 2006). The highly digestible proteins do not exert adverse reaction when consumed (Ladics et al., 2003). The quantity of absorbed antigens together with the effect of enteric inflammation influences the outcome of antigen presentation to the underlying T-cells and directs the immune response toward allergy or tolerance (Heyman, 2001). Large dose soluble antigen almost always stimulates tolerance (Strobel and Mowat, 1998). The development of clinical food hypersensitivities may be highly dependent on the dose of dietary antigen at the time of first exposure (Lamont et al., 1989).

4-Route of administration

In repeated antigen challenge, both free drinking water and daily gavage develop IgE-dependent intestinal allergies while cell mediated immunity was more obvious in daily gavage group (Ogawa et al., 2004).

5-Host related factors

Immediate type hypersensitivity is age-dependent (Barbee et al., 1976). The IgE-antibody response is less frequent in old people (Delespesse et al.,1977) while it increases in young aged rats (Pauwels et al.,1979).Feeding of ovalbumin to adult mice can result in reduced humoral and cell-mediated immune response (Mowat and Ferguson ,1981). Calves were susceptible to soybean proteins at 2 weeks than older ages (Silva et al., 1986). Strong differences in the immune response to orally administrated antigen have been observed between animal's species. Mostly rabbit produce high level of antibodies against oral wheat gluten, in guinea pigs no serum antibodies can be detected, while rats react to an intermediate extent (Coombs and MacLanghlin, 1984).

Oral tolerance is a mechanism preventing food allergy in healthy individuals (Mowat, 1987).The induction of a systemic antibody response by

ingested antigen may be due to a breakdown of tolerance or insufficient induction of tolerance (Kamingawa et al., 1999).

The system preventing food-induced immune responses is complex:

The mucosal barrier is the primary mechanism of host defense. Secondly, the innate immune system that can neutralize the food antigens. Thirdly, the adaptive immune system that is in a state of oral tolerance. Only, if these mechanisms fail, the immune reactions against food antigens can be occurred (Seibold, 2005). Several barriers and specific mechanisms contribute to the prevention of antigens to present to the immune system. The chemical barriers including digestive enzymes, extremes gastric PH, pancreatic proteases as well as bile salts are responsible for degradation of potential immunogenic substances to low or non-antigenic particles such as amino acids is an important protective factor The physical barrier including, the intact epithelium ;established by the tight junctions between the epithelial cells at their apical poles, the intestinal mucus layer, peristalsis and the secretion of several protective substances as enzymes and defensins that are secreted from the Paneth cells (Podolsky ,1999).

The innate immune system is composed of physical and chemical barrier, blood proteins including members of the complement system and finally, phagocytes such as macrophages, neutrophils and natural killer cells.

The acquired immune system consisting of B and T lymphocytes responds to foreign antigens with the help of antigen presenting cells in association with molecules of the major histocompatibility complex. The adaptive immune response in the intestine is oriented towards tolerance. The tolerance is probably mainly due to tolerogenic dendritic cells and regulatory T cells producing anti-inflammatory cytokines such as transforming growth factor-β (TGF- β) secreted from Th3 cells and IL-10 secreted from T-regulatory 1-cells (Tr1 cells) .

Pathological features of food allergy:

The pathological features observed in food allergy were, increase of goblet cells, mucus hypersecretion, replacement of normal epithelial cells by cuboidal immature crypts cells and erosion of the villi tips (Kuitunen 1966; Barratt et al., 1978; Parish, 1983 and Zimmermann et al., 2003).

In food allergy, the lamina propria showed edema, bleeding, degeneration of blood vessels and progressive inflammatory exudates including large numbers of polymorphs, mast cells, IgE- bearing cells, CD4 and CD8 T-cells (Reid and Brunser, 1964; Eastham and Walker, 1979; Sutanto, 1982; Parish, 1983; Businco et al., 1984; Walker-Smith et al., 1984; Lin et al., 2002 and Westerholm--Ormio, 2004).

a-Eosinophils

Increased number of eosinophils was observed in all types of hypersensitivity including allergic diseases (Jorma et al., 1999).

Eosinophils were present in the gastrointestinal(GIT) mucosa in the epitjelium and in the lamina propria (Maluenda et al., 1984; Djukanovic et al., 1990; Colombel et al., 1992; Hogan et al., 2000 and Westerholm-Ormio 2004). In the jejunal mucosa, the presence of the eosinophils just beneath the surface epithelium of the flatted villi may suggest their participation in the mucosal damage in Celiac disease (Colombel et al., 1992). This change may be due to the toxic cationic proteins released from the lytic or intact eosinophils (Gleich and Adolphson, 1986; Dvorak et al., 1991 and Weller, 1991).

B-Intraepithelial lymphocytes (IELs)

Very high counts of IELs may be found in normal villi in patients with cow milk enteropathy and in celiac disease while normal count may be in a flat biopsy from celiac patients (Ferguson and Murray, 1971; Marsh, 1993; Arranz and Frguson 1993; Marsh 1995 and Marsh and Crowe, 1995). Elevation of IE γ δ^+ T cells was without mononuclear cells infiltration in the lamina propria of the duodenum and ileum with cow milk allergy (Paajanen,2005).Increased number

of IELs in the villous region of distal duodenal or jejuna biopsy forms the most sensitive histological index in early stage of gluten sensitivity (Goldstein and Underllhill,2001; Wahab,2002; Biagi et al., 2004; Jarvinen et al.,2004 and Collin et al.,2005).The number of IELs was significantly higher in untreated and treated celiac patients than in healthy control as well as in the untreated when compared with treated celiac patient (Corazza et al.,1984). Increased apoptosis is an antigen related phenomenon and not a constitutional defect. This phenomenon might be a compensatory mechanism of maintaining homeostasis and reducing the number of the IELs during repeated antigen stimulation (Augustin, 2005). An increased number of IELs expressing TIA-1, Granzyme A (cytotoxicity related proteins) are a characteristic finding in cow milk sensitive enteropathy (Hankard et al., 1997 and Augustin, 2005). Granzyme B expression by lymphocytes is increased in celiac disease (Augustin et al., 2005). Most of IELs are suppressor cytotoxic $CD8^+$cells in food sensitive enteropathy (Nagata et al., 1995).These findings confirm the importance of perturbed cell mediated immunity and lymphocytes toxicity in this condition .

c-Villi changes

Marked glandular hypertrophy and villi swelling with increase in the subvillous mucosal thickness were the moderate lesions in acute tropical sprue (England and O'Brien, 1966). Marked reduction of villi heights with thinning of the intestinal mucosa were in more sever lesions of tropical sprue and in milk enteropathy (England and O'Brien, 1966 and Hill etal., 1989).The reduction of the villi heights and the crypts elongation in cow milk enteropathy occur at the same time (Kuitunen et al., 1975 and Verkasalo et al., 1981) or the crypts elongation were owing to the decrease in the villi heights (Walker-Smith et al., 1978 and Maluenda et al., 1984).

Villous atrophy and crypts hyperplasia with net increase of mucosal volume were the characteristic features in food allergy (Fontaine and Navarro,

1975; Kuitunen et al., 1975; MacDonald and Ferguson, 1976; Walker-Smith et al., 1978; Verkasalo et al., 1981 and Wingren et al., 1986).

Villous atrophy with crypts hyperplasia and increased cell renewal rate has been associated with Celiac disease in man (Kosnai et al., 1980 and Augustin, 2005). In Celiac disease, the most sever villous changes were located in the proximal parts of the small intestine, as highly inflamed mucosa and total villous atrophy are observed in the distal duodenum and jejunum and no enteropathy is seen in the ileum (Dobbins, 1991; Oberhuber, 2000 and Meijer et al., 2003). Varying degree of villous atrophy and crypts hyperplasia with expansion of IELs population and infiltration of the lamina propria with lymphocytes, macrophages and eosinophils were recorded in cow milk enteropathy, celiac disease and cell-mediated chronic food allergies (Verkasalo et al., 1981; Walker-Smith et al., 1990; Nagata et al., 1995; Hwang and Kim, 1998 and Green and Jabri, 2003).

In cow milk protein intolerance, the villous atrophy recorded with slight increase of IELs (Stern, 1981) or with marked increase of IELs and marked increase of IgE-containing cells and slight plasma cells, eosinophils granulocytes and mononuclear cells infiltration in lamina propria (Rosekrans et al., 1980).

Flat intestinal mucosa lacking villi accompanied by intraepithelial lymphocytosis with crypts hyperplasia, numerous crypt mitosis and increased lymphocytes and plasma cells in lamina propria were the important features in gluten sensitive enteropathy (Dobbins, 1991; Antonioli, 2003 and Goldstein, 2004).

Lacking of villous atrophy and or the mononuclear cells infiltration in the lamina propria had been found in delayed type food allergy (Wakefield et al., 2000 and Veres et al., 2003).

The jejunal biopsies in tropical sprue revealed variable changes in the villi shapes as stunted, branched villi and blunted with cuboidal epithelium and

disturbed nuclei polarity. Fusion of villi along its side as well as the apex was facilitated by increased number of goblet cells resulting in broad synechia formation with firm adhesion and disappearance of columnar epithelium at the point of contact. Finally broad villous with central core contained the epithelial cells of the two original fused villi (Mehta et al., 1977).

d- Immune mechanism

The inflammatory reaction and the increase of immunoglobulin-containing cells in the lamina propria suggested that immunologic mechanisms were behind the loss of jejunal villi in intestinal soy allergy (Perkkio et al., 1981).

A higher densities of lamina propria IL-2, IL-4 and IFN-γ positive cells are detected in celiac diseased patients suggesting that inflammatory markers can be identified long before villous changes are visible (Westerholm-Ormio et al., 2002).

Villous atrophy and crypts hyperplasia were the result of mucosal T-cells activation (MacDonald and Spencer, 1988), but loss of ileal villi was recorded in T-cell deficient mice (Dohi et al., 2003).

The intestinal damage as a result of cell mediated food allergy lead to malabsorption due to decrease intestinal absorptive surface and decrease digestive enzymes levels in the intestinal cells (Savilhati, 1986; MacDonald and Spencer, 1988; Ferguson, 1992; Nagata et al., 1995 and Eigenmann, 2002).

In delayed type gastrointestinal food allergy, activation of immune cascade was much weaker and accumulation of lymphoid cells in the form of nodules with mild increase of $\gamma\ \delta^+$ T cell had been reported (Spencer et al., 1991; Kokkonen et al., 2000 and Kokkonen et al., 2001).

Increasing frequency of lymphoid follicles with germinating centers, and slight increase of intraepithelial $\gamma\ \delta^+$ T cells with mild increase of eosinophils density were observed in delayed cow milk allergy. These changes were not accompanied by either villous atrophy or the increase of mononuclear cells

infiltration in lamina propria (Kokkonen, 1999; Kokkonen et al., 2000; Kokkonen et al., 2001 and Turunen et al., 2004). The presence of germinating lymphoid follicles with elevation of the denisity intraepithelial $\gamma\ \delta^+$ T cell were the only characteristic findings in delayed cow milk allergy (Paajanen, 2005).

Animal's food allergy

In animals, food allergy may play primary role in gastrointestinal disorders especially in calves and piglets (Van-Dijk et al., 1988). Food allergy is the third most common type of allergic disease in dogs, with approximately 8% of canines of all ages and breeds and both genders being affected. The occurring allergy is non seasonal with a generalize pruritis of varying degrees of severity and distribution. In 10 to 15% of the affected dogs the dermatological signs were concurrent with gastrointestinal symptoms including vomiting, diarrhea, bloating and cramping (Helm et al., 2003). A higher incidence of mild diffuse inflammation was recorded in the duodenum and colon of the dogs suffering from dietary sensitivity (Zentek et al., 2002). In horses, food allergy is uncommon and poorly understood disease. The symptoms can be gastrointestinal, dermatological or both (Logas, 2009). Type I, type II and type III hypersensitivity reactions have been observed in the food allergic horse including pruritis, erythema, urticaria, alopecia, vasculitic lesions and popular eruption.

Soyabean food allergy in calves

Poor utilization of soybean protein by calves was attributed to a gastrointestinal allergy (Smith and Sissons, 1975; Sissons and Smith, 1976; Kilshaw and Sissons, 1979 and Pedersen and Sissons, 1984). These digestive disturbances may be due to insufficient secretion of IgA and IgM to prevent the absorption of intact or partially digested soybean proteins (Barratt and Porter 1979). This in turn leads to the formation of complexes between soybean antigens and systemic IgG antibody with activation of complement system, increased vascular permeability and tissue damage (Sissons, 1982).

In calf intestinal villous atrophy with crypts elongation and hyperplasia were observed after intake of soyabean meal (SBM) containing feed. These changes were accompanied by increased gut permeability to macromolecules, intestinal mucosal inflammation and high levels of circulating IgG antibodies

(Barratt et al., 1978; Kilshaw and Slade, 1982; Pedersen and Sisson, 1984 and Silva et al., 1986). Blunting and shortening of villi of calves' small intestine were recorded after 4 weeks of soy feeding (Seegraber and Morrill, 1986). Villous atrophy and increased densities of T and B lymphocytes in the intestinal mucosa of calves can be observed after intake of heated soybean flour (Lalles et al., 1996). Feeding milk replacers containing antigenic or hypo-antigenic soya protein to calves reversibly depressed villus height and the specific activity of a number of brush border enzymes of the proximal jejunum (Montagne et al., 1999).

Peanut food allergy in piglets

In peanut-sensitized piglets, the small intestine showed marked edema, mucus secretion, epithelial denudation and vascular congestion with hemorrhage and minor increases in IL-4 in small intestine cytokine analysis, (Helm et al., 2002 and Helm et al., 2003).

Egg allergy in rat and mice

The major shock organ responding to anaphylaxis in rat was the small intestine (Sanyal and West, 1958), and the lesions associated with intestinal anaphylaxis included hyperemia, secretion of mucus and epithelial shedding (Miller et al., 1983 and King and Miller, 1984). It has been found that the infusion of antigen into the duodenum of orally immunized rats lead to the release of mucous from goblet cells and enhanced vascular and mucosal permeability (Lake et al., 1979 and Lake et al., 1980). Goblet cell mucus release was dependent on the dose of antigen infused (Lake et al., 1980). This response was antigen specific to limit the access of antigen absorption by intestinal epithelial cells. Therefore the mucus can exert its inhibitory effect on intestinal anaphylaxis (Lake et al., 1980).

Egg albumin challenge of sensitized rats resulted in decreased total villus-crypt length and villi heights in the jejunum of anaphylactic animals (D'Inca et al., 1990 and Crowe et al., 1993). Significant reduction in villi heights

and increase the crypts depths with increased the number of lymphocytes in the rat intestinal mucosa were recorded in daily gavage **OVA**-sensitive rats and these alterations were mediated by cell mediated immunity (Ogawa et al., 2002 and Ogawa et al., 2004). Separation of intact epithelium from the villous tip or from the sides of villous (blebbing) or where villous edema with focal degeneration and necrosis of the crypt epithelium in the rat jejunum were observed during anaphylaxis (Scudamore et al., 1995). Although the brown Norway rat is a high immunoglobulin responder strain with a genetic predisposition to over produce IgE response to antigens, the hyper-IgE stimulation can disturb the mucosal immune mechanisms to result in a cell mediated reaction against oral antigen exposure (Ogawa et al., 2004).

In mouse model of food-sensitive enteropathy, the proliferative response of **IELs** and lamina propria lymphocytes to **OVA** with villous atrophy and crypt hyperplasia increased in a dose dependent manner after the antigen challenge in the OVA sensitive mouse model (Ohtsuka et al., 1996). In oral ovalbumin-challenged mice, the duodenum, jejunum and ileum revealed vascular congestion, edema and prominent eosinophils infiltrate observed interspersed throughout the lamina propria and the villi cores of small intestine (Hogan et al., 2000). OVA/alum sensitized mice show extensive mucosal mast cell hyperplasia and degranulation after repeated doses of intragastric OVA, while connective tissue mast cells were less significantly affected (Brandt et al., 2003). Mast cells were significantly increased and observed in perivascular region underneath muscularis mucosa with villous edema in the duodenum of OVA induced food allergy in mice (Fujitani et al., 2007). Adminestiration of OVA caused significant increase of mast cells and eosinophils in the small intestine of mice (Yeun et al., 2008). Eosinophilic venulitis without mast cells was induced by OVA in the small intestine of mice (Bui et al., 2011).

In murine model of food antigen induced Th-2 dependent enteropathy, the jejunal tissue showed crypts elongation, partial villous atrophy, thickened muscular layer, goblet cell hyperplasia and increased number of paneth cells as

well as villous blunting without significant inflammatory infiltration which indicated moderate degree of inflammation under mucosal repair (Nakaiima-Adachi et al., 2006 and Pali-Scholl et al., 2008).

In murine model of rice allergy villi edema, lymphocytes infiltration and goblet cells hyperplasia were observed in the jejunum (Chen et al., 2011).

Treatment of food allergy

(I) Oral desensitization protocol:

This procedure relies mostly on, a daily ingestion of a certain amount of food able to keep a partial tolerance against larger quantities (Patriaca et al., 1998). It was found that the use of standardized hazelnut extract can establish good tolerance to hazelnut food allergy (Enrique et al., 2005).

(II) Diet elimination protocol:

Eliminating the offending allergic foods may be the only treatment of food allergies, if the individual is allergic to only one or two types of food (Pastorellow et al., 1989 and Logas, 2009).

(III) Medications and supplements:

1-**Anti-IgE antibodies:**

Non anaphylactic **anti-IgE antibodies** can remove IgE - antibodies from the fraction cristalizable (Fc) epsilon R1 on mast cells and basophils. Therefore, inhibit IgE-mediated local or systemic anaphylactic reactions (Sampson, 2001 and Leung et al., 2003).

(2) Anti-IL-5 antibodies:

In mouse model of food allergy, intraperitoneal administration of anti-mouse IL-5 antibody (a-m IL-5 mAb) 30 min before the oral challenge significantly inhibited the eosinophil cells infiltration into gut (Bae et al., 1999).

(3)Anti-TNF-α antibody:

Inhibition of TNF-α by anti-TNF-α antibody **(Infliximab)** resulted in neutralization of TNF-α dependent inflammatory response (Geboes et al., 2003).

(4) Cytokines:

Oral administration of **IL-12** could suppress the anaphylactic reactions in murine model of peanut hypersensitivity by promoting TH-1 type response (Lee

et al., 2001). **IL-10** had anti-inflammatory effects through inhibition of histamine, TNF-α And IL-8 released from mast cells (Royer et al., 2001).

(5) Immunomodulatory agents:

Frossard et al., (2001) had used high-molecular weight polysaccharide λ-carrageen for prevention or treatment of food allergy.

(6) Bacterial agents:

The use of **Lactobacillus GG** in an extensive formula can improve the clinical score for atopic dermatitis during the month study period (Majamaa and Isolauri, 1997). Administration of probiotic to children with allergy has an effect on both prevention and treatment of food allergy (Erkkia et al., 2008) by activating the innate immunity and production of IL10. Probiotics could prevent the occurrence of ovalbumin allergy in mice and rats by modulating Th1/Th2 cytokine balance (Yeun et al., 2008 and Wen-jing et al., 2010).

(7) Enzyme-Modified cheese (EMC)

EMC could prevent ovalbumin allergy in rats by enforcing the intestinal barrier and inhibiting allergen permeation (Isobe et al., 2008).

(8) Flavonoid quercetin

Flavonoid quercetin could suppress peanut allergy in rats (Shishehbor et al., 2010).

(9) Fructooligosaccharides (FOS)

FOS tended to prevent ovalbumin allergy in mice by reducing the mast cells number and villous edema (Fujitani et al., 2007).

(10) Vaccination:

Effective treatment of allergic diseases was obtained by induction of protective humoral anti-IgE response through vaccination with **native IgE fragments** (Kricek et al., 2001).

(11) Complementary medicine:

Chinese herbal tee formula **(FAHF-1)** was able to reduce peanut specific-IgE levels, mast cell degranulation and histamine release as well as diminish peanut antigen induced TH-2 cytokines production with subsequent blocking of peanut- induced anaphylaxis in mice (Li et al., 2001).

(12) Adhesion molecule antagonists:

Monoclonal antibodies against **α 4 B7- integrin** treated the experimental colitis in animal by reduction of inflammatory infiltrate (Hesterberg et al., 1996). In a recent study**, anti-α 4 integrin** antagonist had beneficial effects in patient with active Cohn's diseases (Ghosh et al., 2003).

(13) Chemokine receptor antagonists:

A monoclonal antibody against chemokine receptors (CCR_3) for eotaxin was able to block eosinophils migration (Heath et al., 1997).

(14) Histaglobin:

The anti-allergic drug **histaglobin i**nhibited the OVA-induced allergic responses in mouse through down regulation of the release of IL-1 beta, TNF-α, IL-6 and IL-10 (Ayoub et al., 2001).

(15) Mast cell stabilizer

A- Disodium cromoglycate:

Beneficial effects of **cromoglycate** have been described for treatment of gastrointestinal food allergy (Lessof, 1983 and Stefanini et al., 1986). **Cromoglycate** can prevent the release of mediators from connective tissue mast cells in many but not all species (Kallos and Kallos, 1982) but did not inhibit antigen-induced histamine secretion by mucosal mast cells (Pearce et al., 1982). Disodium cromoglycate could reduce eosinophil exudation in active ulcerative colitis through inhibition of chemotactic factors released from mast cells (Rampton et al., 1982).

B-Doxantrazole

Doxantrazole can stabilize both mucosal and connective tissue-type rat mast cells (Pearce et al., 1982).

(16) Histamine (H) receptors antagonists:

(A) H-2 receptor antagonists (Famotidine):

Large oral dose of 100 mg/ kg **famotidine** was able to inhibit immediate hypersensitivity and chronic inflammation in mice and rat (Kaneta et al., 1993).

B) H-1 receptor antagonists:

In human challenge models, **terfemadine, azatadine and Ioratadine** were capable of reducing IgE- mediated histamine release (Jiang et al., 2000)

Mizolastine inhibited anaphylactic release of histamine from rodent mast cells, LTC_4 and LTB_4 release from mouse bone marrow - derived mast cells, LTC_4 release from rat intestinal mast cells and 5- lipoxygenase activity of polymorphnuclear neutrophils of guinea pig intestines (Baroody and Naclerio, 2000).

(17) Anti-serotonin drugs (5-hydroxy tryptamine [5-HT] antagonists):

Pretreatment with **ketanserin** 200 µg/ kg (5-HT2 antagonist) or **grainsetron** 300µg/ kg (5-HT3 antagonist) subcutaneously, partially inhibited intestinal water and electrolyte movement during gut anaphylaxis (Mourad et al., 1995).

Administration of 30 µg / kg of **alosetron** (5-HT3 receptor antagonist) markedly attenuated the response to luminal antigen during intestinal anaphylaxis in rats (Jiang et al., 2000).

In experimental model of oral - allergen - induced diarrhea in mice , the intravenous injection of 60 µg **ketanserin** and 0.25 mg **azasetron** (5-HT3 receptor antagonist) in combination with 66 µg of **CV6209** (**PAF receptor antagonist**) significantly suppressed allergic diarrhea (Brandt et al., 2003).

(18) Beta2-adrenergic receptor agonists (Salbutamol):

Beta2-adrenergic receptor agonists, have anti-inflammatory activity in treatment of allergic diseases by inhibiting release of histamine, prostaglandin D2 as well as TNF-α from mast cells (Bissonnette and Befus, 1997).

(19) Sulfapyridine:

Administration of 1 and 10 µg/ kg of **sulfapyridine** could inhibit mast cell-mediated allergic reactions in vivo and in vitro (Kim et al., 2000).

(20) Caffeine:

Caffeine could inhibit anaphylactic shock via inhibition of mast cell degranulation (Shin et al., 2000).

(21) Vitamins:

(A) Vitamin C (or ascorbic acid):

Oral administration of **ascorbic acid** 1 gm daily for 3 days could result in a reduction of blood histamine level (Clemetson, 1980). **Vitamin C** was able to control allergy by stimulating the glucocorticoid mechanism of the patient (Kodama et al., 1994).

(B) Vitamin E (alpha-tocopherol):

Alpha-tocopherol was capable to alleviate the increase in IgE-production by unsaturated fatty acids (Yamada et al., 1996 and Hung et al., 1997).

(22) Corticosteroids:

Steroids suppress the intestinal permeability by decreasing the permeability in the capillary beds (Benditt et al., 1950). **Steroids** are immunosuppressant and have inhibitory action on fibroblasts (Grieco and Ushman, 1970).

Corticosteroids are generally effective in treating non IgE-mediated gastrointestinal disorders including dietary-induced enteropathy, but the side effect of its protracted use are unacceptable (Sampson, 2003).

Corticosteroids are potent widely used anti-inflammatory and anti-allergic drugs in man and domestic animals (King et al., 1985 and Kamingawa and Nanno, 2004).These drugs have ability to potentiate the effects of endogenous adrenaline with subsequent increasing the tone of the microvasculature and decreasing its permeability as well as cause bronchodilatation (Geddes and Lefcoe, 1973 and Geddes et al., 1974). These effects are due to the inhibition of prostaglandins production (Brink et al., 1977) and preventing of the generation and release of inflammatory mediators (Fahey et al., 1981 and Heinman and Crews, 1984). **Corticosteroids** can abrogate the systemic anaphylaxis in rats through its inhibitory action on mast cells degranulation (King et al., 1985). **Corticosteroids** act to impair the mitochondrial function (Grosman and Jensen, 1984).

Glucocorticoids perform their anti-inflammatory action by stabilizing cellular and lysosomal membranes (Weisman and Thomas, 1964). Thus they prevent the release of chemical mediators of inflammation and lysosomal proteolytic enzymes. The anti- inflammatory effects of glucocorticoids could be attributed to the synthesis of a family of proteins referred to as lipocortins that could inhibit the phospholipase A2 catalyzing the release of arachidonic acid from membrane phospholipids (Blackwell et al., 1980).

All glucocorticoids suppress all aspects of inflammation including early responses (vasodilatation, edema, and leucocytes migration), later events (collagen deposition, fibroblast and capillary proliferation) and finally scar formation irrespective of the cause; physical chemical or immunological trauma; (Eyre, 1980).

Glucocorticoids affect cell mediated immunity by inhibiting the proliferation of lymphoid tissue, reducing the chemo-attraction of lymphocytes,

modulating lymphotoxin production and preventing accumulation of macrophages (Eyre, 1980). **Glucocorticoids** can acceletate apoptosis of lymphocytes in lymphoid tissue including peyer's patches (Ruiz-Santana et al., 2001; Goya et al., 2003; Pearse, 2006 and Totini et al., 2006) and suppressing the proliferative capacity of lymphocytes in lymphoid follicles (Norrman et al., 2003 and Menge and Dean-Nystrom,2008).

Glucocorticoids effectively suppressed the late allergic responses $CD4^+$ T cells and eosinophils infiltration (Durham and Kay, 1985). In human it was found that glucocorticoids induce an immediate blood eosinopaenia, this action may be due to inhibition of tissue and circulating eosinophil responses to granulocyte-macrophage colony stimulating factor **(**GM-CSF) (Lamas et al., 1991) or mediated by sequestration of leucocytes to lymphoid organs and inhibition of the release of cells from bone marrow (Schleimer and Bochner, 1994). In contrast, **glucocorticoids** were found to enhance bone eosinopoiesis through glucocorticoids receptors, in normal and allergic murine model (Maria et al., 2000).

Glucocorticoids suppressed autocrine survival of mast cells by inhibition of IL-4 and expression of intercellular adhesion molecule-1; ICAM-1; (Yoshinkawa et al., 1999) and inhibited mast cell degranulation (Krishnaswamy et al., 2001).

Dexamethasone is routinely used to modulate cells migration into sites of inflammation and this action is accomplished in part by a potent effect on the synthesis of pro-inflammatory cytokines and chemokines (Schleimer, 1990) and reducing the degree of leucocytes responsiveness (Mancuso et al., 1995).

Single intra-peritoneal injection of 1mg **dexamethasone** resulted in macrophage engulfment and destruction of rat mucosal mast cells without granular mediator release and local inflammatory effects in jejunal mucosa (Soda et al., 1993).

Dexamethasone inhibited eosinophils accumulation in mice (Das et al., 1997).This effect may be due to induction of apoptosis (Kawabori, et al., 1991) or inhibition of eosinophil production in rat bone marrow (Pasquale et al., 1999).

Dexamethasone reduced endogenous transforming factor-B1 synthesis (TGF-B1), which involving in the homing mechanism of cells to endothelial venules; markedly alter enterocytic antigen presentation and reducing the aberrant state of activation of mucosal immune cells (Ruemmele et al., 1999).

Dexamethasone inhibited the synthesis of IL-9 which involving mast cells proliferation, eosinophils function, IgE production and in stimulation of mucus production (Holz et al., 2005).

Dexamethasone induced apoptosis of IELs (Brunner et al., 2001 and Norrman et al., 2003) ,depressed CD8+ T cells function (Lo et al., 2005) and reduced number of $\gamma\ \delta^{+}$ T cells (Menge and Dean-Nystrom,2008).

Dexamethasone induced lymphocytes apoptosis and thymus atrophy through inhibition of antioxidant enzymes activity and increasing reactive oxygen species (ROS) and (Orzechowski and Ostasewski, 2002 and Kis, 2010).

Dexamethasone could repair the intestinal mucosal lesion through stimulation of enterocytes proliferation and migration (Nobili et al., 1997) .Thus it was capable to increase the villi heights and crypts depths (Iordache et al., 2005). Vise versa **dexamethasone** can inhibit small intestinal groth via both increasing protein degradation and decreasing protein synthesis (Burrin et al., 1999).

(23) Omega- 3 fatty acids (fish oil supplement):

Food-derived materials could prevent allergy by counteracting at least one step in the cascade of allergic reactions, as they contain substance able to prevent an allergic reaction (Nagafuchi al., 2000; Nagura et al., 2002; and Takano et al., 2004).

The unsaturated fatty acids consist of monounsaturates (MUFA) and polyunsaturates **(PUFA)**. PUFA are further divided into two classes **omega-3** and **omega-6** polyunsaturated fatty acids. These fatty acids are essential because mammals can not synthesize them de novo and must obtain them in their diets. **Omega-6** fatty acids are represented by linoleic acid while **omega-3** fatty acids are represented by alpha-linolenic acid. Linoleic acid **(omega-6)** is plentiful in nature and is found in the seeds of most plants except coconut, coca and palm. Marine algae carryout chain elongation and desaturation of Alpha linolenic (**omega-3)** acid to yield eicosapentaenoic acid **(EPA)** and docosa-hexaenoic acid **(DHA).** These long chain omega-3 polyunsaturated fatty acids transfer through food chain to fish and they are found in abundance in some marine fish oil (Teitelbaum and Walker, 2001). Linoleic and Linolenic acids as well as their long derivatives are important components of animal and plant cell membranes. However, cell membranes require them to maintain their structure, fluidity and function. In mammals and birds the **omega-3** fatty acids are distributed selectively among lipid classes. Linolenic acid is found in triglycerides, cholesterol esters and in very amounts in phospholipids. **EPA** is found in cholesterol esters, triglycerides and phospholipids. **DHA** is found mostly in phospholipids and is one of the most abundant components of the brain's structural lipids (Teitelbaum and Walker, 2001). Animal's cell can convert dietary **omega-3** into eicosapentaenoic acid **(EPA).** The conversion of EPA into docosa hexaenoic acid **(DHA)** involves 4 steps (Voss et al., 1991). The linoleic acid is converted into arachidonic acid (AA) via gamma-linoleic acid and dihomo-gamma-linoleic acid.

The eicosanoids (prostaglandins**,** thromboxanes, and leukotrienes) derived from **EPA** tend to be weaker in terms of their pro-inflammatory actions. For example, $\mathbf{LTB_5}$ is less potent as a chemotactic factor for neutrophils than $\mathbf{LTB_4}$; arachidonic acid (AA)-derived eicosanoids; (Goldman, et al., 1983 and Charleson, et al., 1986). The individual consuming an **EPA-enriched diet** will

produce **LTB_5** at the expense of **LTB_4** and therefore dampened inflammatory reaction to a stimulus (Wallace, 1990).

The immune-modulator and anti-inflammatory effects of PUFAs on specific components of the immune system.

Dewille, et al., (1979) stated that the **essential fatty acids** play a crucial role in maintaining the functional integrity of humoral immunity.

The therapeutic effects of **fish oil** supplement are chiefly attributed to anti-inflammatory properties through reduction of the release of IL-1, IL-2, IL-6, IL-4 and TNF-α (Meydani et al., 1991 and Fernandes et al., 1994). Feeding **fish oil** could diminish the antigen presenting cell activity of dendritic cells migrating from the gut (Sanderson et al., 1997). Rat fed on diet with high **fish oil** content (20 % by weight) for 10 week showed suppression in lymphocytes activation (Yaquoob et al., 1994). Daily administration of **fish oil** by gavage (0.4 % of body weight) in rat could affect on the metabolism of lymphoid organs and possibly immune function (Miyasaka et al., 1996).

In inflammatory bowel disease, **olive oil** exerts some important beneficial effects such as a free radical scavenging (Budiarso, 1990) and inhibition of eicosanoids formation (Petroni et al., 1995).

Omega-3 fatty acids can act as anti-inflammatory agents and use in the treatment for various chronic inflammatory conditions including inflammatory bowel disease. This effect may be mediated by a lower production of the most powerful arachidonic acid metabolite;leukotriene B1, thromboxane A2 and leukotriene-B4 (Lee et al., 1985; Rampton and Collins, 1993 and Seibold, 2005) which is elevated in the inflamed intestinal mucosa (Sharon and Stenson,1984), while promoting the formation of less inflammatory 3-series prostaglandins and thromboxanes (Belluzzi et al., 1996). In cell culture and animal studies, the **omega-3** fatty acids have potent immunomodulatory effects through modulation of eicosanoid synthesis and through an inhibitory effect on the pro-inflammatory

cytokine IL-1 (James et al., 2000; Jones and Papamand-Jaris, 2001 and Simopoulos, 2002).

Omega-3 fatty acids act as free radicals scavengers (Fisher et al., 1986). **Omega-3** rich diets were frequently associated with diminish hypersensitivity reactions via lowering histamine production or release (Ishihara et al., 1998).

Cell mediated immune responses are initiated when mononuclear phagocytes process and express antigens on their surface membranes for recognition by appropriate T cells (Teitelbaum and Walker, 2001). IFN-gamma typically up-regulates the expression of MHC II. However when IFN-gamma activated monocytes were incubated with **fish oil** the expression of MHCII was inhibited (Hughes and Pinder, 1997).T-cell proliferative response to antigen is proportional to the number of MHC II on the surface of the antigen presenting cells (Matis et al., 1983). Supplementation of human diet with **omega-3** rich fish oil for 3 week resulted in a decreased level of MHCII expression on the surface of peripheral blood monocytes (Hughes et al., 1996).

Omega-3 PUFA regulates or modulates the immune response by specifically impairing T cell responses (Erickson et al., 1980; Chandra, 1980 and Beisel et al., 1981). **EPA and DHA** inhibit the proliferation of lymphocytes isolated from rodent lymph nodes, spleen and thymus as well as human peripheral blood (Jeffery et al., 1996; Jeffery et al.,1997 a&b). This effect on lymphocyte proliferation may be modulated via DHA's effect on surface markers involved in T cell proliferation (Sasaki et al., 1999). Furthermore, **EPA and DHA** can suppress the production of IL-2; which is necessary for the lymphocytes proliferation and regulation of function of cytotoxic lymphocytes, natural killer, B cells and macrophages; (Calder et al., 1992; Das, 1994 and Devi and Das, 1994). **Unsaturated fatty acids** at higher concentrations have a suppressive effect on cell-mediated immunity via eicosanoid release, receptor affinity changes or interactions with intracellular signal transduction (Miura et al., 1998).

Omega- 3 fatty acids suppress excessive activation of T cells (Fujikawa et al., 1992 and Hughes and Pinder, 2000).

Omega-3 fatty acids- rich diets were associated with a lower percentage of activated T and B- cells (Robinson and Field, 1998).

Dietary **omega-3** able to attenuate T cell-mediated inflammation. The suppressive effects may result from either reducing lymphocytes proliferation or enhanced apoptosis of activated T cells or both (Switzer et al., 2004).

In mice model of OVA-induced food sensitive enteropathy, **omega-3 fatty acid-enriched diet** was efficient in attenuating intestinal mucosal damage (Yamashiro et al., 1994). **Fish oil** supplementation (Primarily **Omega-3** fatty acid) reduced intestinal necrosis while decreasing intestinal platelets activating factor (PAF) and leukotriene concentrations (Akisu et al., 1998). **Omega-3** produced increase of blood flow of the terminal ileum and its gut associated lymphoid tissue of rats (Matheson et al., 2002).

Polyunsaturated fatty acids (PUFA) supplementation reduced the incidence of intestinal necrosis (Caplan et al., 2001) through its ability to modulate the production or the effect of cytokine mediators (Blok et al., 1996).

Effect of PUFA in intestinal structure and function:

Fish oil may induce enterocyte hyperplasia, thereby increasing the mucosal surface area with a corresponding increase in intestinal absorption of nutrients and improvement of nutrition (Vanderhoof et al., 1994 and Belluzzi et al., 1996).

Microvillar membranes of intestinal epithelial cells are associated with a layer of carbohydrate-rich material. The biosynthesis of this glycol-protein is highly sensitive to nutritional and developmental variations (Biol, 1992). The intestinal glycosyl transferase activities are involved in cell differentiation and postnatal maturation of small intestine. **Deficiency of PUFA** decrease the intestinal glycosylation of brush border and goblet cell mucus (Alessandri et al., 1995), and the animal supplemented with **omega -3** had increased in intestinal

glycosylation of intestine and goblet cells with subsequent it can play a role in intestinal cell differentiation.

Tight junctions are the apical most structures in epithelial and endothelial cells and play a key role in the control of permeability. The treatment of endothelial cells with **gamma-linolenic** acid increased the trans-endothelial cell resistance and reduced the peri-cellular permeability to large molecules (Jaing et al., 1998). In addition occluden; a transmembrane protein integral in the formation of tight junctions, was found up-regulated by **EPA** (Jaing et al., 1998). These findings suggest a role of **omega-3** fatty acids in treatment of inflamed mucosa.

In experimental rat model, **fish oil supplement** posses both anti-secretory and anti-ulcerogenic effects (Al-Harbi, et al., 1995) and was able to prevent peptic ulcer (Manjori and Das, 2000).

Omega–3 could increase villi heights and crypts depths via increasing cell proliferation, inhibiting enterocytes apoptosis and decreasing intestinal mucosal injury (Rosa et al., 2010; Sukhotnik et al., 2010 and Sukhotnik et al., 2011).

The polyunsaturated fatty acids mechanisms in immunomodulation:

1- Modulation of eicosanoid synthesis.

Omega-3 PUFA replacement of arachidonic acid (AA) in the phospholipids layer modulates the immune cell function by eicosanoid mediated effects.

When human ingested fish or fish oil, **the omga-3** fatty **acids EPA and DHA** compete with arachadonic acid for prostaglandin and leukotriene synthesis at the cyclooxygenase and lipoxygenase level (Lands, 1992) and partially replace the AA in cell membranes including the membranes of platelets, erythrocytes, neutrophils, monocytes and hepatocytes so that as a result, ingestion of **EPA** and **DHA** leads to decrease prostaglandin E2 production (Teitelbaum and Walker, 2001). Increased membrane **EPA and DHA** with a corresponding decrease AA leads to decrease in thromboxane A2 (a potent

platelets aggregator and vasoconstrictor) and decrease in leukotriene B4 formation (an inducer of inflammation and a powerful inducer of leukocyte chemotaxis and adherence). Furthermore increase in thromboxane A3 (a weak platelet aggregator and a weak vasoconstrictor) and increase in prostacyclin (PG13; an active vasodilator and inhibitor of platelet aggregation). Finally there is increase in leukotriene B5 (a weak inducer of inflammation and a weak chemotactic agent (Weber et al., 1986 and Lewis et al., 1986).

2- Alteration of membrane fluidity.

Fatty acids also have important roles in membrane structure and can thus affect membrane protein function. Both membrane bound proteins and receptors are sensitive to their fatty acid environment. The changes in membrane fluidity may be dependent on the effects of fatty acids on the conformation of the protein complex (Stubbs and Smith, 1984; Brunner, 1984 and Murphy, 1990).

3- Signal transduction.

PUFA may have further immune-modulatory effects via an effect on signal transduction. As there is evidence that these fatty acids able to alter the intracellular free calcium concentration often a key component in the intracellular signaling pathway via its direct effects on the receptor operated calcium channels (Chow et al., 1990).

4-Effects on intra luminal bacteria.

EPA significantly inhibited the growth of colonic bacteria by disruption of the outer membrane (Thompson and Spiller, 1995) and through these changes **fish oil** may have secondary effects on intestinal inflammation.

5-Changes in gene expression.

Fatty acids affect the expression of genes involved in hepatic fatty acid and lipoprotein metabolism. The effect may be mediated by their interaction with other mediators such as eicosanoids which in turn alter gene expression

(Teitelbaum and Walker, 2001). Rosa et al., (1996) suggest that **PUFAs** alter gene products responsible for carbohydrate and protein metabolism as a means of immune modulation. It had been found that; **omega-3** can decrease the lymphocyte proliferation through its effects on glucose and glutamine utilization; which are essential for lymphocytes proliferative capacity; (Teitelbaum and Walker, 2001).

Dietary **omega-3** able to attenuate T-cell-mediated inflammation and promote activation-induced cell death (AICD) in CD4T-cells induced (Switzer et al., 2004).

The goal of the study is to evaluate the effects of **dexamethasone and omega-3** treatments in experimentally induced **ovalbumin allergic enteritis** in the three intestinal segments of the small intestine of rats. By using the morphological indices of the intestinal inflammation as alteration, exudation and proliferation and the measurement of villi heights and crypts depths and intraepithelial lymphocytes (IELs) count.

MATERIALS AND METHODS

I-Materials

(1) Animals

4 weeks young albino rats of both sexes were used and obtained from Assiut University Animal House, Faculty of Medicine, Egypt. The rats were housed in an animal room maintained at 23 ± 3 °C and a relative humidity of 30- 70 % during the experiment. The animals were housed in stainless- steel wire cages in groups of 5 and had free access to food and tap water. The rats were raised on a commercially available rodent diet that was hen egg white protein free and divided randomly into 4 groups.

(2) Ingredients

The antigen source was **albumin egg powder** (El -Nasr pharmaceutical chemicals,Egypt, purity: 79- 81 %).

Dexamethasone was manufactured by The Egyptian co. for chemicals & pharmaceuticals ADWIA 10th of Ramadan City, Egypt.

Code liver oil was manufactured by Unipharma for Novotec Pharma, Egypt.

II –Methods

1-Experimental design

(A)- Local anaphylaxis protocol

All rats except the control group were exposed to chicken egg albumin by daily gavage dosing, using 18-gauge stainless steel animal feeding needle with standard dose 1 mg protein/ ml tap water, 1 ml/ animal for 44 days without the use of an adjuvant.

(1) The first group (n= 10)

This control group was consisted of un-manipulated rats.

(2) The second group (n= 40)

These animals received only chicken egg albumin by daily gavage dosing for 44 days without the use of an adjuvant.

(3) The third group (n= 40)

These animals received chicken egg albumin by daily gavage dosing for 44 days without the use of an adjuvant and treated with single intra-peritoneal injection of 1 mg of dexamethasone per week.

(4) The fourth group (n= 40)

These animals received chicken egg albumin by daily gavage dosing for 44 days without the use of an adjuvant and treated with daily gavage dosing with 0.1 ml of code liver oil (that provide 6.8 mg eicosapentaenoic acid **(EPA)** and 4.9 mg docosahexaenoic acid **(DHA).**

(B) -Systemic anaphylaxis protocol

Four groups of animals were used as followed:

(1) The first group (n= 10)

This control group was consisted of un-manipulated rats.

(2) The second group (n= 40)

These animals received the sensitization dose which was consisted of intra-peritoneal injection of 10 µg of chicken egg albumin protein and 10 mg of aluminum hydroxide [Al (OH) 3] as adjuvant in 0.9 % saline. **After 15 day sensitization**, the rats were exposed to 1 mg chicken egg albumin protein / ml tap water, 1 ml per animal by daily gavage dosing for 44 days.

(3) The third group (n= 40)

These animals received sensitization and challenge dose of chicken egg albumin and were further treated with single dose of intra-peritoneal injection of 1 mg dexamethasone per week for 44 days.

(4) The fourth group (n= 40)

These animals received sensitization and challenge dose of chicken egg albumin and were treated with daily gavage dosing with 0.1 ml of code liver oil (that provide 6.8mg eicosapentaenoic acid **(EPA)** and 4.9mg docosa-hexaenoic acid **(DHA).**

2-Histopathological examination

Tissue samples were taken from the three small intestinal segments, duodenum, jejunum and ileum and fixed in 10% neutral buffered formalin. The tissues were dehydrated in ascending grades of ethyl alcohol, cleared in methyl benzoate and embedded in paraffin wax. Sections of 5 microns thick were prepared by using rotatory microtome and stained with H&E (Bancroft et al., 1996) for morphometric analysis, intraepithelial lymphocytes counting and pathological examination.

Morphometric analysis

The villi heights and crypts depths were measured in the three small intestinal segments, duodenum, jejunum and ileum. The morphometrical analysis was applied on H&E sections by using Image analysis system (Leica Q500MC). 10 villi heights and 10 crypts depths were randomly measured per section at 4 X magnification. The measurements were performed in 3 sections per animal and the results were expressed as the mean value of villi heights and crypts depths of the 3 animals per each slaughtered group.

The intraepithelial lymphocytes (IELs) counts

The IELs were counted manually within the epithelium covering the villi and crypts at 40 X magnification in the three small intestinal segments, duodenum, jejunum and ileum. The counting was in 10 villi and 10 crypts per section. The counting was performed in 3 sections per animal and the results were expressed as the mean value of the 10 villi and crypts IELs counts of the 3 animals per each slaughtered group.

Morphopathological examination

The histopathological examination was performed in the three small intestinal segments, duodenum, jejunum and ileum in H&E sections to detect any pathological alterations in the villi and crypts lining epithelium, blood vessels and lacteals in the villi core, lamina propria submucosa and serosa. As well as the inflammatory cells infiltrating mucosa and submucosa and the presence of reactive or resting follicles. In addition any abnormalities appeared in muscular and serosal layers.

3-Statistical analysis

The statistical analysis was performed by using Students t-test using GraphPad Prism version 5.01 Program by Graph Pad software Inc. To determine the significance differences between animal groups in term of IELs count, length of villi heights and crypts depths. The results were considered significant if probability (P value) < **0.05**.

RESULTS

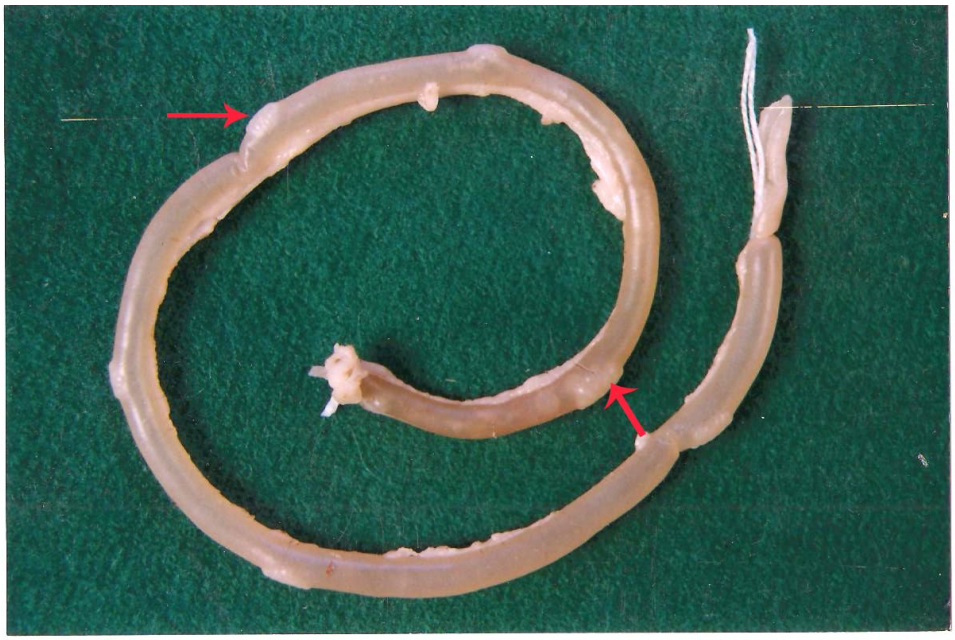
Oral dosing of egg albumin as allergen initiated enteritis in the three segments of the small intestine: duodenum, jejunum and ileum. The inflammation was classified according to duration of the experiment and pathomorphological criteria into acute from the beginning until the seventh day, subacute from the seventh day until the fifteenth day and chronic from the sixteenth day until the day 44 i.e. the end of the experiment.

I-Gross picture

The macroscopical picture of the duodenum, jejunum and ileum revealed sever hyperemia**; picture (1)** with multiple enlarged lymphoid follicles extended allover the three segments**; picture (1&2)** in both local and systemic food allergy. In local food allergy these changes started to appear after 20 days. In systemic food allergy it was from the 7^{th} day.

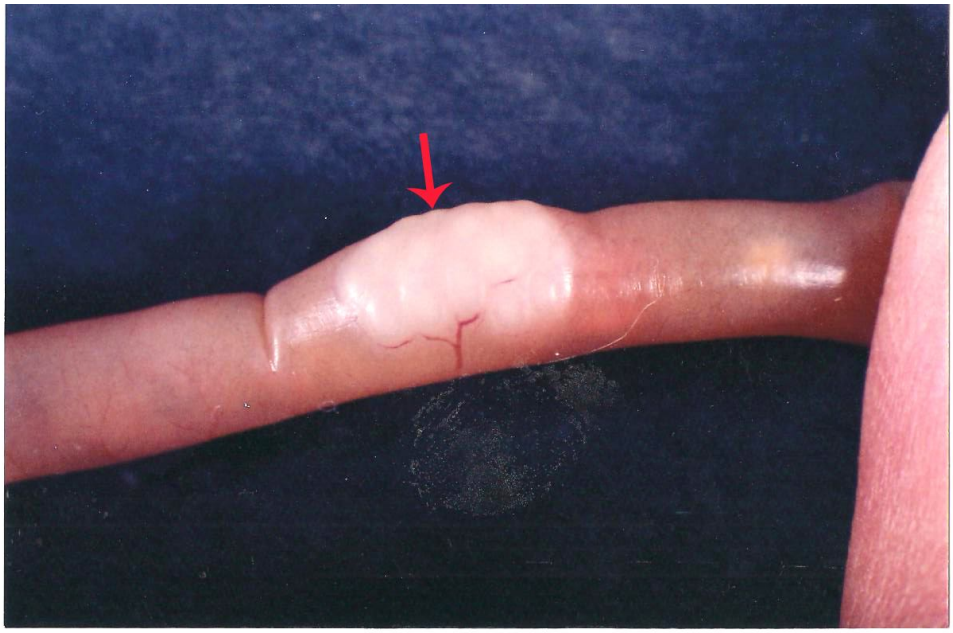
Picture (1): Local allergic duodenitis.

Sever hyperemia in the serosal blood vessels.



Picture (2): Local allergic jejunitis.

Multiple enlarged lymphoid follicles (➜).



Picture (3): Local allergic jejunitis.

Multiple enlarged lymphoid follicles(➜).

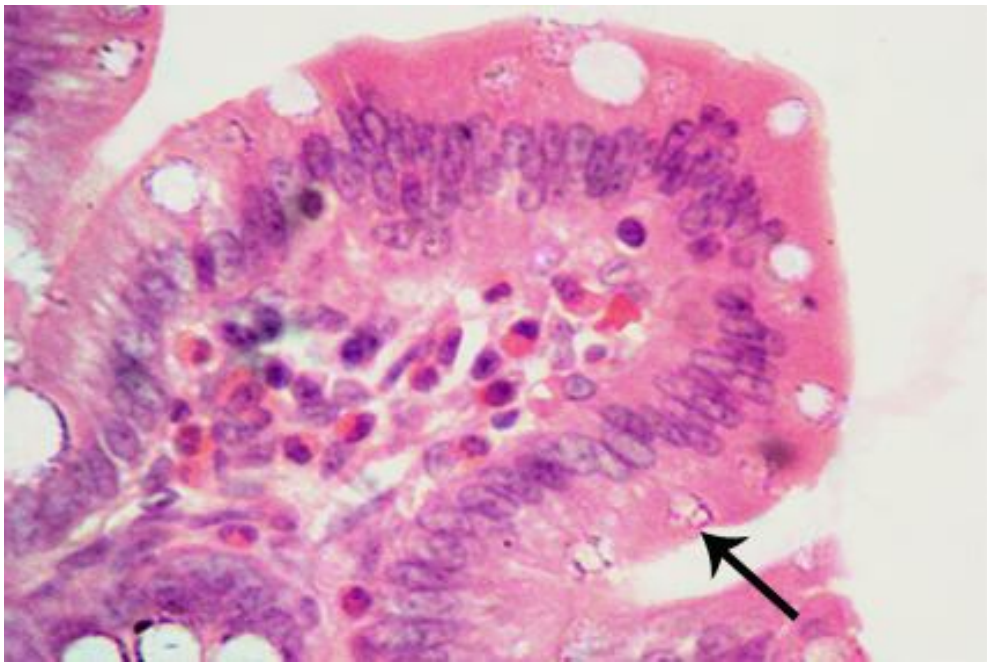
Higher magnification .

II-Histological analysis

A -Local food allergy

Acute allergic serous duodenitis

The lining epithelium of the villi and crypts was more or less normal except degeneration of some goblet cells**; picture (4).**



Picture (4): Local allergic acute serous duodenitis.

Serous exudates rich in eosinophils with degeneration of goblet cells (➔).

4 days post oral allergen HE X 40.

The intraepithelial lymphocytes (IELS) increased in the duodenal villi from one to three from the first day of observation; **table (1) & figure (1).** It steadily increased during the acute, subacute and chronic phase. From the day 25 chronicity, the number sharply raised gradually; because of competency; to the end of the experiment to reach 17. The increase was statistically significant from the day 4to the end of the experiment.

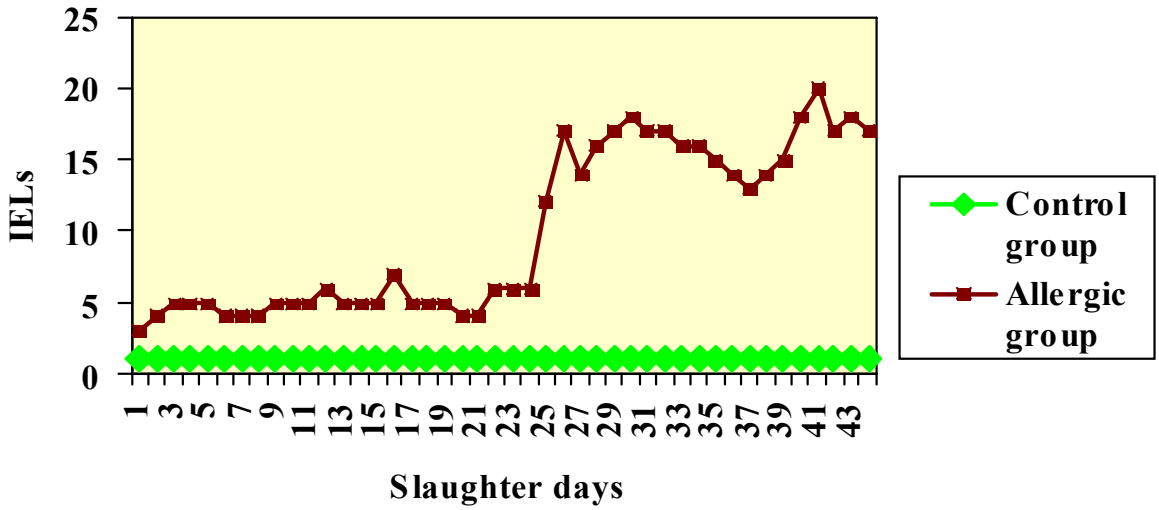
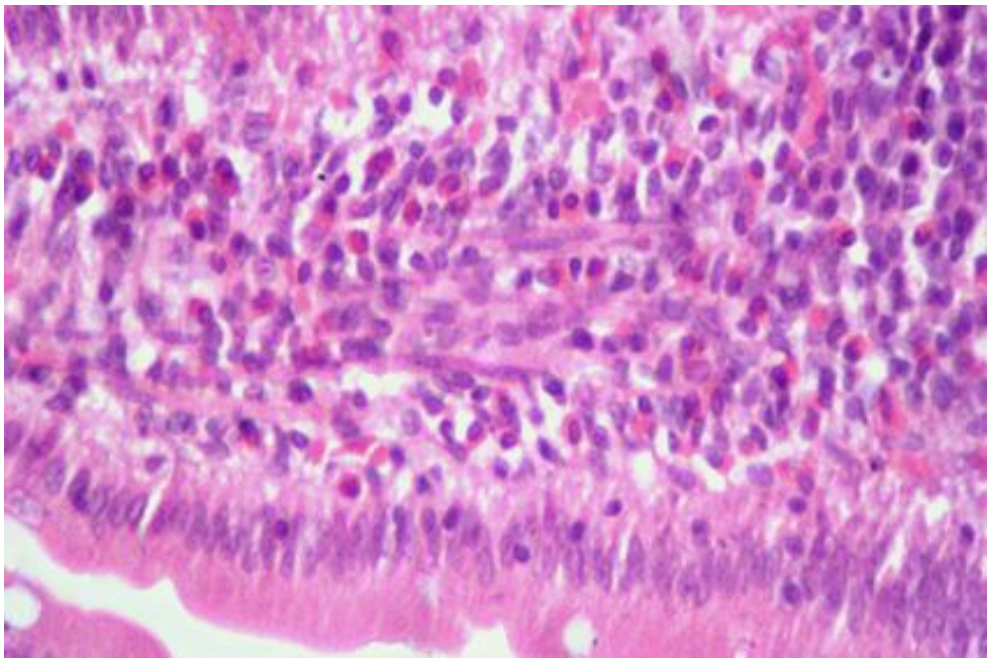
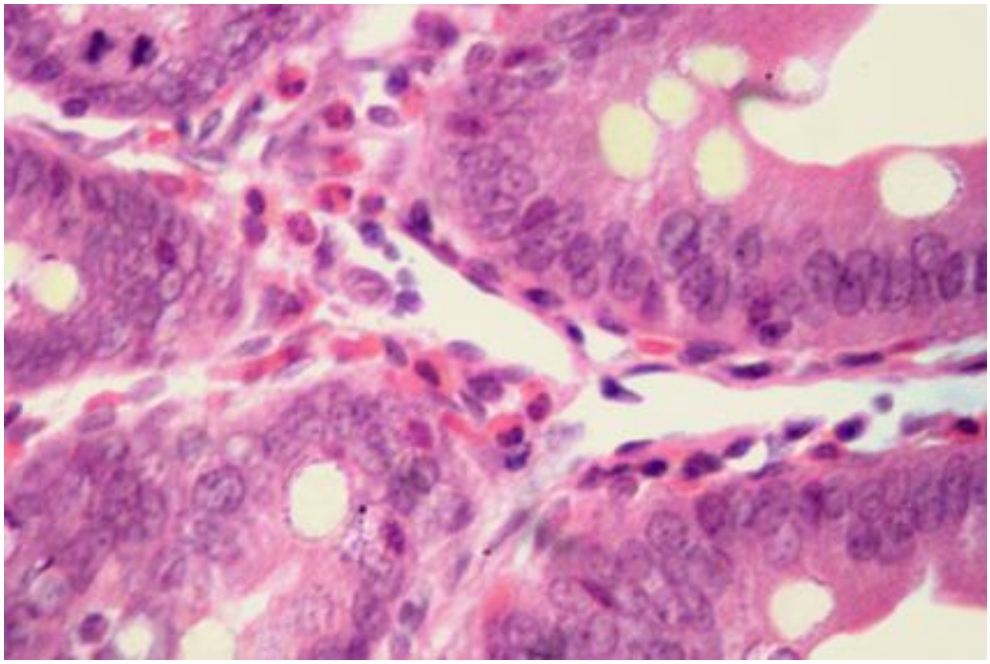


Figure (1): The mean number of intraepithelial lymphocytes in the villi of control and local allergic duodenum.

The villi were increased in width by the presence of serous exudates rich in eosinophils and macrophages**; picture (4) & (5).** These exudates infiltrated the lamina, submucosa and serosa**; picture (6).**



Picture (5): Local allergic acute serous duodenitis.
Serous exudates rich in macrophages.
4 days post oral allergen H&E X25.



Picture (6): Local allergic acute serous duodenitis.

Serous exudates rich in eosinophils infiltrating lamina propria .

4 days post oral allergen H&E X 40.

Shape changes in the villi included also decrease in the villi heights and crypt depths**.Villi heights** significantly decreased from the 6 day when it was from 348.18 to 287.60 microns to the end of the experiment. The decrease coincided with the duration of the experiment. The villi heights were lower in the subacute phase than the acute and in the chronic phase**; table (2) & figure (2).**

The crypts depths epithelium in the acute phase was more or less normal except few degenerative changes. **The IELs** in the crypts in the acute and subacute phases were more or less normal as there was no statistical significance in the increase or decrease**; table (1) & figure (3).**

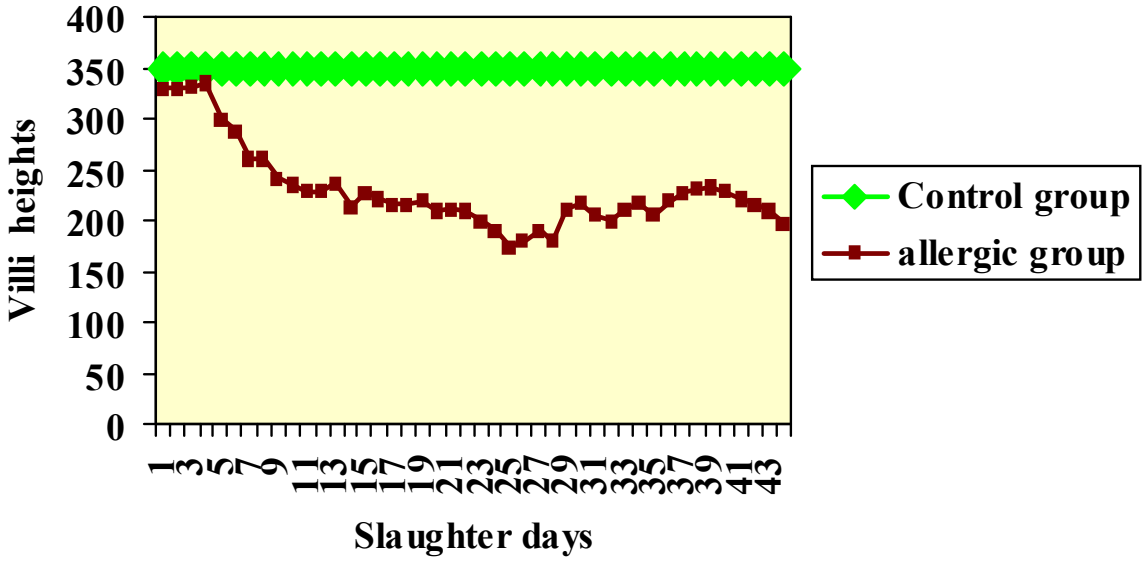


Figure (2): The length of villi height in microns of the control and local allergic duodenum.

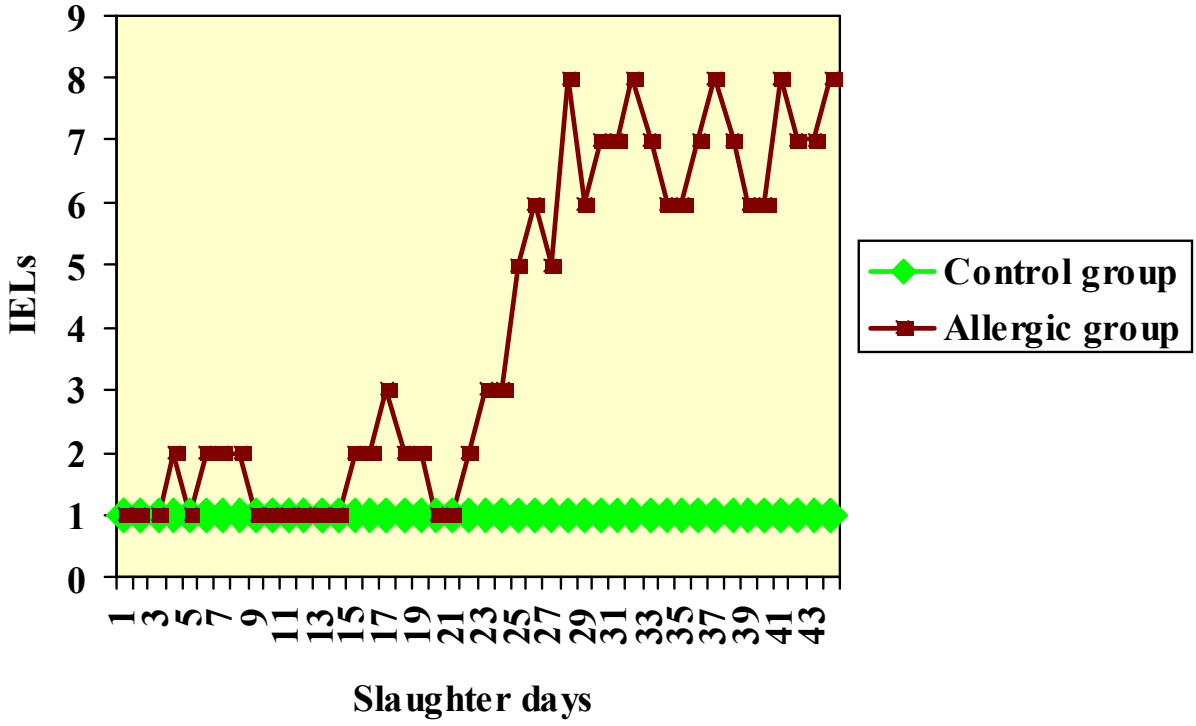


Figure (3): The mean number of intraepithelial lymphocytes in the crypts of control and local allergic duodenum.

The crypts depths decreased from the first day of the experiment when it were from 105.25 to 100.99 microns and reached to 70.36 microns at the end of the experiment .The decrease coincided with the duration of the experiment. The **crypt depths** were lower in the sub- acute phase than in the acute and in the chronic than in the subacute**; table (2) & figure (4).** The decrease was significant from the day 6 to the end of the experiment.

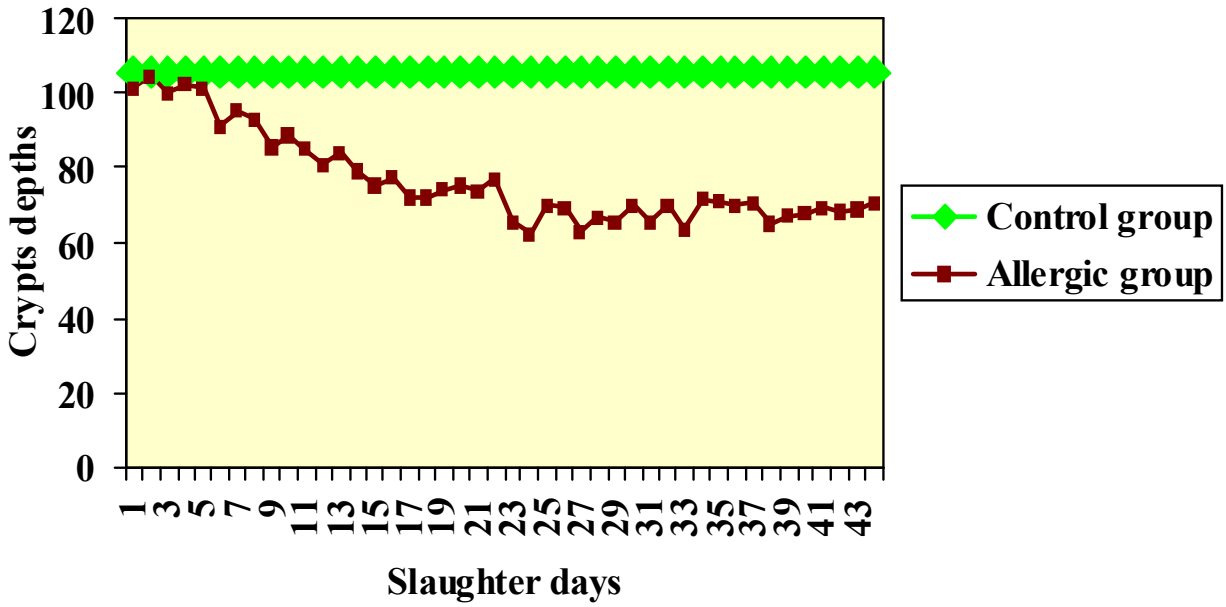
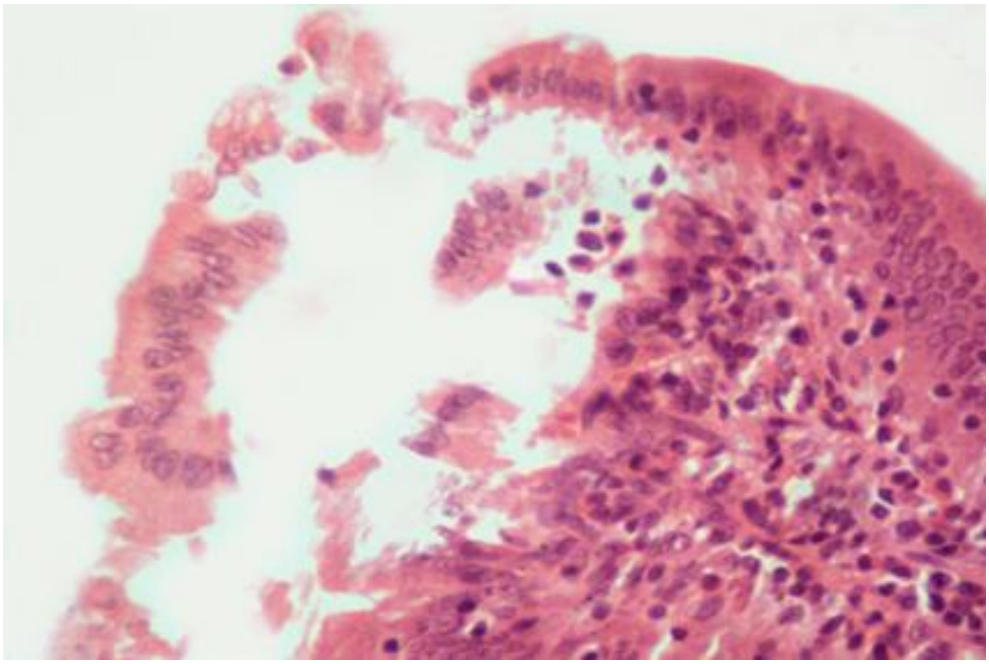


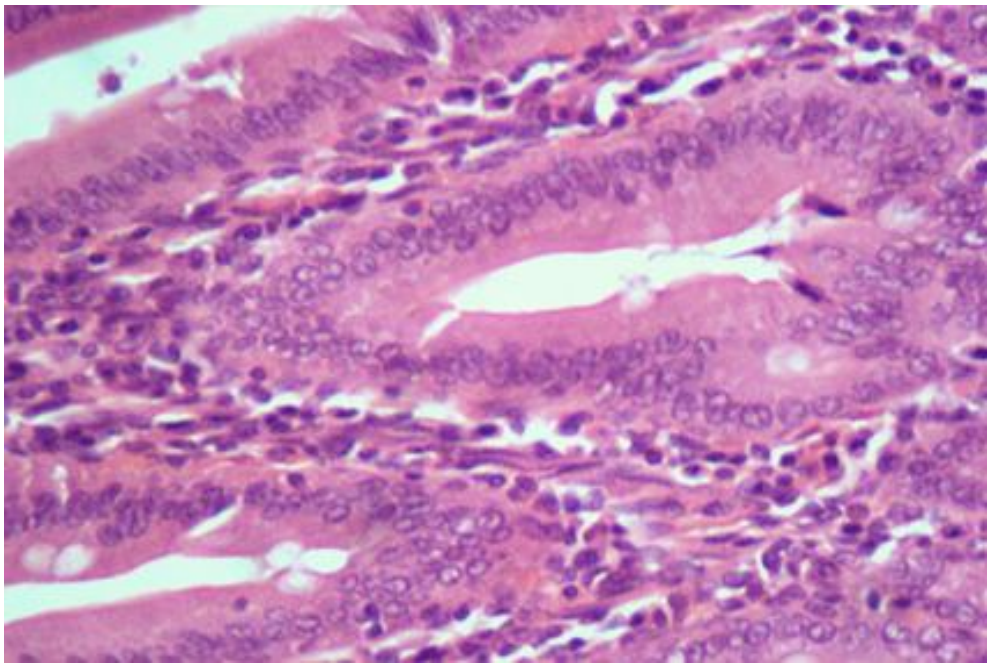
Figure (4): The length of crypts depths in microns of the control and local allergic duodenum.

Allergic subacute serous duodenitis

The lining epithelium of the villi and crypts proceeded to suffer from necrobiosis and desquamation**; picture (7).** A process of regeneration has started patchy in the surface epithelium represented by the presence of mitotic figures, basophilic tint staining the cytoplasm and loss of goblet cell differentiation**; picture (8).** Atypical regeneration was demonstrated by hyperplasia and metaplasia**; picture (9), (10) & (11).** The **IELs** in the duodenal villi in the subacute phase started to increase from 1 to 4 at the day 8and reached to 5 at the day 15**; table (1) & figure (1). The serous exudate** infiltrating the villous core became rich in lymphoid cells**; picture (12).** Fibroblast, fibrocytes and macrophages started to appear in the core of some villi**; picture (13).**



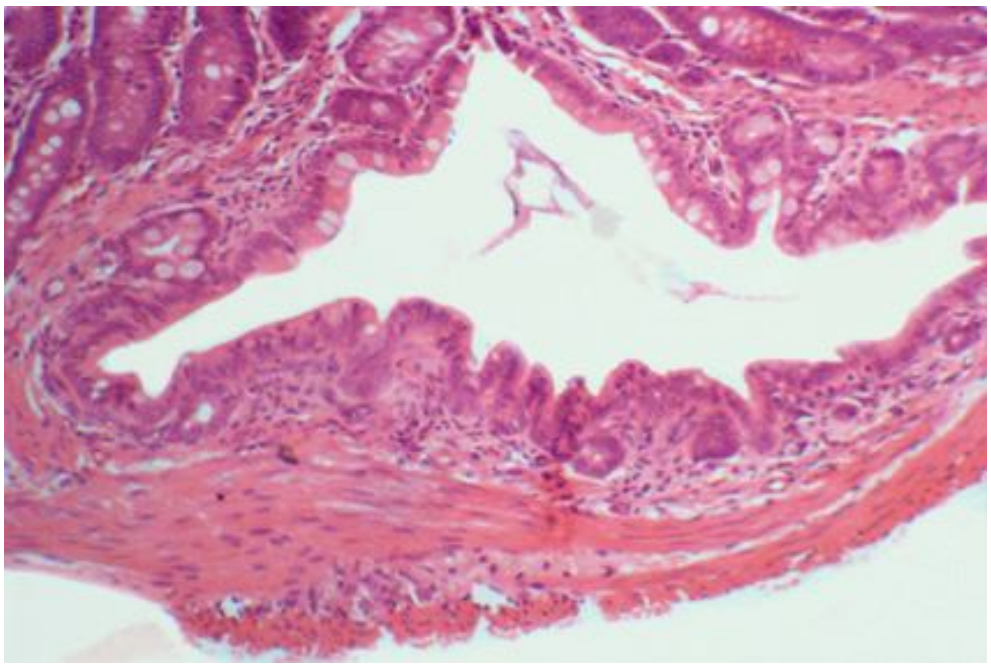
Picture (7): Local allergic subacute serous duodenitis.
Necrobiosis and desquamations of the epithelium with serous exudates.
13 days post oral allergen H &E X 25.



Picture (8): Local allergic subacute serous duodenitis.

Regeneration of villous base, mitotic figures, basophilic tint staining the cytoplasm and loss of goblet cells differentiation.

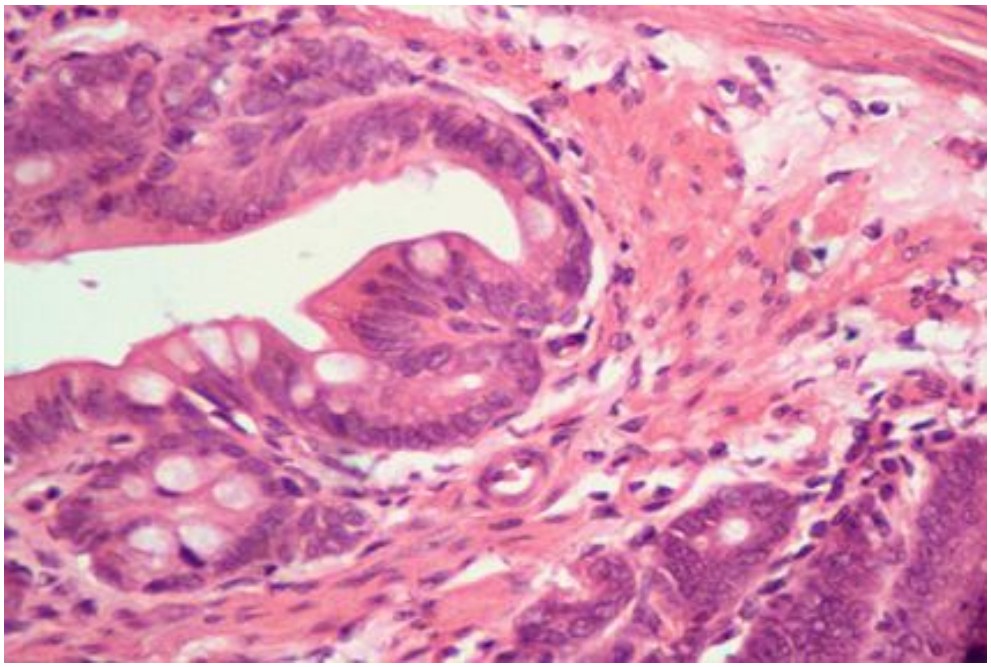
10 day post oral allergen H & E X 15.



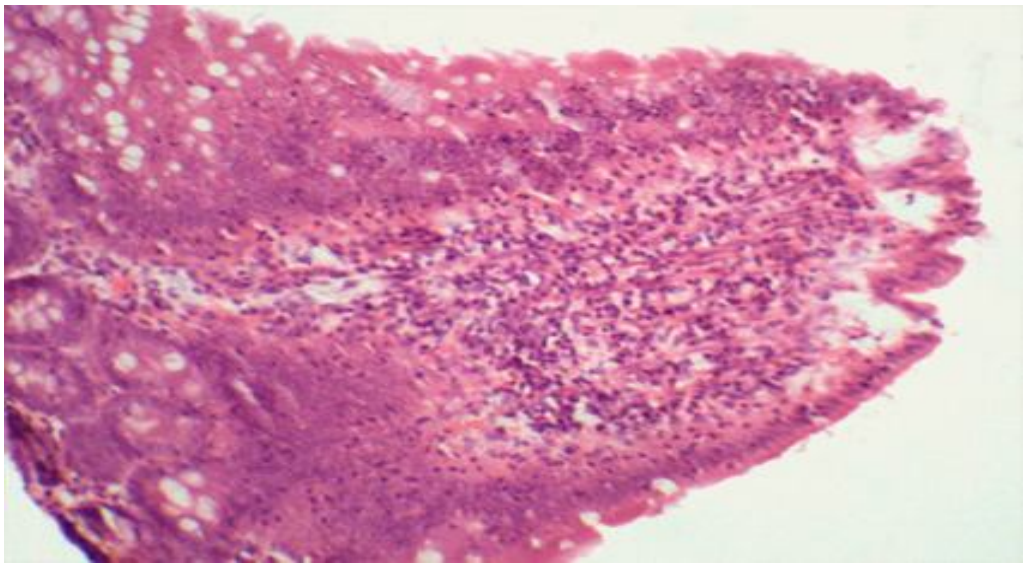
Picture (9): Local allergic subacute serous duodenitis.

Hyperplasia of surface epithelium.

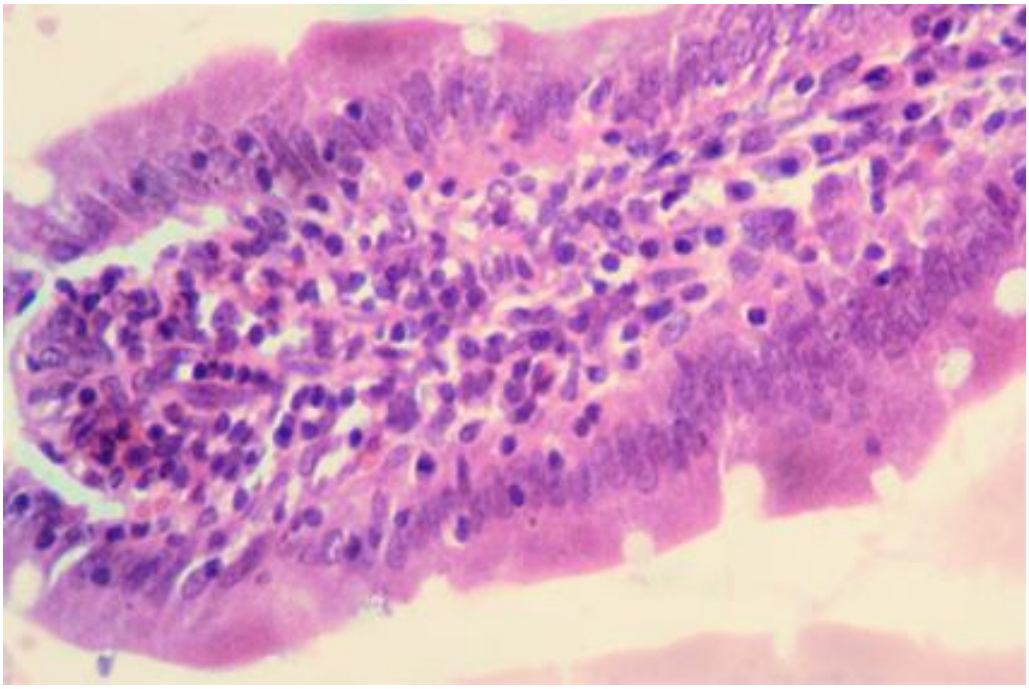
10 days post oral allergen H &E X10.



Picture (10): High power of the upper figure. H& E X 40 .



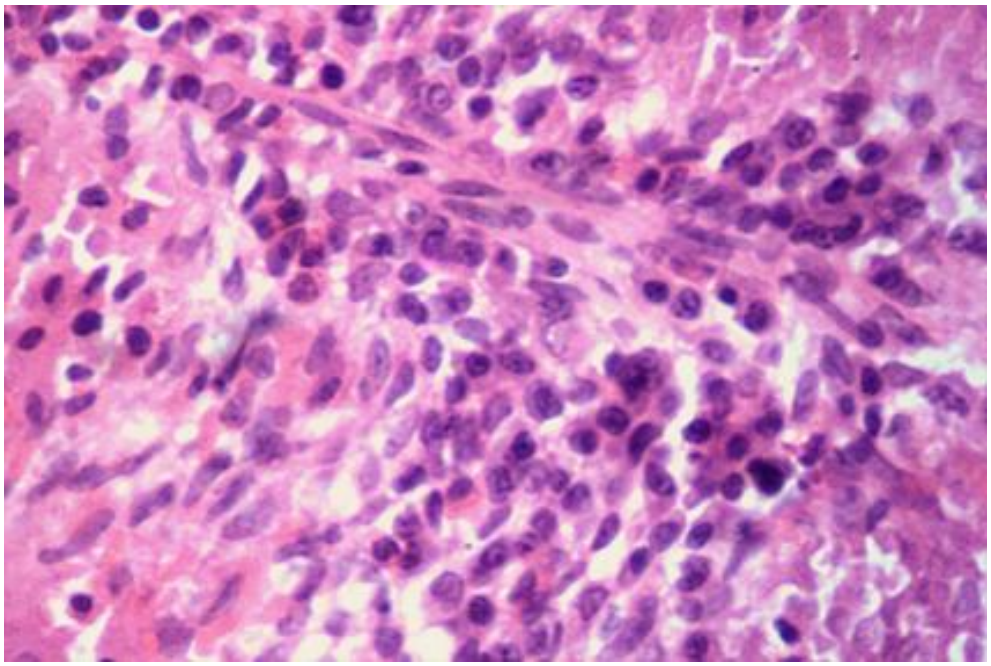
Picture (11): Local allergic subacute serocatarrhal duodenitis.
Metaplasia of surface epithelium with hyperplasia of goblet cells and dense inflammatory cells.
15 days post oral allergen H & E X10.



Picture (12): Local allergic subacute serous duodenitis.

Lymphoid cell reaction in villous core.

13 days post oral allergen H & E X25

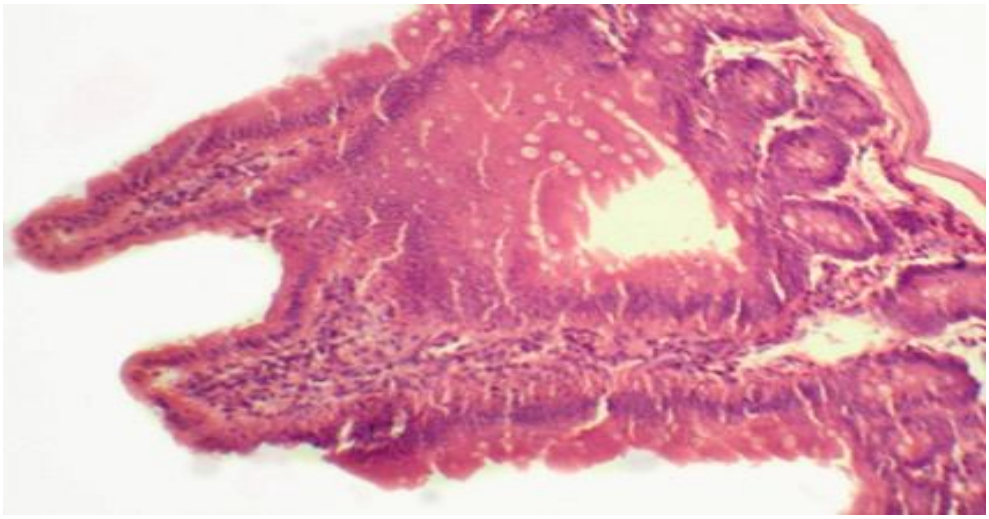


Picture (13): Local allergic subacute serous duodenitis.

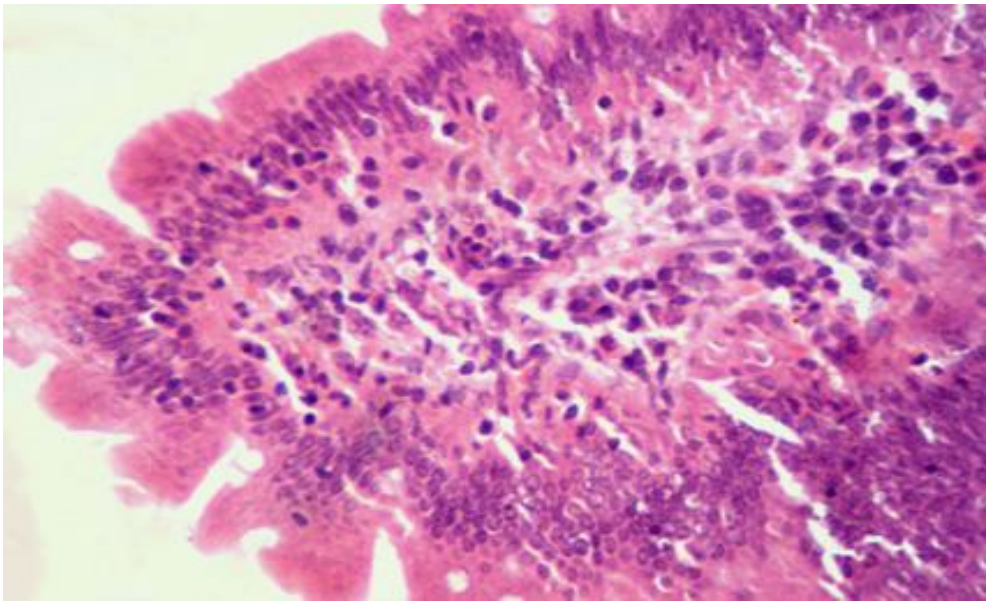
Fibroblasts, fibrocytes and macrophages in the villous core.

13 days post oral allergen H& E X 40.

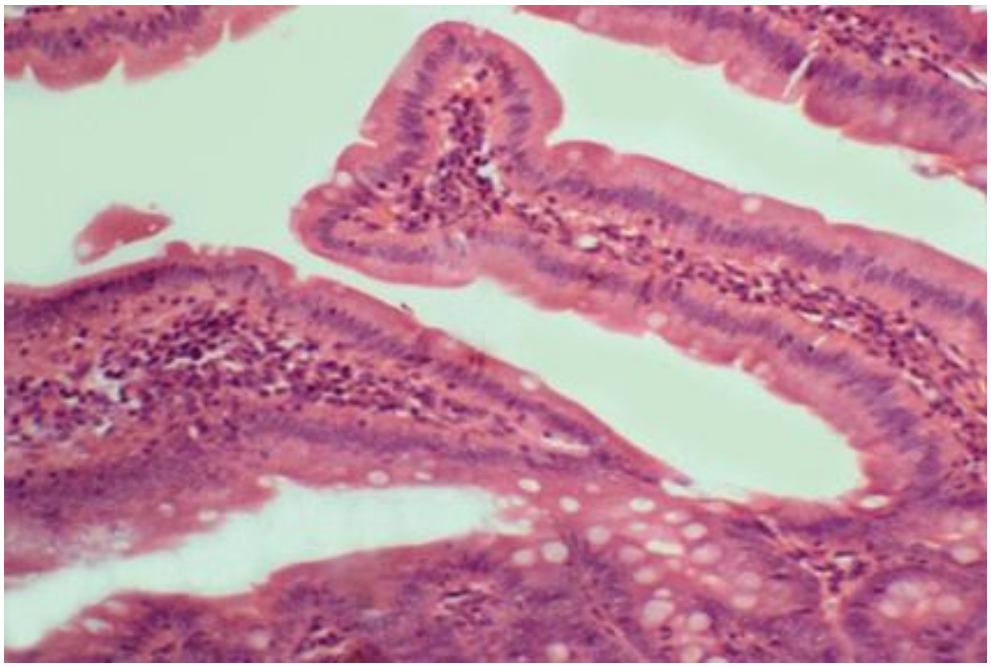
The villi shape changes included fusion**; picture (14)**, broadness**; picture (15)**, branching**; picture (16)** and lengthening**; picture (17).**



Picture (14): **Local allergic subacute serous duodenitis.**
Villous fusion.
11 days post oral allergen H & E X10.



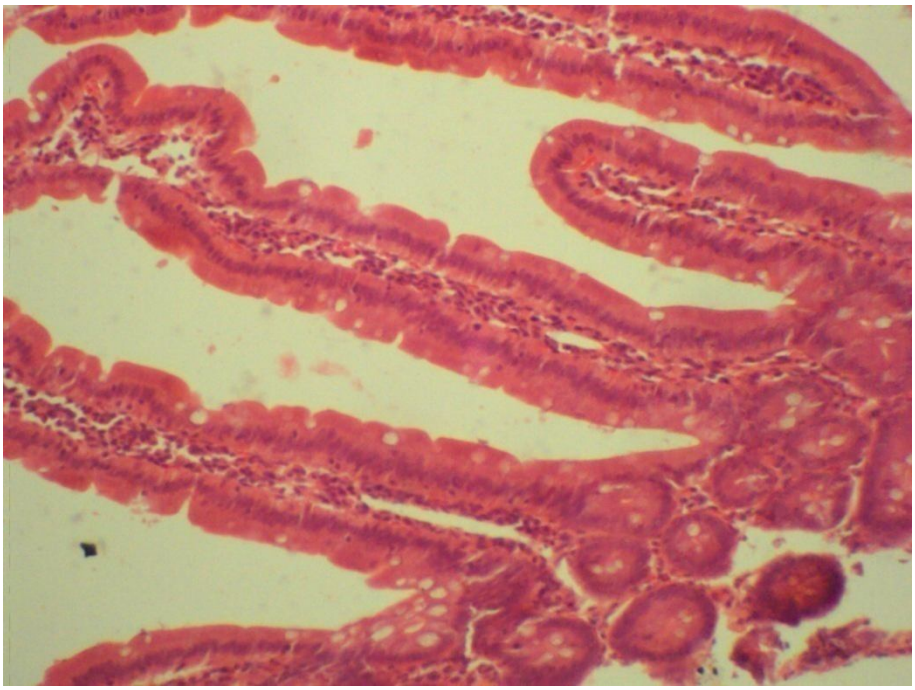
Picture (15): Local allergic subacute serous duodenitis.
Broad villous.
13 days post oral allergen H & E X 25.



Picture (16): Local allergic subacute serous duodenitis.

Elongated villous with branching tip.

15 days post oral allergen H &E X 25.



Picture (17): Local allergic subacute serous duodenitis.

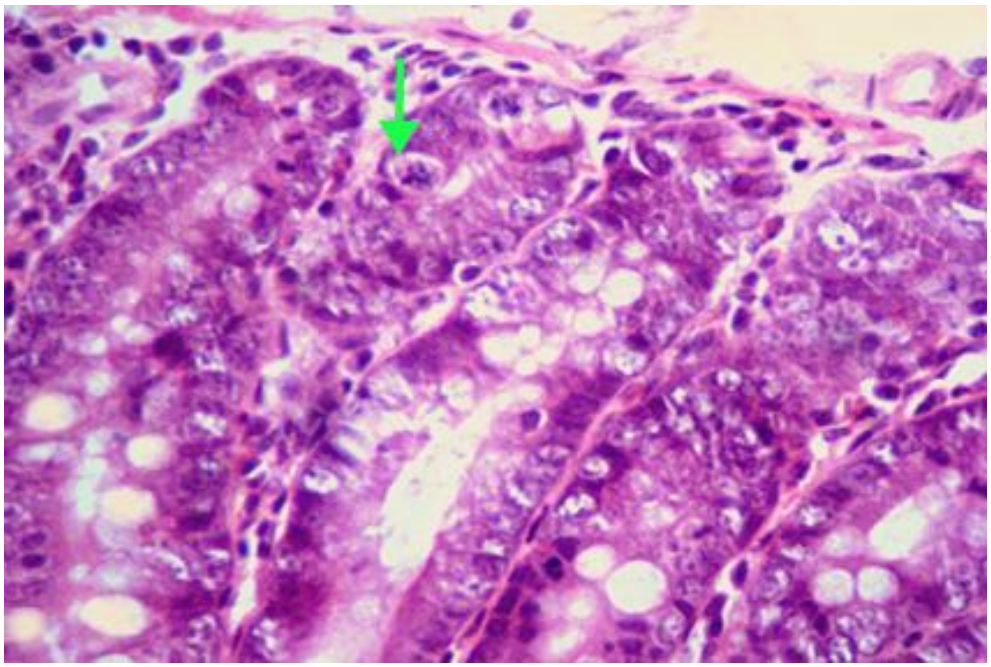
Long ramified villi.

15 days post oral allergen H &E X 10.

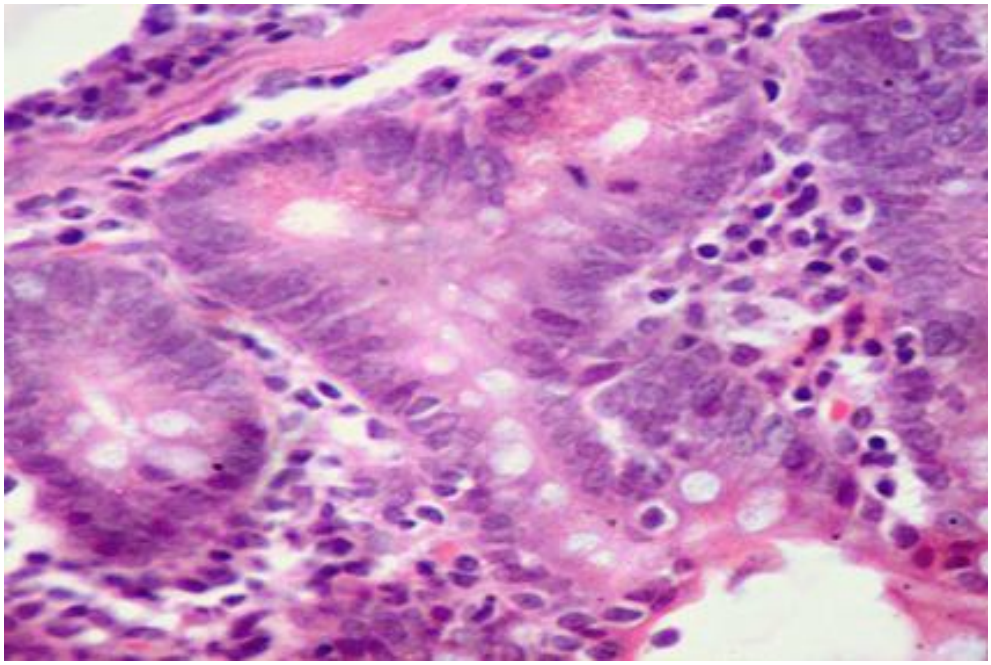
The villi heights were lower in the subacute phase than in the acute. Starting from the day 8 it was from 348.18 to 260.05 microns and reached to 228.12 microns at the day 15**; table (2) & figure (3).**

The crypt epithelium suffered from necrobiotic changes starting from the subacute phase**; picture (18).** Also atypical regeneration represented by mitotic figures and branching of the crypts base was observed**; picture (19).** This resulted in crypts hyperplasia**; picture (20). The IELs** in the crypts in the subacute phase were statistically non-significance**; table (1) & figure (2).**

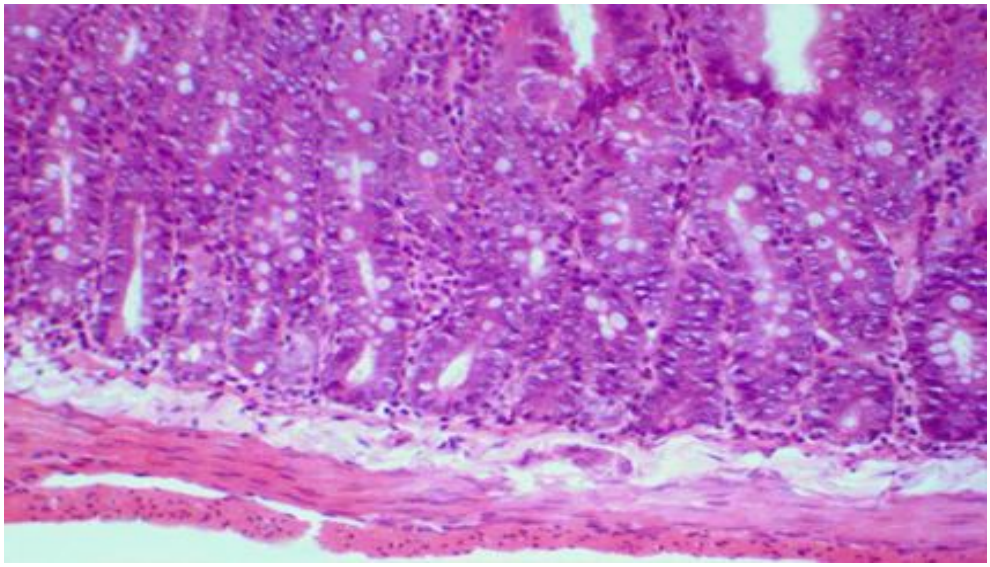
The crypts depths were lower in the subacute phase than in the acute. Starting from the day 8 it was from 105.19 to 93.20 microns and reached to 75.26 microns at the day 15**; table (2) & figure (4).**



Picture (18): Local allergic subacute serous duodenitis.
Necrobiotic changes in the crypts (➔) .
13 days podt oral allergen H & E X 25.

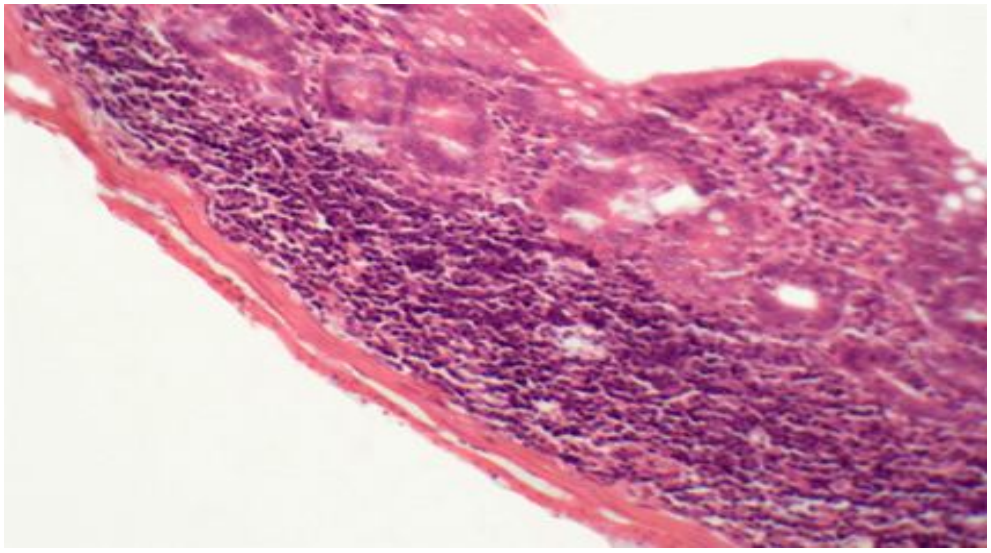


Picture (19): **Local allergic subacute serous duodenitis.**
Branching of the crypt base with mitotic figure .
15 days post oral allergen H E X 40.

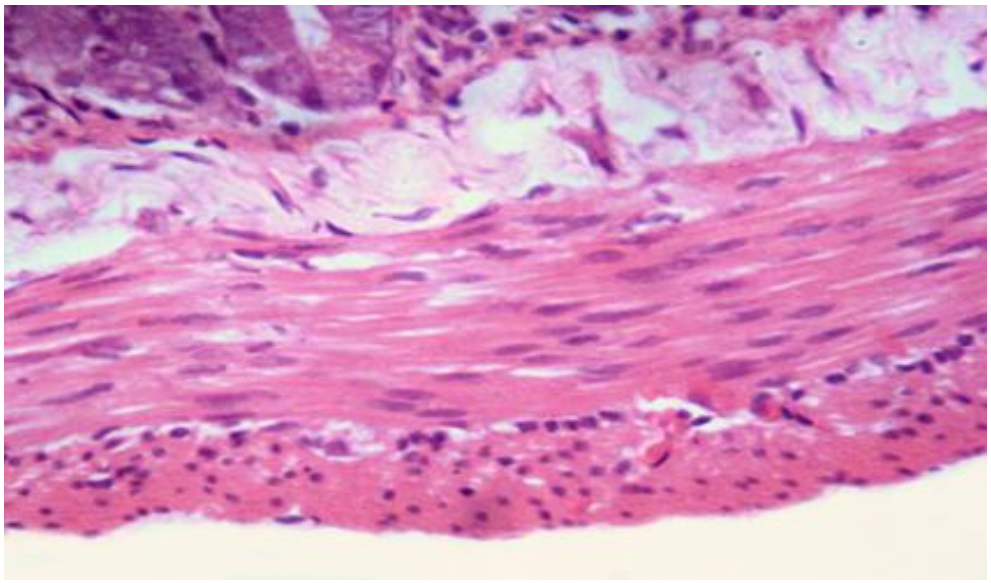


Picture (20): **Local allergic subacute serous duodenitis.**
Crypts hyperplasia.
13 days days post oral allergen H &E X 10

There was a diffuse lymphocytic reaction allover the sub-mucosa**; picture (21).** The serous exudates wided between the muscle fibers of the muscularis where lymphocytes were permeating**; picture (22).**

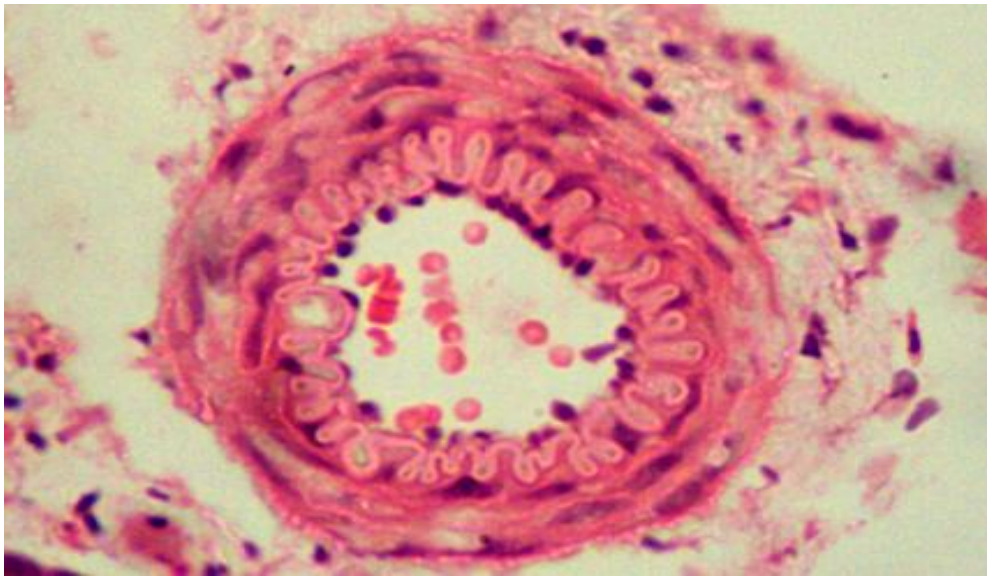


Picture (21): **Local allergic subacute serous duodenitis.**
Diffuse lymphocytic reaction allover the submucosa.
11 days post oral allergen H &EX 10.

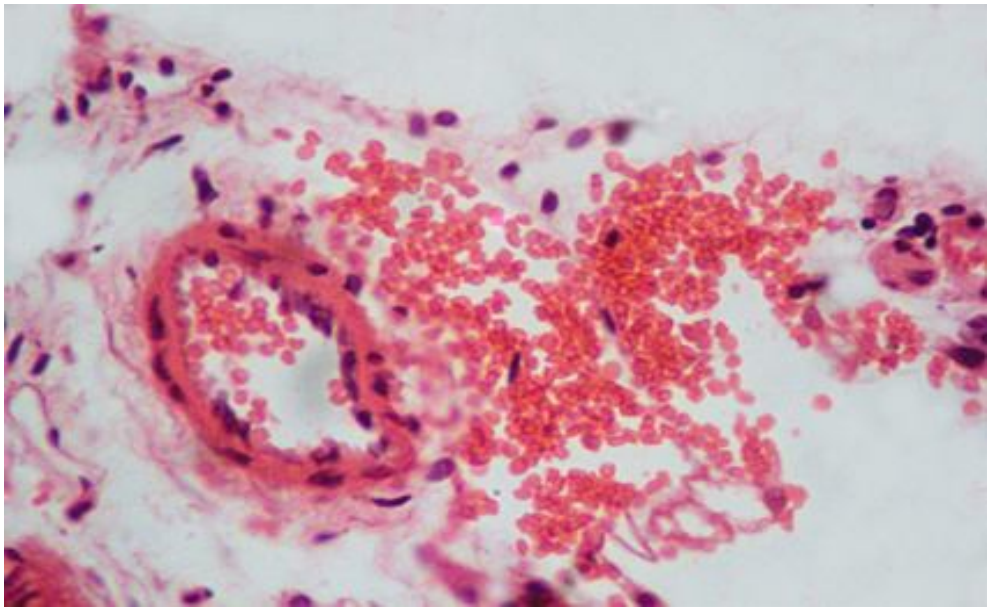


Picture (22): **Local allergic subacute serous duodenitis.**
Serous exudation infiltrating submucosa and muscularis.
13 days post oral allergen H&E X 25.

Serous serositis, arteritis and serositis with hemorrhages**; picture (23) & (24).**



Picture (23): **Local allergic subacute serous duodenitis.**
Serous serositis, arteritis and serositis.
13 days post oral allergen H & E X 25.



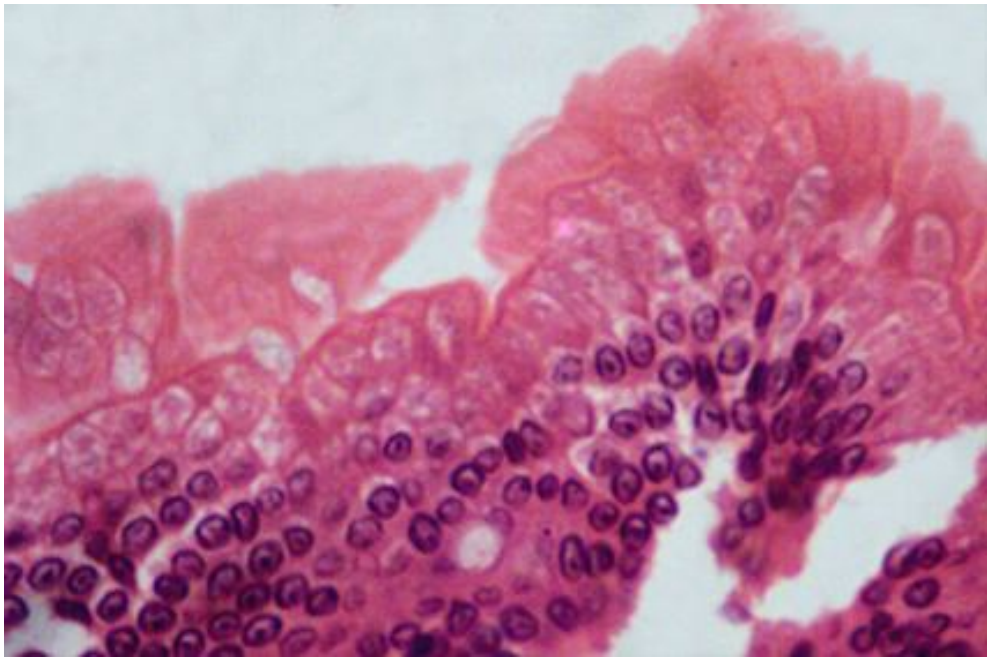
Picture (24): Local allergic subacute serous duodenitis
Serous serositis with hemorrhages.
15 days post oral allergen H&E X 25.

Allergic Chronic Serous Duodenitis

The lining epithelium necrobiosis proceeded to a massive area of coagulative necrosis involving many villi at the day 27**; picture (25).**

The IELs in the duodenal villi increased gradually from the day 25 (12) to reach 17 at the end of the experiment**; table (1) & figure (1)** and **picture (26).**

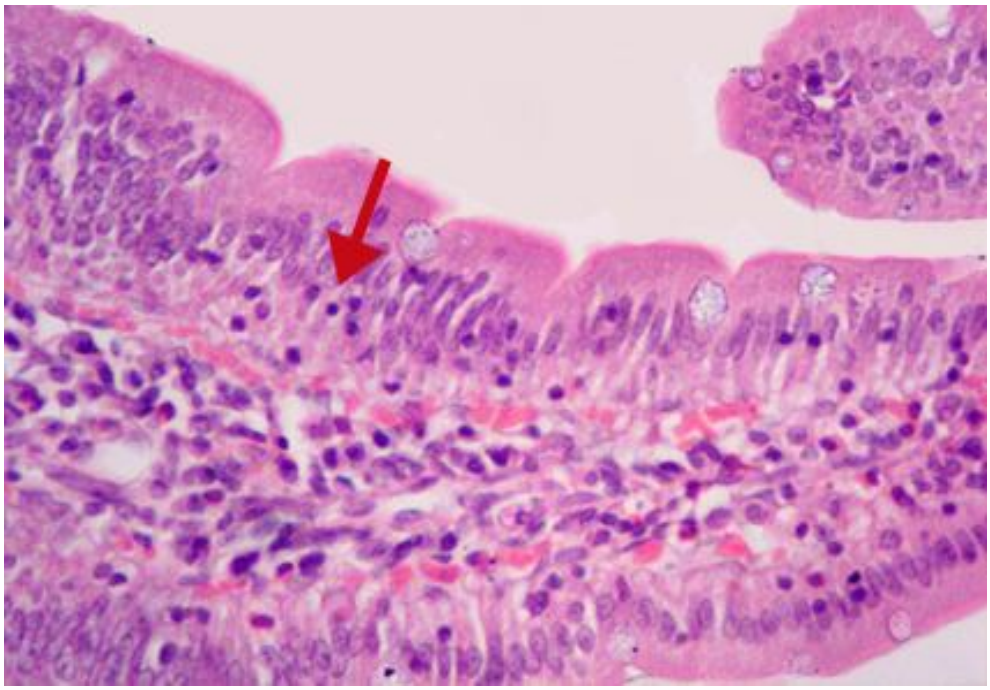
The lymphocytic reaction of the subacute phase became dense widening the villi at the day 25**; picture (27). Capillary thrombosis** started with the chronicity at the day 21 when agglutinating RBCs were seen in the capillaries of the villous core; **picture (28). Red thrombi** were seen in the post capillary venules of the villous base and lymphoid follicles at the day 30**; picture (29)** and in the submucosal vessels at the day 42**; picture (30).The villi heights** were the lowest in the chronic phase; **table (2) & figure (3).**



Picture (25): Local allergic chronic duodenitis.

Massive areas of coagulative necrosis involving villous epithelium.

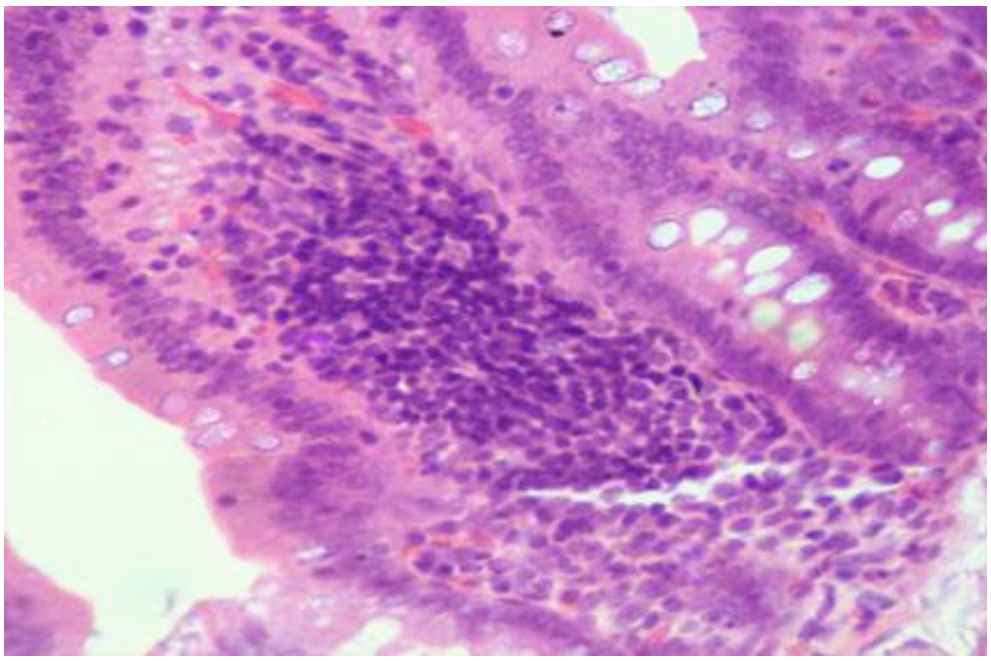
27 days post oral allergen H&E X 40.



Picture (26): Local allergic chronic serous duodenitis.

Intraepithelial lymphocytes (➔).Subsiding hyperemia with Serous exudates rich in lymphocytes.

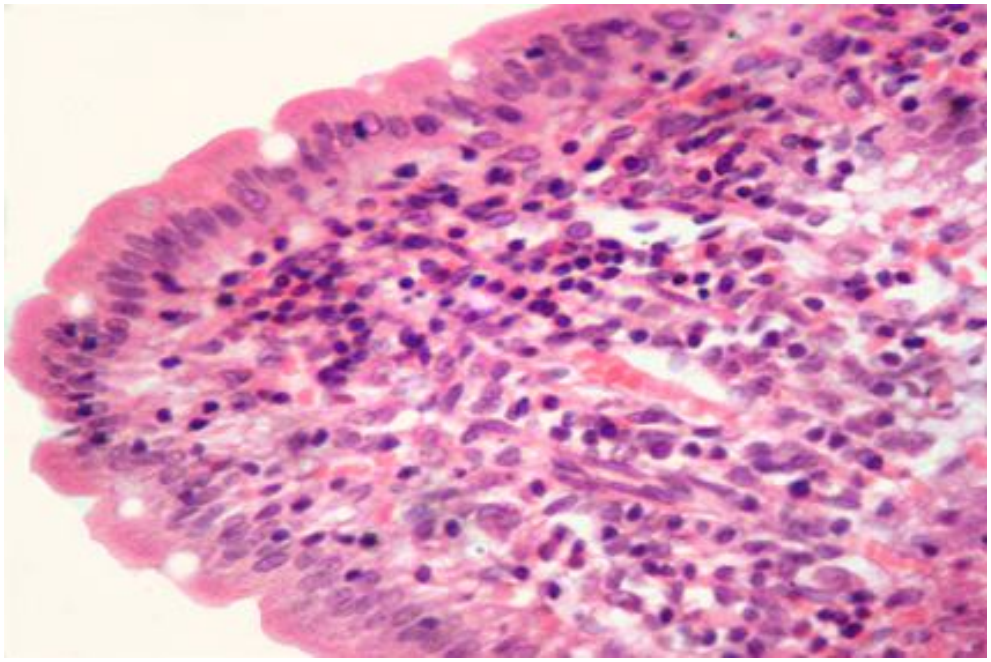
21 post oral allergen H&E X 25.



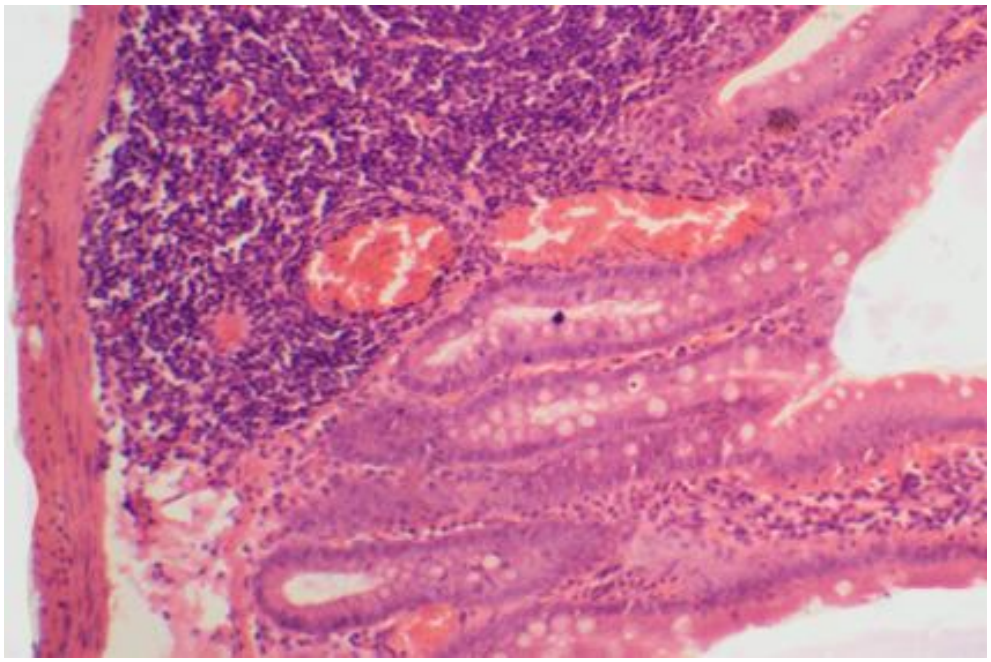
Picture (27): Local allergic chronic serous duodenitis.

Dense lymphocytic reaction widening the villi

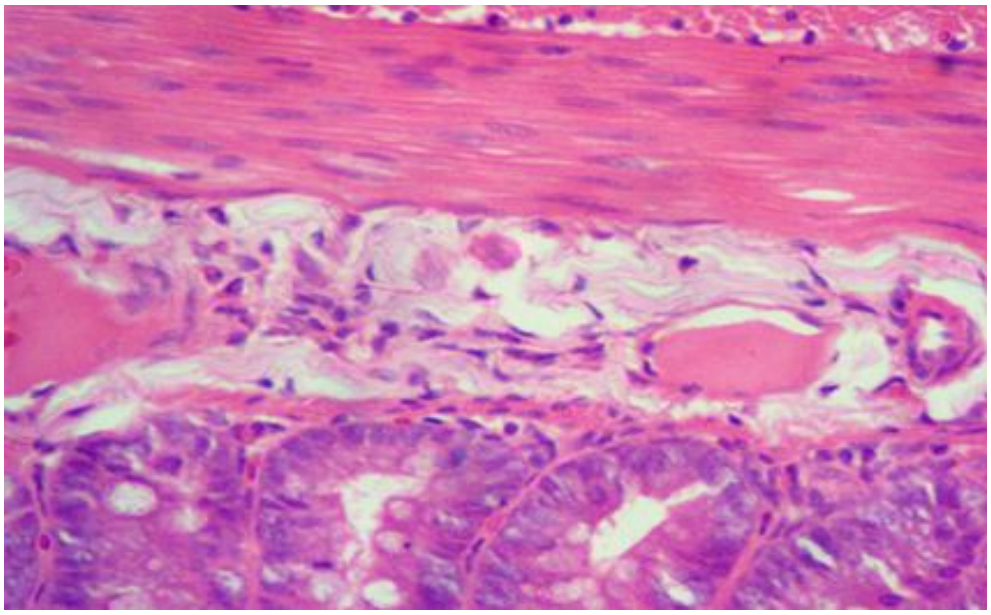
25 days post oral allergen H&E X 25.



Picture (28): Local allergic chronic serous duodenitis.
Agglutinated RBCs in hyperemic capillaries of villous core.
21 days post oral allergen H&E X25.

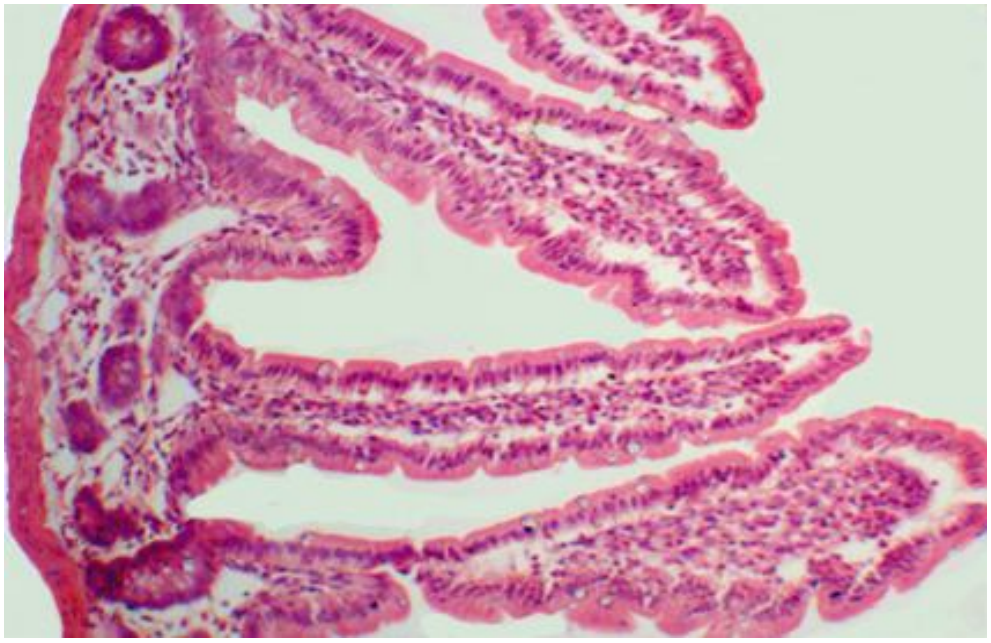


Picture (29): Local allergic chronic serous duodenitis.
Thrombosis in the post capillary venules of the villous base and lymphoid follicle.
30 days post oral allergen H&E X10.

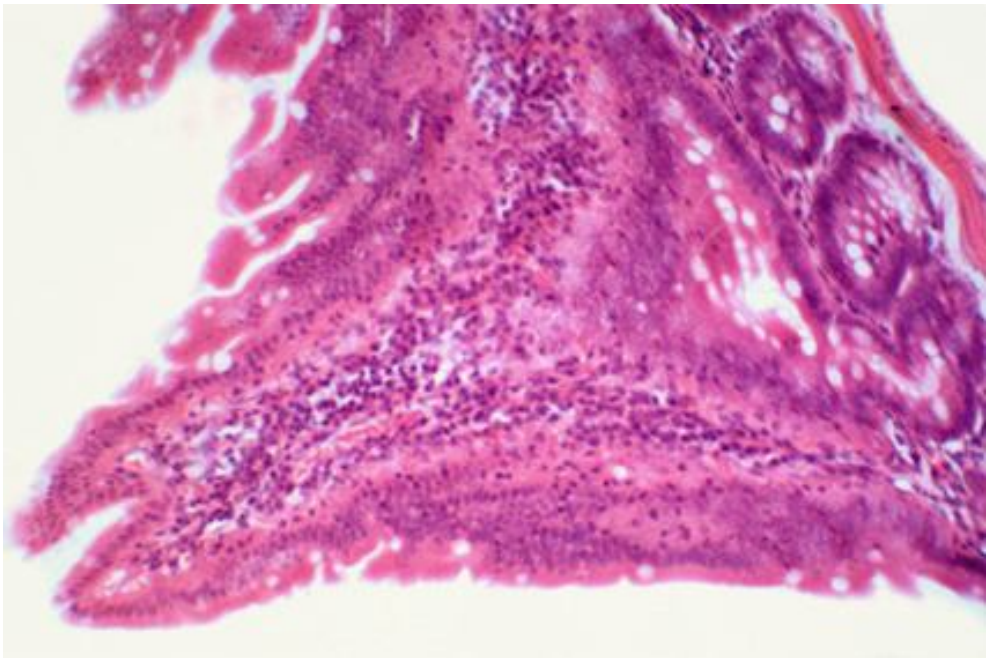


Picture(30): allergic chronic serous duodenitis.
Red thrombus with edema in the submucosa.
42 days post oral allergen H&E X 25.

The villi shape changes were seen as widening**;picture (28)**, widening of the upper half**; picture (31)** and wide base with branched tip**; picture (32).**



Picture (31) : Local allergic chronic serous duodenitis.
Villous widening of the upper half.
18 days post oral allergen H&E X 10.

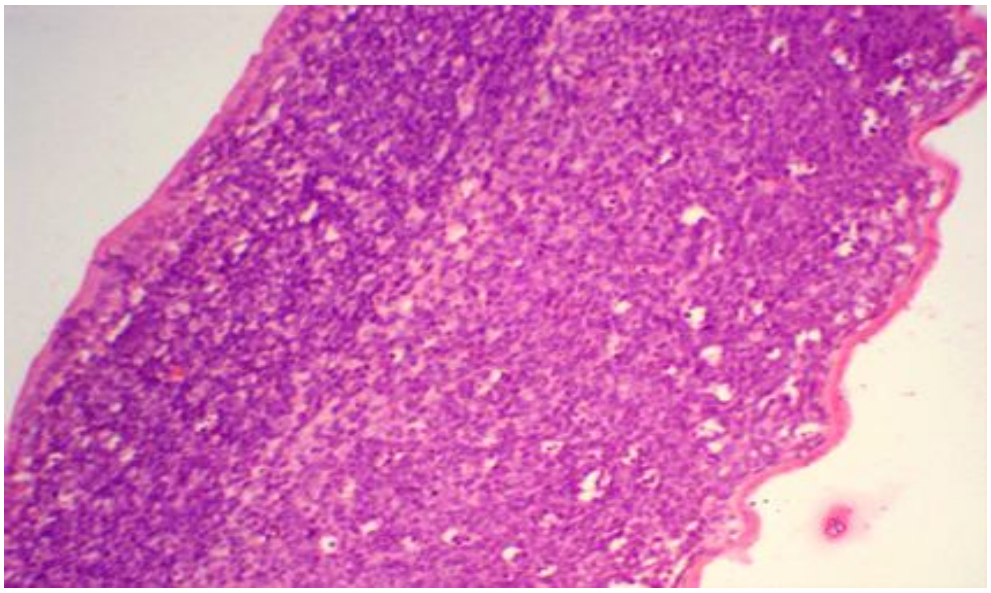


Picture (32): Local allergic chronic serous duodenitis.
Wide base with branched tip villous.
28 days post oral allergen H&E X10.

The IELs increased in crypt depths during the chronic phase and reached 8 at the end of the experiment**; table (2) & figure (3).**

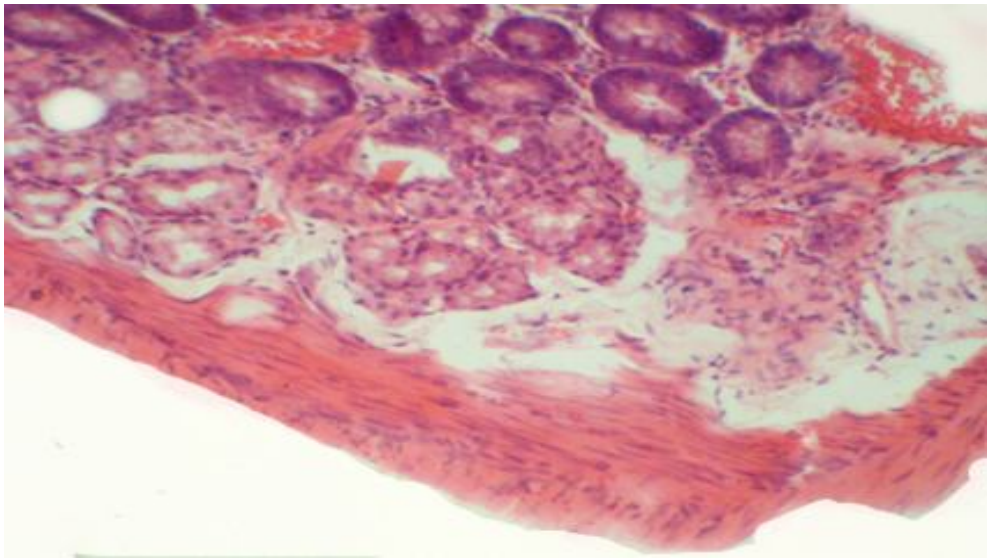
The crypt depth was the lowest in the chronic phase **table (2) & figure (4).**

Germinating submucosal lymphoid follicles were overloaded by diffuse lymphocytic reaction allover the submucosa at the day 25**; picture (33).**



Picture (33): Local allergic chronic serous duodenitis.
Germinating submucosal lymphoid follicle overlaid by diffuse lymphocytic reaction allover the submucosa.
25 days post oral allergen H&E X10.

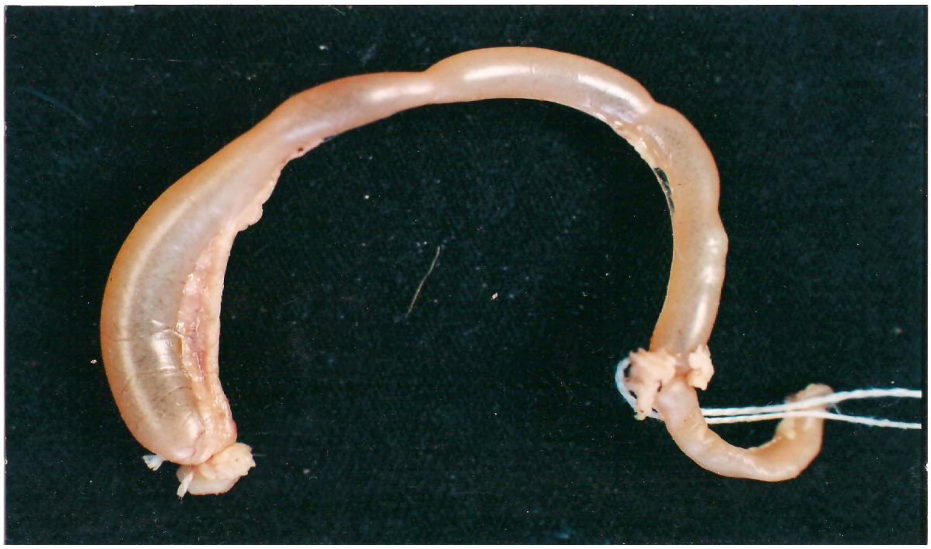
In the chronic phase abnormal shaped degenerating **Brunner's glands** were observed at the day 35**; picture (34).**



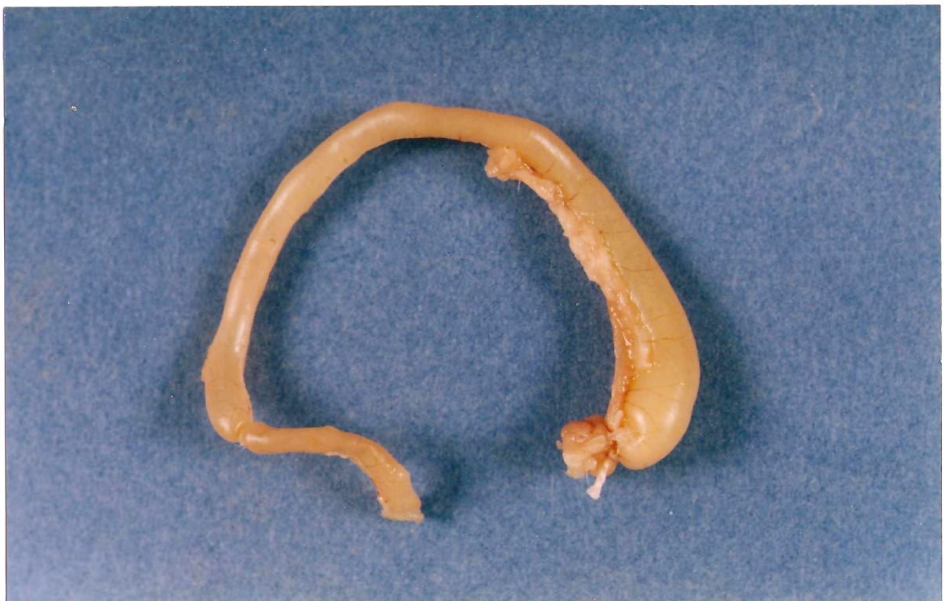
Picture (34): Local allergic chronic serous duodenitis.
Degenerating and abnormal shaped Brunner's glands.
35 days post oral allergen H&E X 10.

Dexamethasone and omega -3 treated group

In these groups, the animals were slaughtered regularly more or less every 3 or 4 days from the start of the experiment to the end. The macroscopical picture in both treated groups showed subsiding of hyperemia from the day 25 to the end of the experiment**; picture (35&36).**

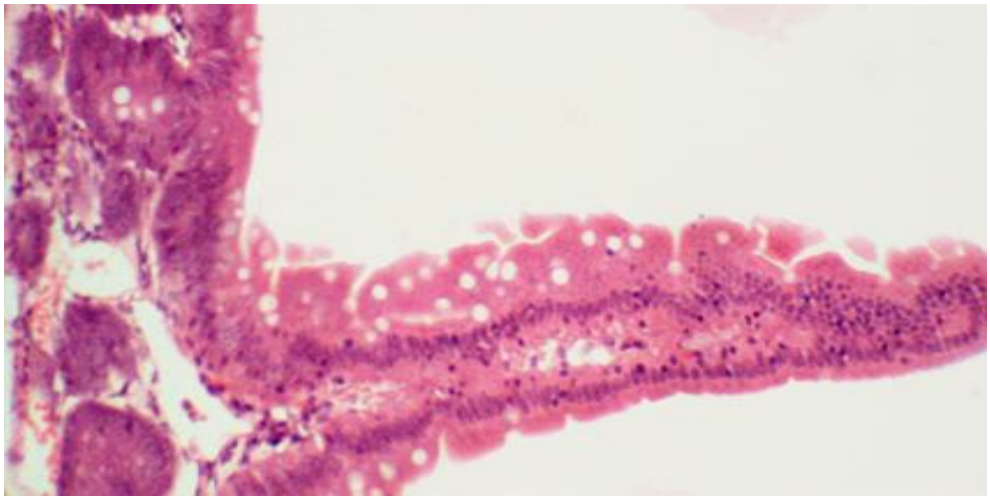


Picture (35): Dexamethasone treated local allergic duodenitis. Subsiding of hyperemia.

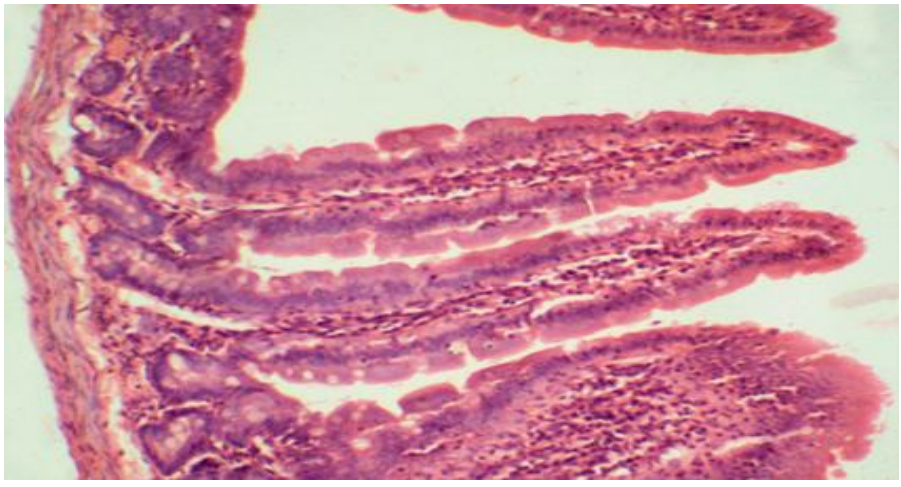


Picture (36): Omega-3 treated local allergic duodenitis. Subsiding of hyperemia.

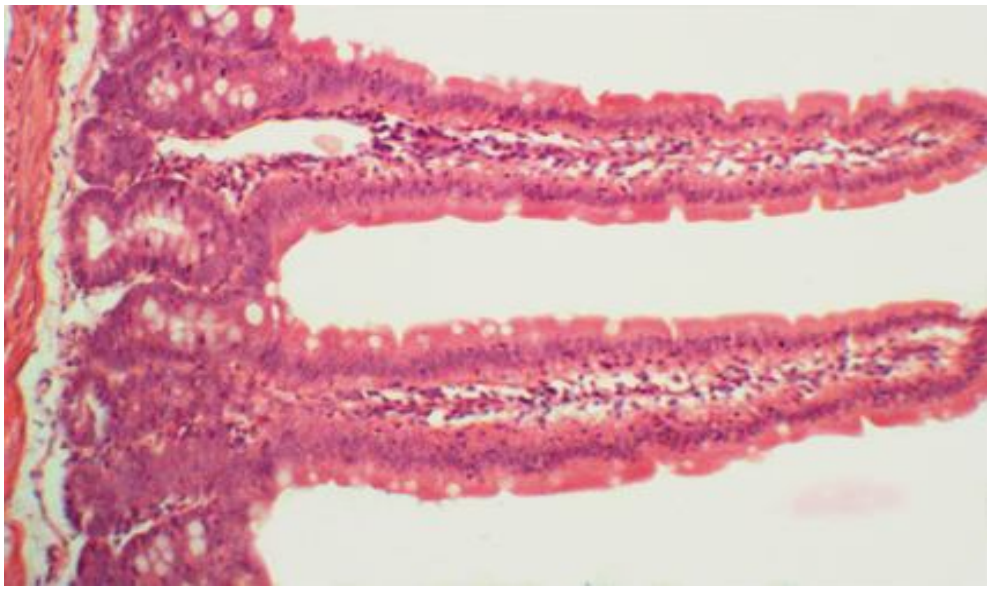
The curative effect of the dexamethasone started at the day 18. Some duodenal villi demonstrated unilateral metaplasia**;picture (37).** At the day 25 most of the villi were more or less of normal epithelium and shapes except few ones**; picture (➔) (38).** At the day 28, the villi were completely of normal epithelium and shape. **In omega-3teated group**, the duodenal villi epithelium and shapes reached complete normality after the day 25 of the treatment**; picture (39).**



Picture (37): Dexamethasone treated local allergic duodenitis.
Unilateral metaplasia of the villi lining epithelium.
18 days post oral allergen H&E X10.



Picture (38): Dexamethasone treated local allergic duodenitis.
Most of the villi were more or less normal except few ones.
25 days post oral allergen H&E X10.



Picture (39): Omega -3 treated local allergic duodenitis.
Complete normality of the duodenal villi.
25 post oral allergen H&E X10.

The IELs of the duodenal villi in **dexamethasone** treated group were under the control level (from1 to 0.0). Statistically the difference was non significant .i.e. the dexamethasone treatment completely prevented the IELs to reach the control level**; table (3) & figure (5).In omega -3 treated group,** the duodenal **IELs** were under the control level (from one to zero) from the day 18 to the day 28. From the day 32 to the end of the experiment, it was exactly as the control .i.e. the omega -3 treatment prevented **IELs** in the duodenal villi to reach the control level. **Omega-3** was better in the correction of **IELs** as it started to be the same as the control from the day 32 to the end of the experiment.

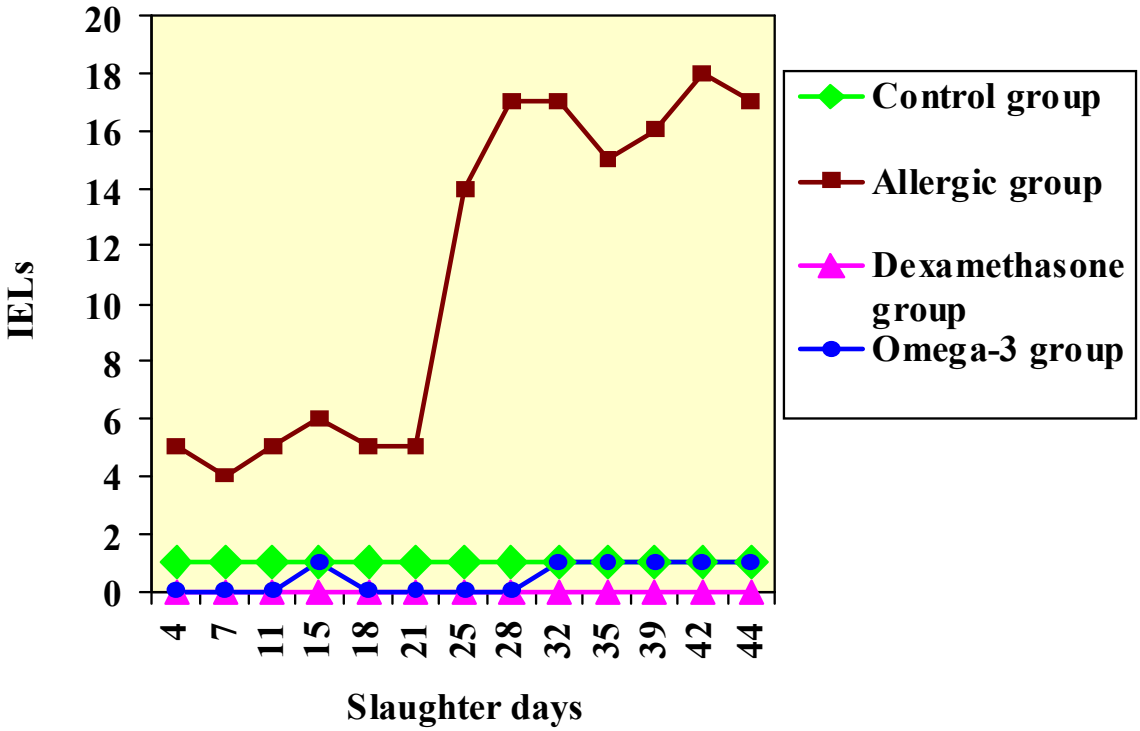


Figure (5): The mean number of intraepithelial lymphocytes per ten villi of control, local allergic, dexamethasone and omega-3 treated duodenum.

Dexamethasone treatment corrected significantly the local allergic duodenal **villi heights** to the control level from the day7 (from 348.26 to 357.92 microns). From the day 21 (from 348.26 to 451.47 microns) to the end of the experiment, the length of the duodenal **villi heights** were higher than the control level**; table (4) & figure (6).** The difference was statistically significant. **Omega-3 treatment** increased significantly the length of duodenal **villi heights** from the day7 (from 348.26 to 381.81 microns) to the end of the experiment. Both treatments repaired the local allergic duodenal villi heights at the same time at the day 11 but the villi heights in omega-3 treatedd group were nearer to the control than the dexamethasone treated one.

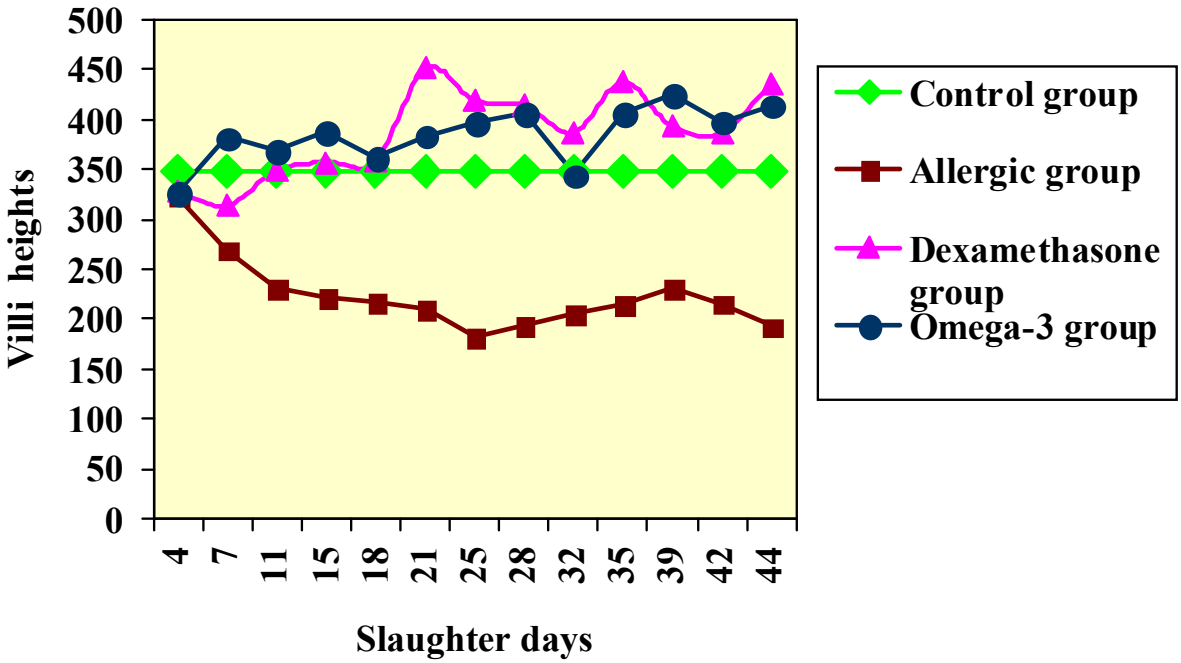


Figure (6): The length of villi heights in microns of the control, local allergic, dexamethasone and omega-3 treated duodenum.

In dexamethasone treated group, the IELs in the duodenal crypts were under the control level (from 1 to 0.0). Statistically the difference was non significance .i.e. the dexamethasone treatment prevented the IELs to reach the control level**; table (5) & figure (7).In the omega -3 treated group, the IELs** in the duodenal crypt depths were under the control level (from 1 to 0.0) from the day 18 to the day 35. From the day 39 to the end of the experiment it was exactly as the control .i.e. the omega-3 treatment prevented the **IELs** to reach the control level. **Omega -3** was better in the correction of the **IELs** in the duodenal crypt depths as it started to be the same as the control from the day 39 to the end of the experiment.

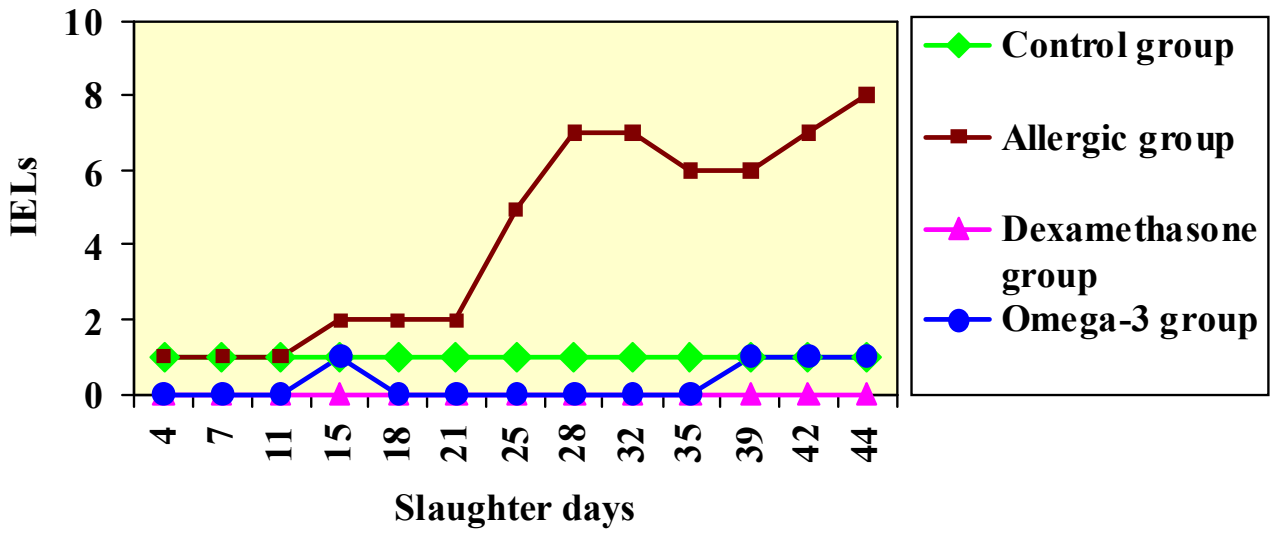


Figure (7): The mean number of intraepithelial lymphocytes per ten crypts of control, local allergic, dexamethasone and omega-3 treated duodenum

Dexamethasone treatment, from the day 4 to the day 15 did not correct the local allergic duodenal crypts depths .The crypts depths were lower significantly than the control level. From the day 18 to the day 32 the crypts depths were corrected as the control level. From the day 35 (from 105.25 to 120.08) to the day 42 (from 105.25 to 115.32) it were higher significantly than the control, to reach to the control level at the end of the experiment**; table (6) & figure (8).Omega -3 treatment** started significantly the correction from the day 11 (from 105.25 to 99.70 microns) to the day 18 (from 105.25 to 100.77 microns) to the control level. From the day 21(from 105.25 to 118.70) to the end of the experiment, it was higher significantly than the control due to atypical regeneration. **Omega-3** corrected the duodenal crypts depths 7 days earlier than dexamethasone treatment. The regeneration was more or less the same in both groups.

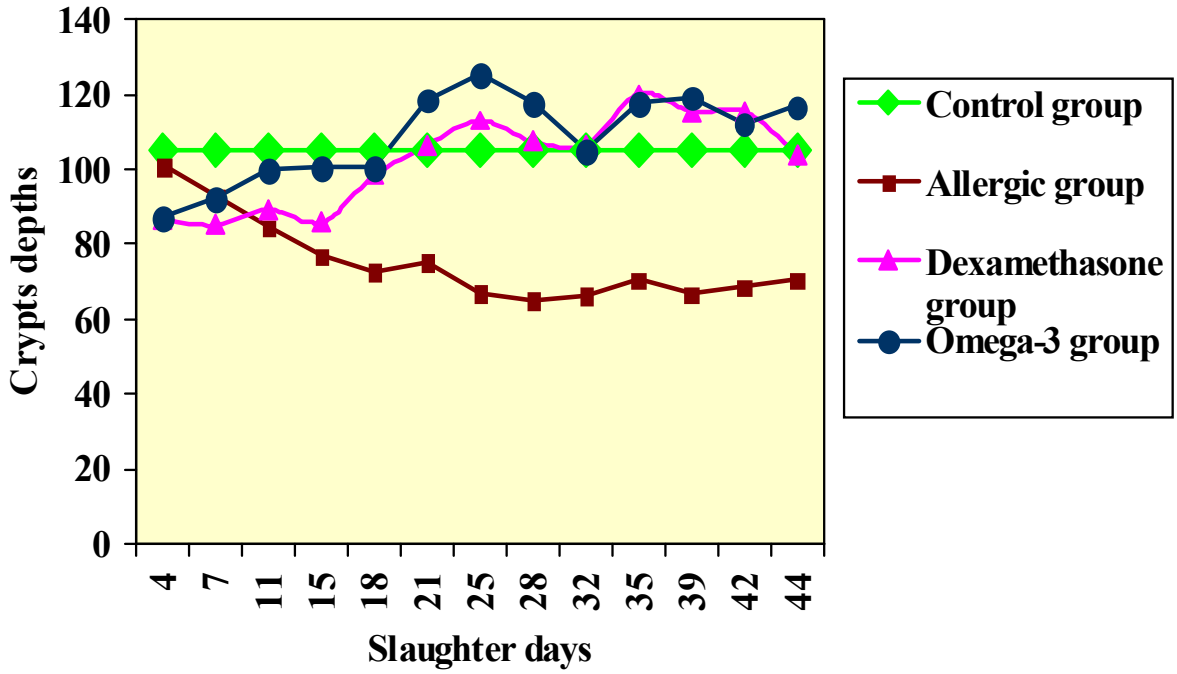
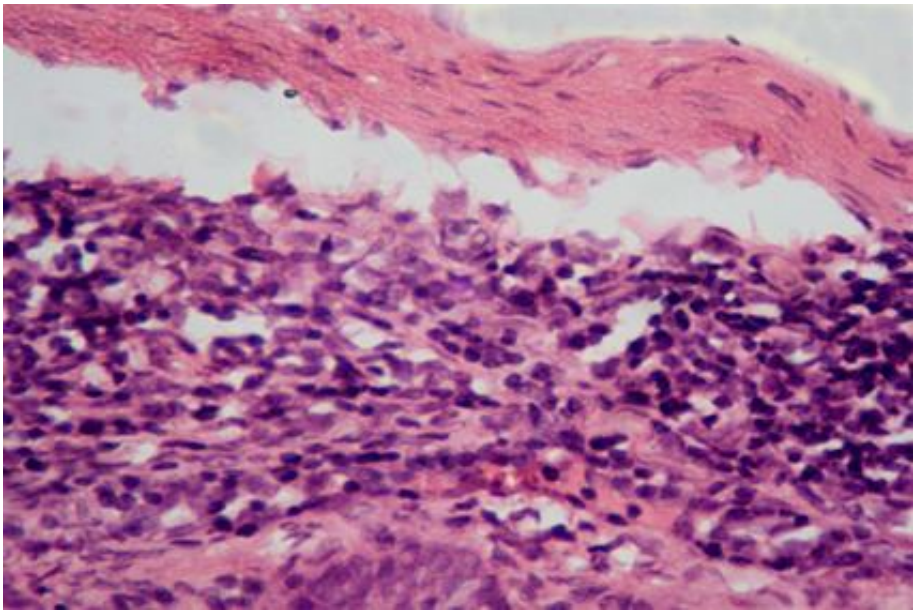
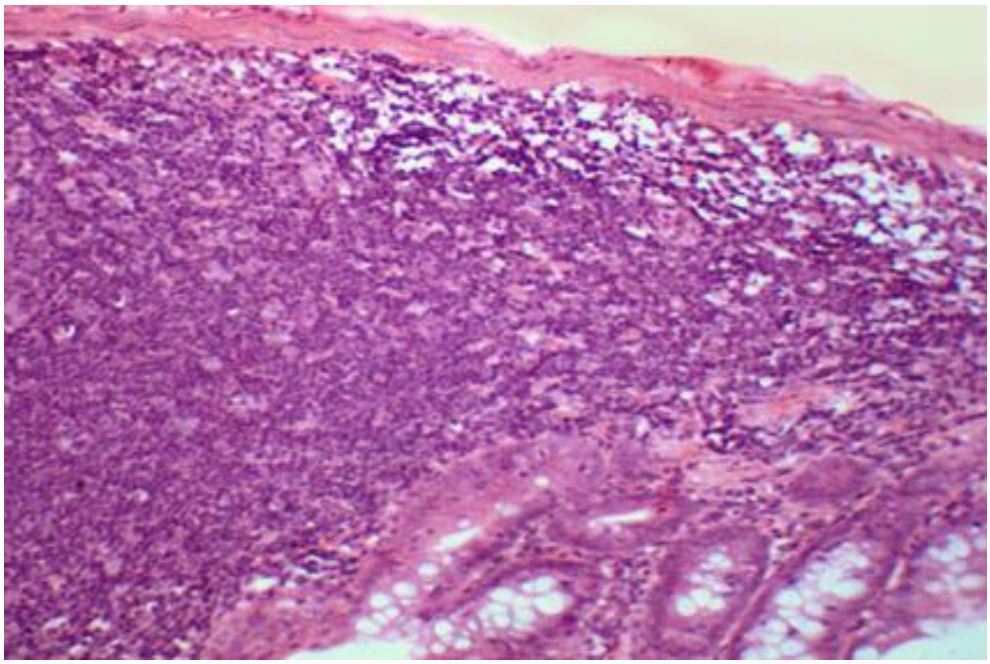


Figure (8): The length of crypts depths in microns of the control, local allergic, dexamethasone and omega-3, treated duodenum.

Lymphoid depletion was observed from the day 18 in the submucosa in the **dexamethasone treated group; picture (40). In omega-3** treated group the lymph follicles were transported to complete diffuse infiltration of the submucosa by mature lymphocytes at the day 18 and persist as such to the end of the experiment.



Picture (40): Dexamethasone treated local allergic duodenitis.
Lymphoid depletion in submucosa.
18 days post oral allergen H&E X25.



Picture (41): Omega-3 treated local allergic duodenitis.
Diffuse infiltration of the submucosa by mature lymphocytes
18 days post oral allergen H&E X10.

Allergic acute serous jejunitis

Within more or less normal epithelium, the IELs increased significantly in the jejunal villi from the day 4 and raised to reach its highest point at the day 10 (from zero to 13); earlier than the duodenum which raised sharply from the day 25 (from one to 12). The raising of the IELs in the jejunal villi continued allover the experimental period**; table (7) & figure (9).**

The jujenal villi heights significantly decreased from the day 4 to the end of the experiment**; table (8) & figure (10).**

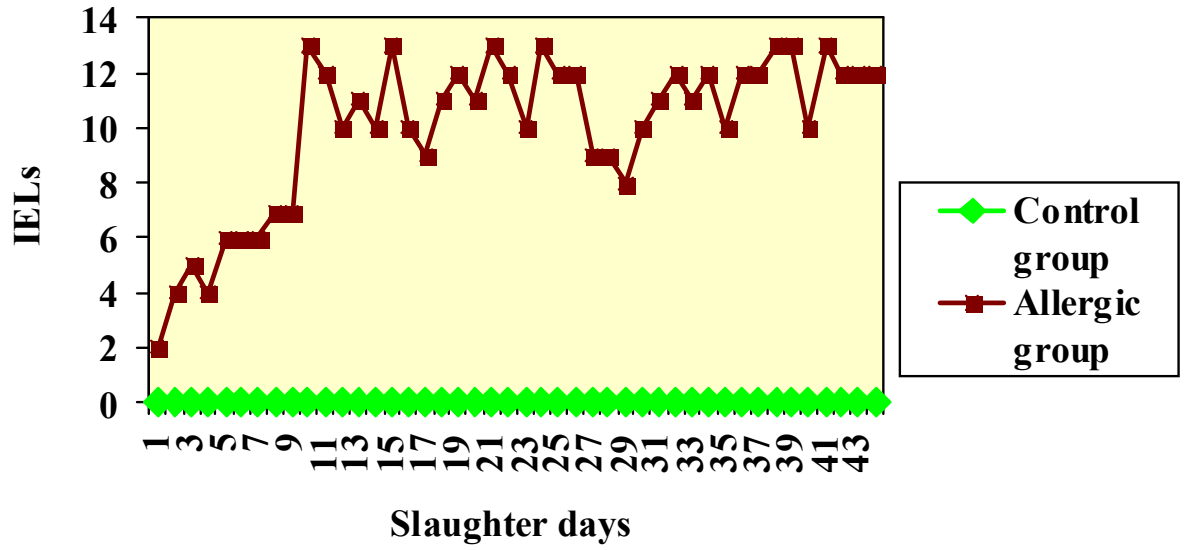


Figure (9): The mean number of intraepithelial lymphocytes per ten villi of control and local allergic jejunum.

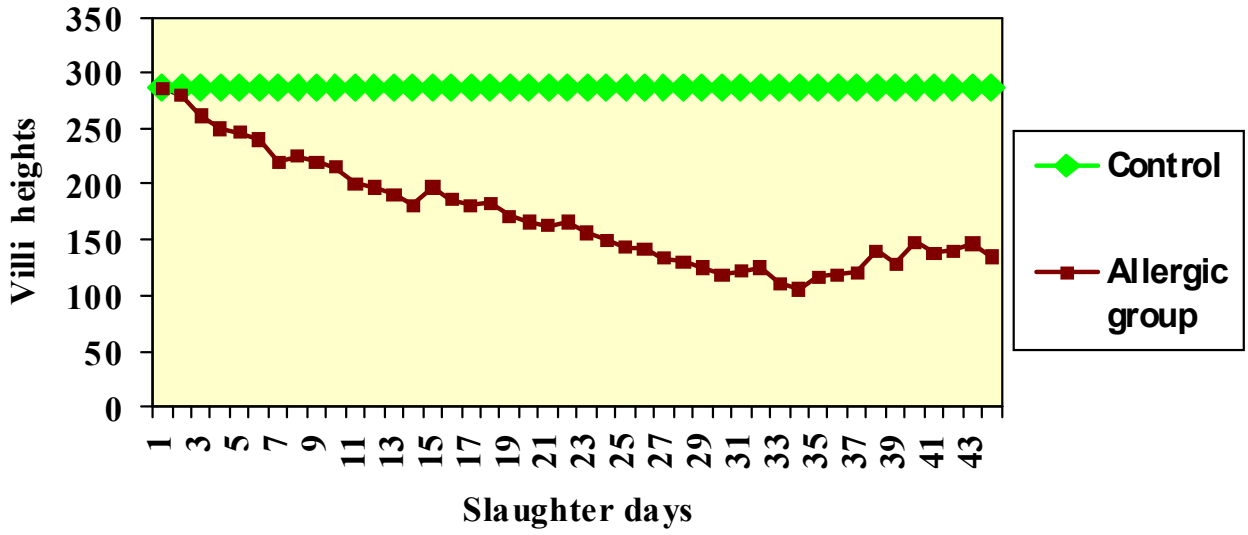


Figure (10): The length of villi heights in microns of the control and local allergic jejunum.

The IELs in the jejunal crypts started earlier from the day 4 (from zero to 3) than the duodenum; from the day 18 (from one to 2). The increase was more or less in steady level reaching 5; lower than the duodenum which was 7**; table (7) & figure (11).** That is to say, the **IELs** in the jejunal crypts started earlier from the subacute period than the duodenum which started in the chronic period.

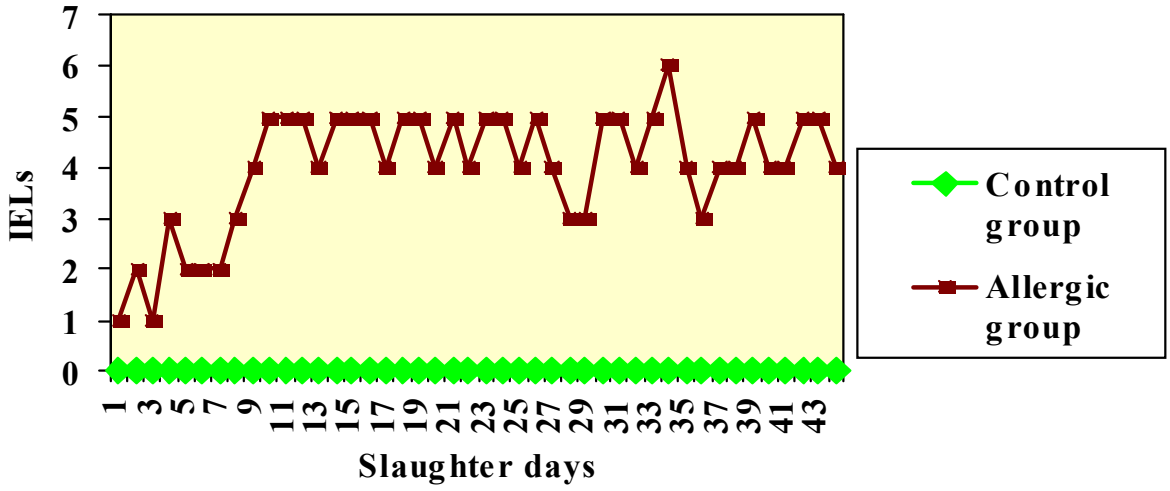


Figure (11): The mean number of intraepithelial lymphocytes per ten crypts of control and local allergic jejunum.

The crypts depths in the jejunum started to decrease significantly earlier from the day 4 visa versa to the duodenum from the day 6 and continued to decrease regularly to the end of the experiment in the same pattern**; table (8) & figure (12).**

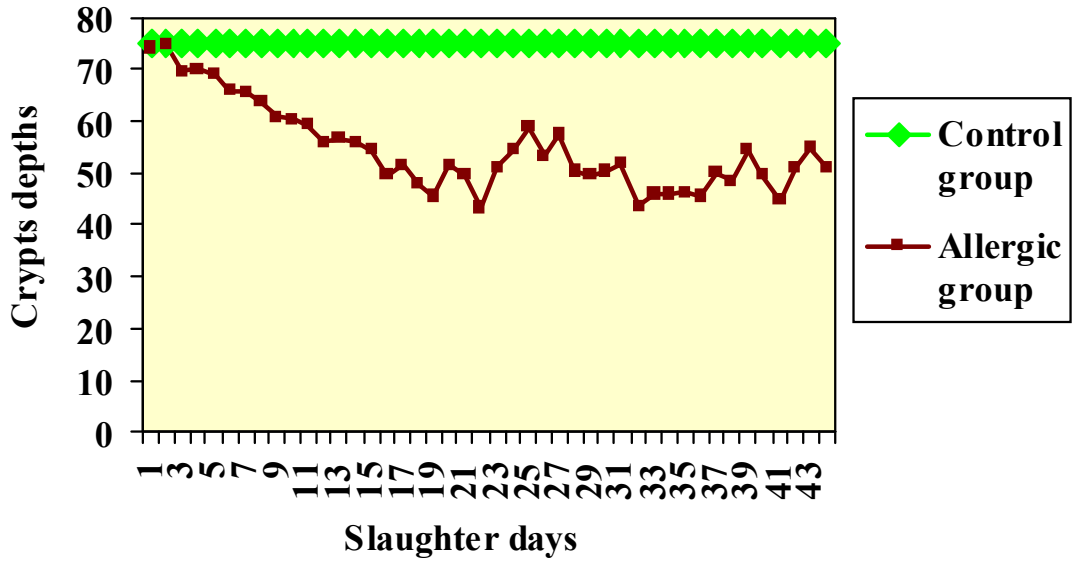
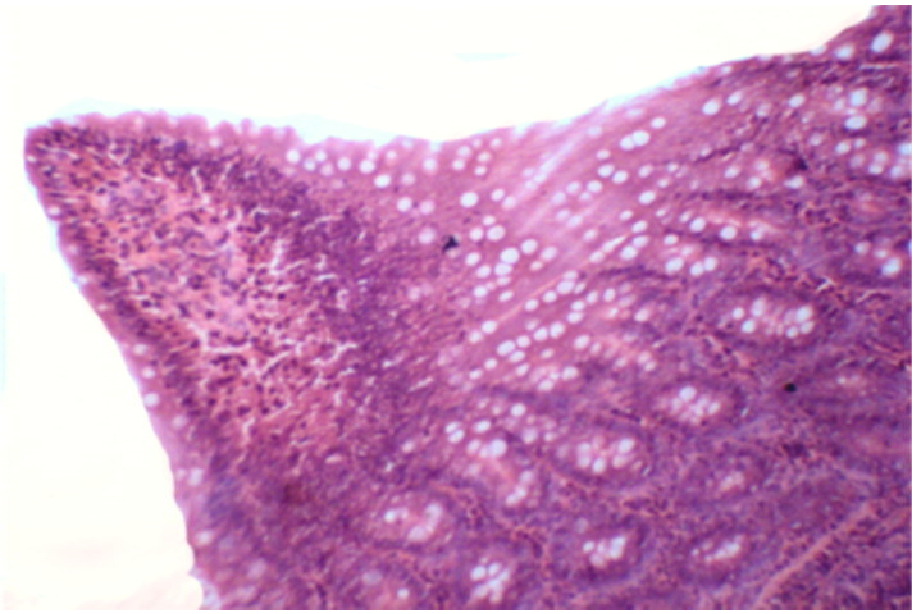


Figure (12): The length of crypts depths in microns of the **control and local allergic jejunum.**

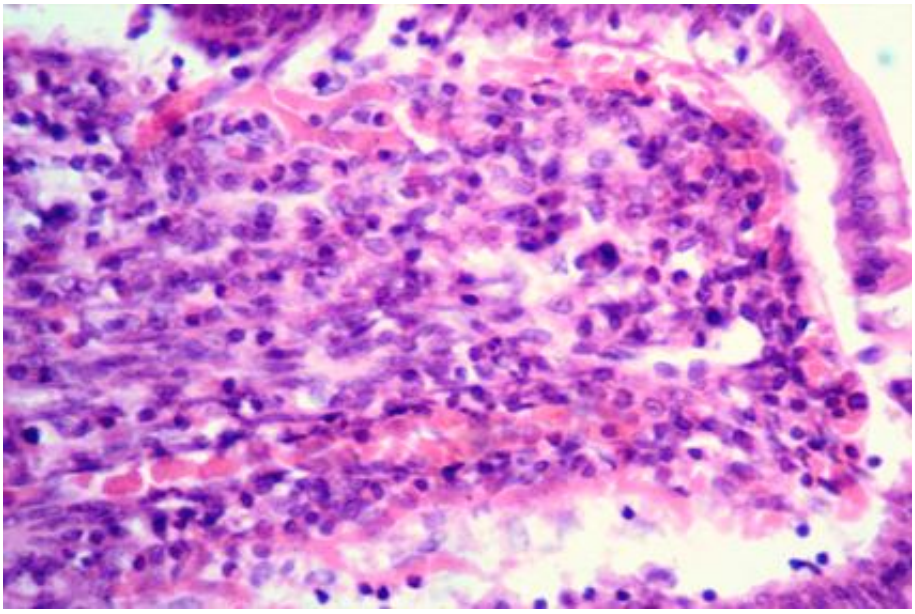
Allergic subacute serocatarrhal jujenitis

The atypical regeneration was demonstrated in the local allergic jejunum by villous hyperplasia and goblet cell metaplasia of the lining epithelium**; picture (42) .**Widening of the villous core was with hyperemia, edema and mononuclear cell infiltration**; picture (43).**These inflammatory changes leaded to abnormal villous shape**; picture (44) .**

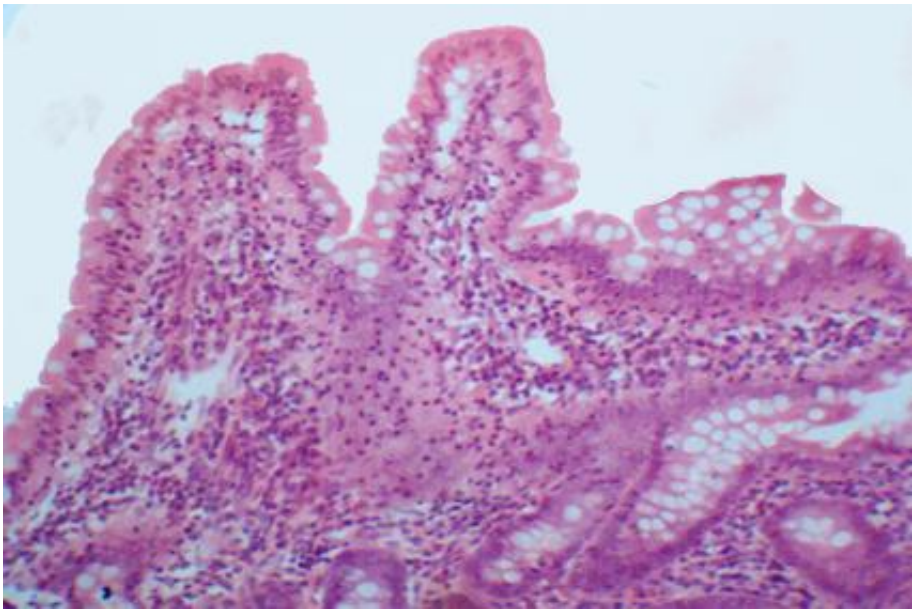
Beside the abnormal shaped villi, the lacteals were still widely dilated with segregation of the lymphocytes and serous exudate rich in lymphocytes separating the intestinal crypts**; picture (45).**



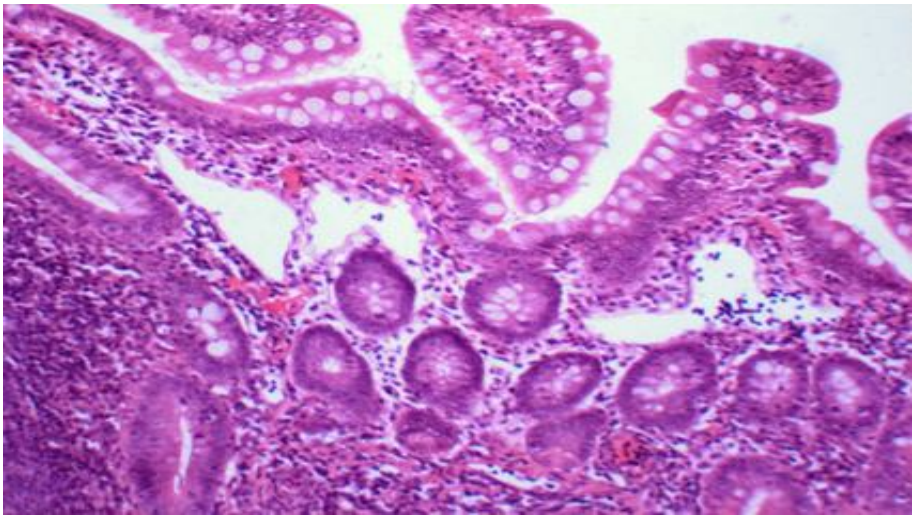
Picture (42): Local allergic subacute serocattahral jejunitis.
Goblet cells epithelial metaplasia .
13 days post oral allergen H&E X10.



Picture (43): Local allergic subacute serocattahral jejunitis.
Hyperemia, edema with monouclear cells infilteration.
14 days post oral allergen H&E X25.

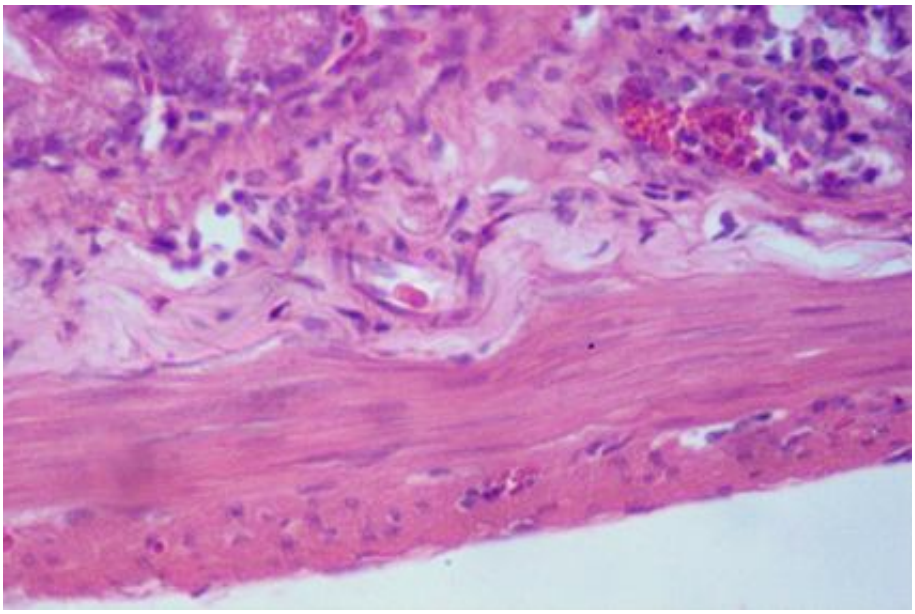


Picture (44): Local allergic subacute serocattahral jejunitis.
Broad branched abnormal villi shaped .
14 days post oral allergen H&E X10.

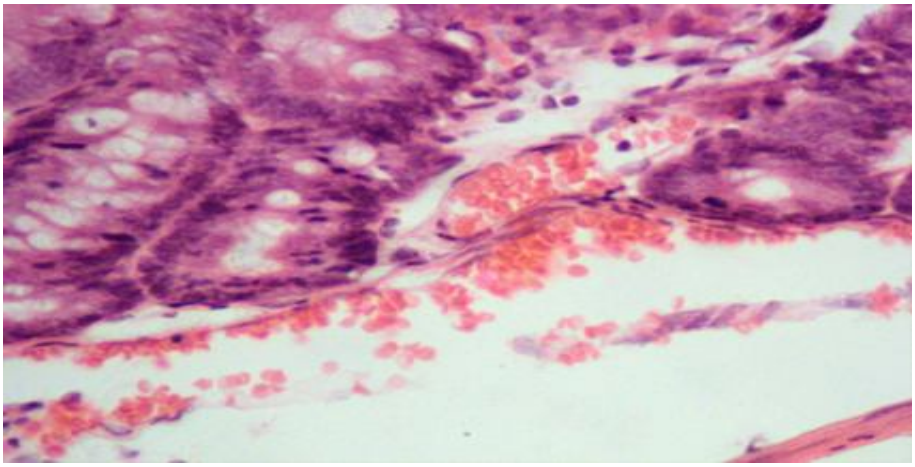


Picture (45): Local allergic subacute serocattahral jejunitis.
abnormal shaped villi with dilated lacteals , hyperemia and serous exudate between intestinal crypts .
14 days post oral allergen H&E X10.

The serous inflammatory exudate also involved the submucosa**; picture (46)** with submucosa hemorrhage**; picture (47).**

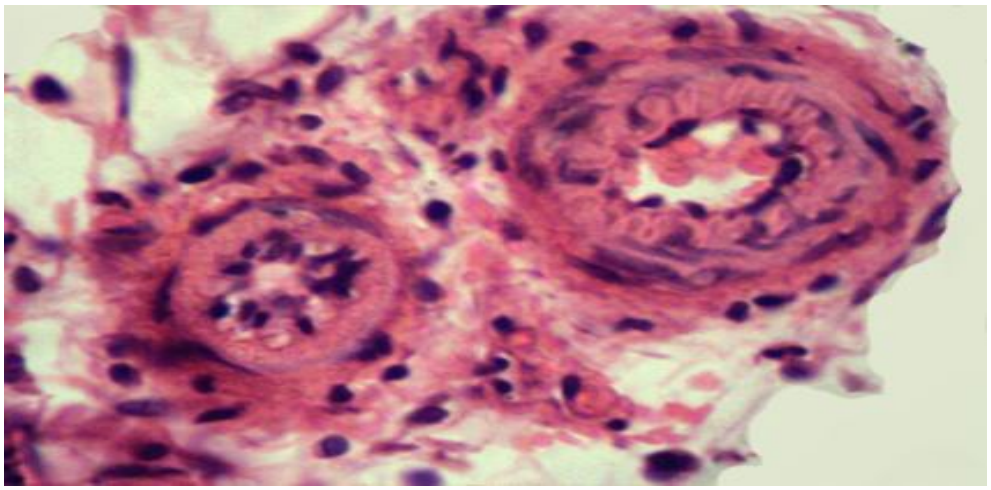


Picture (46): Local allergic subacute serocattahral jejunitis.
Submucosal serous exudate.
14 days post oral allergen H&E X25.



Picture (47): Local allergic subacute serocattahral jejunitis.
Hyperemia and hemorrhages in the lamina propria and submucosa
14 days post oral allergen H&E X25.

Serous arteritis was demonstrated by proliferation of endothelial cells, infiltration of muscular wall by inflammatory cells as well as periartetiolar infiltration**; picture (48).**

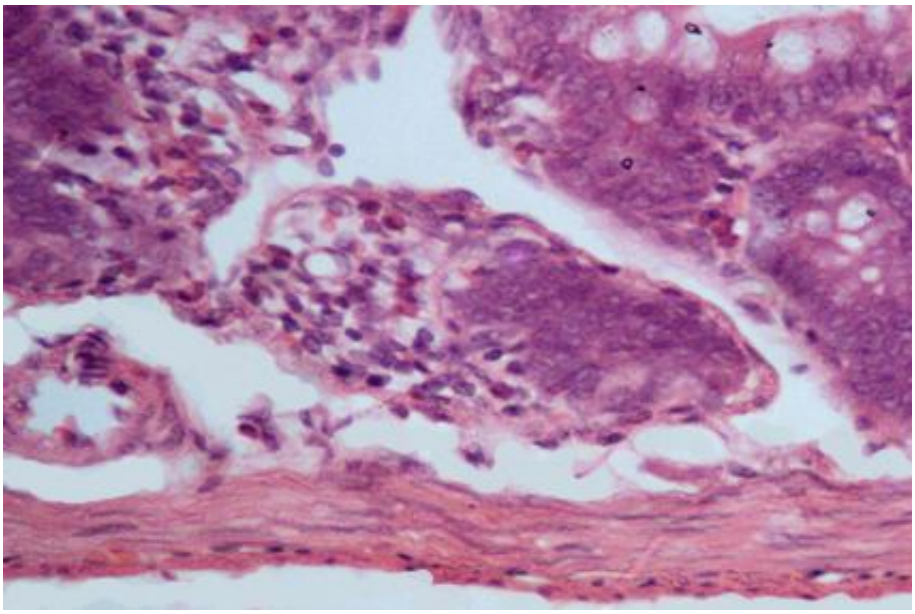


Picture (48): Local allergic subacute serocattahral jujenitis.
Serosal arteritis , endothelial proliferation and infilteration of the wall with inflammatory cells .
13 days post oral allergen H&E X40.

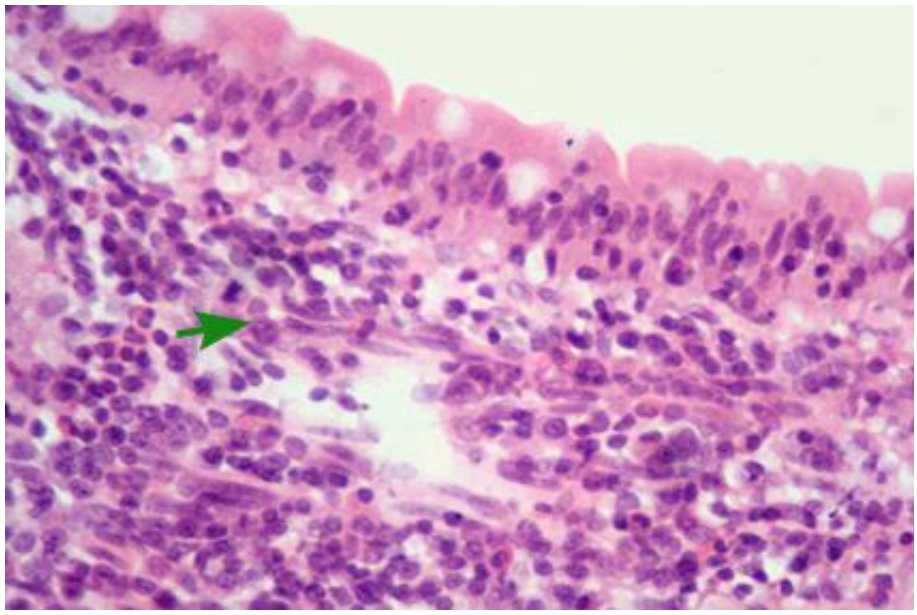
Allergic chronic catarrhal jejunitis

Differential for chronic jejunitis was the necrosis extending deeply to involve the intestinal crypts; **picture (49),** the exceeding number of IELs together with the appearance of fibrocytic proliferation between the mononuclear cells of the villous core**; picture (50)** and the fibroblastic proliferation in the submucosa**; picture (51).**

Hemorrhages were present between the intestinal crypts and in the submucosa**; picture (52).**



Picture (49): Local allergic chronic cattahral jejunitis.
Necrosis involving intestinal crypts .
20 days post oral allergen H&E X25.

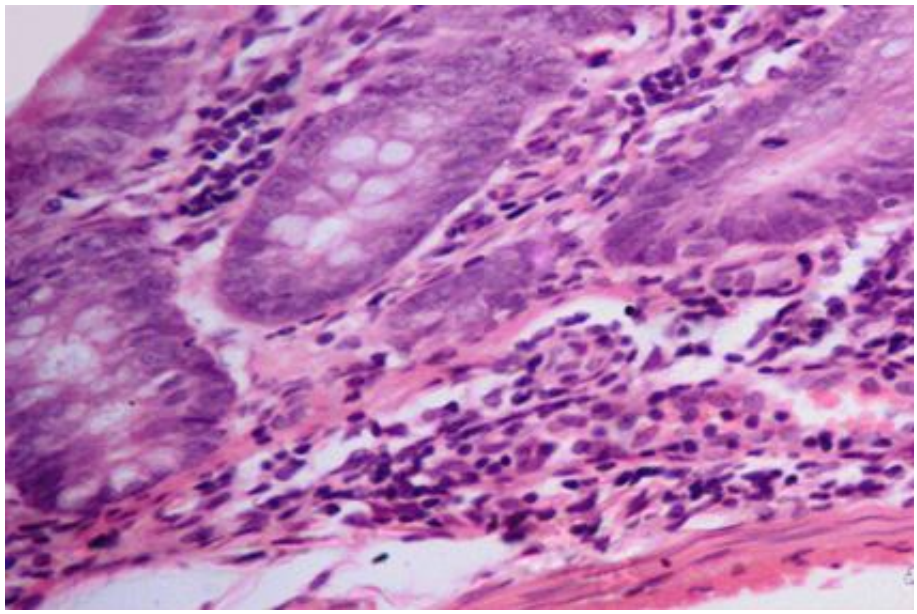


Picture (45):Local allergic chronic cattahral jujenitis.

IELs with fibrocytic proliferation and mononuclear cells

Infilterating villi cores.

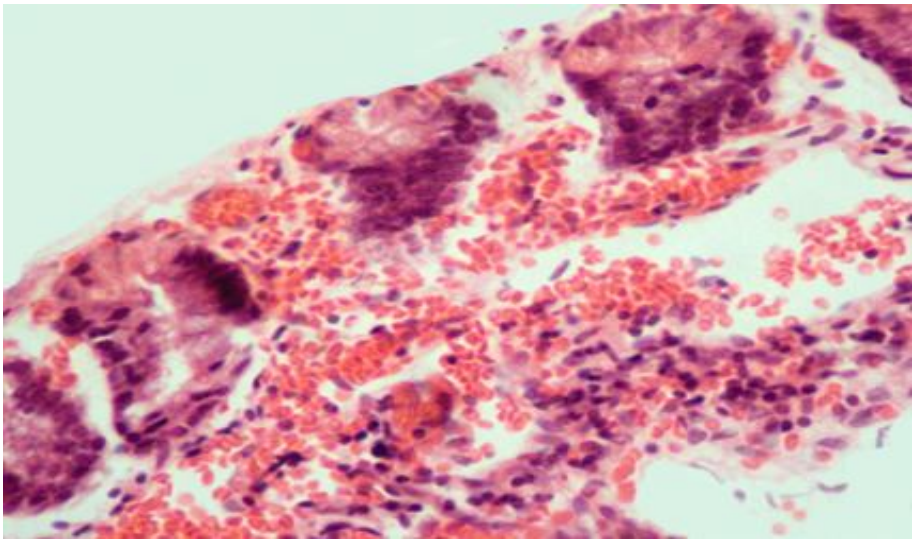
18 days post oral allergen H&E X25.



Picture (51): Local allergic chronic cattahral jujenitis.

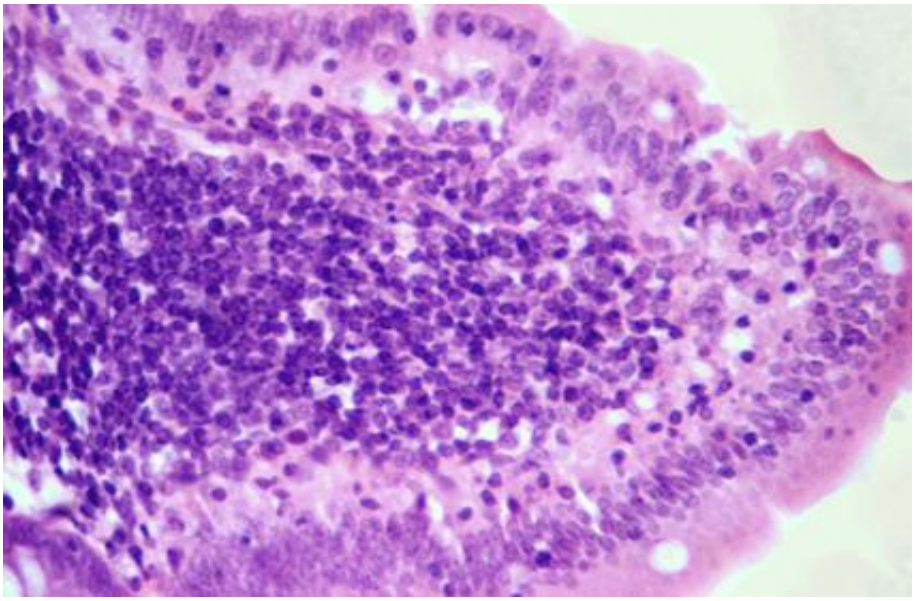
Fibroblastic proliferation in the submucosa .

20 days post oral allergen H&E X25.

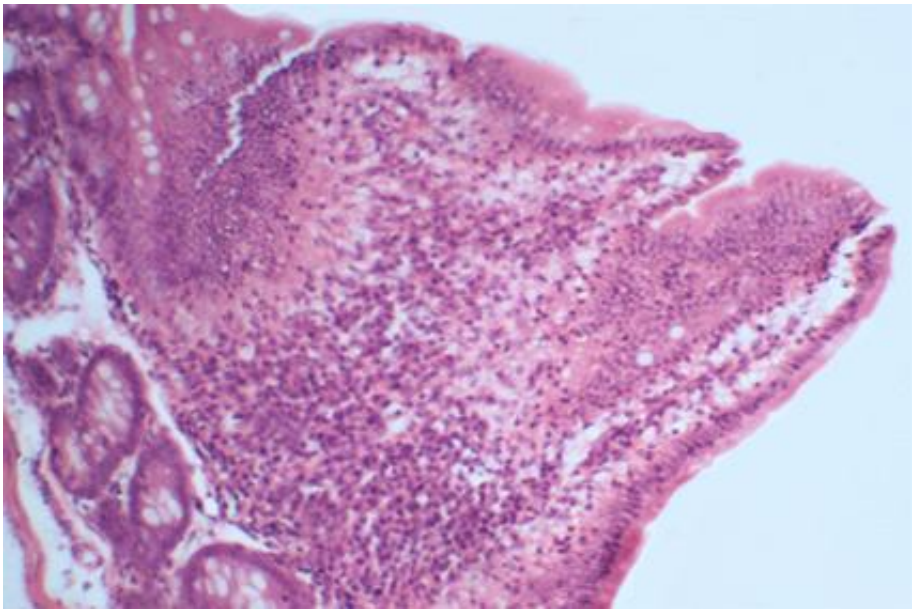


Picture (52): Local allergic chronic cattahral jejunitis.
Hemorrhages between intestinal crypts and submucosa .
34 days post oral allergen H&E X25.

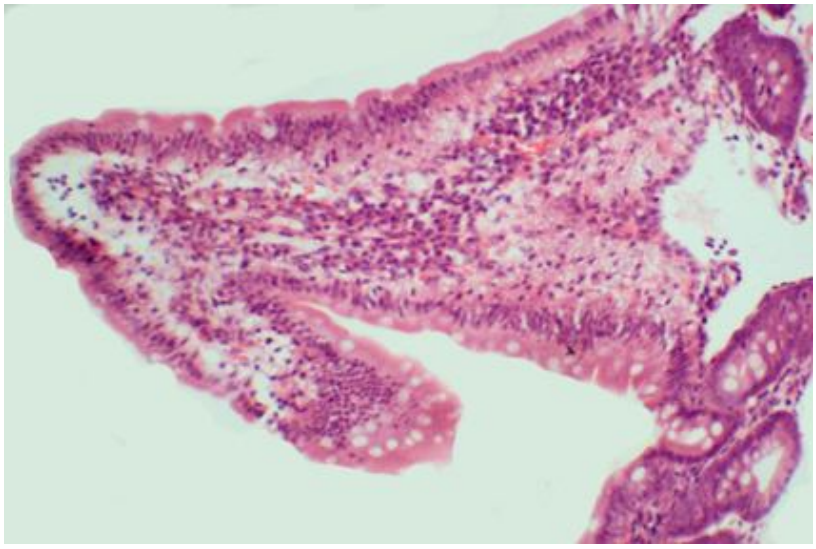
The lymphocytic infiltration of the villi core became intensive and leaded to wide extension of the villi width**; picture (53).** These processes leaded to severe changes of the villi shape, like fusion **; picture (54)** and branching**; picture (55).**



Picture (53): Local allergic chronic cattahral jujenitis.
Lymphocytic infelteration in the villous core.
21 days post oral allergen H&E X40.

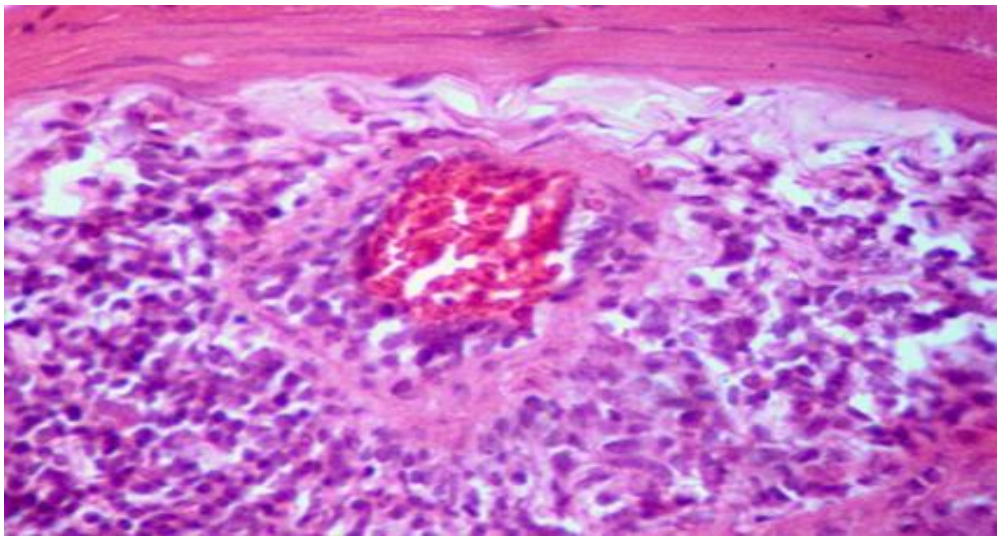


Picture (54): Local allergic chronic cattahral jejunitis.
Villous fusion.
25 days post oral allergen H&E X10.

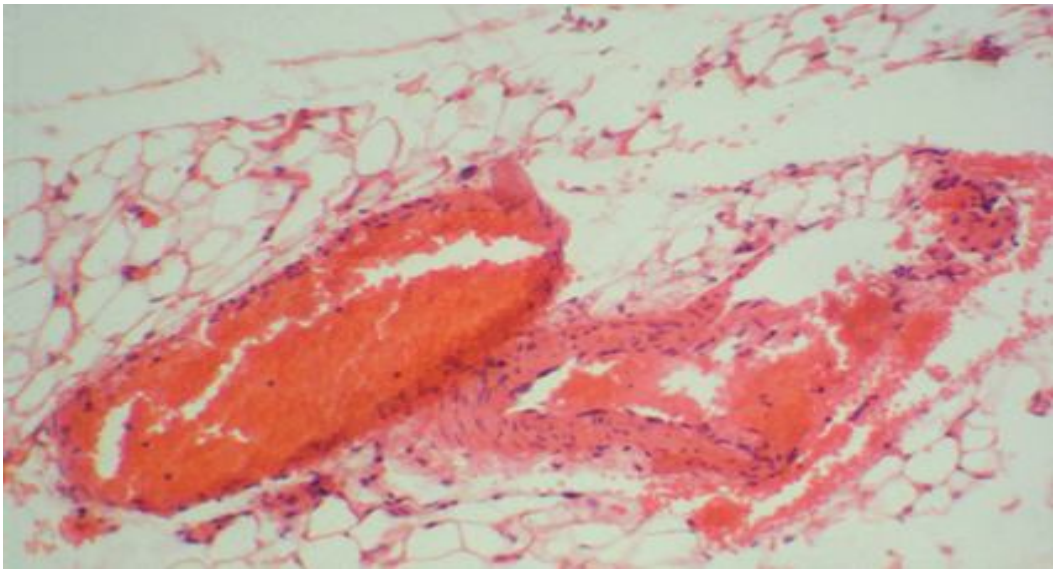


Picture (55): Local allergic chronic cattahral jejunitis.
Villous branching .
25 days post oral allergen H&E X10.

Very characteristic for chronic jejunitis was the type III allergic vasculitis which was manifested in the form of diffuse fibrinoid necrosis of the wall with inflammatory cells infiltration**; picture (56).** Diffuse and severe thrombosis of serosal blood vessel was seen**; picture (57).**



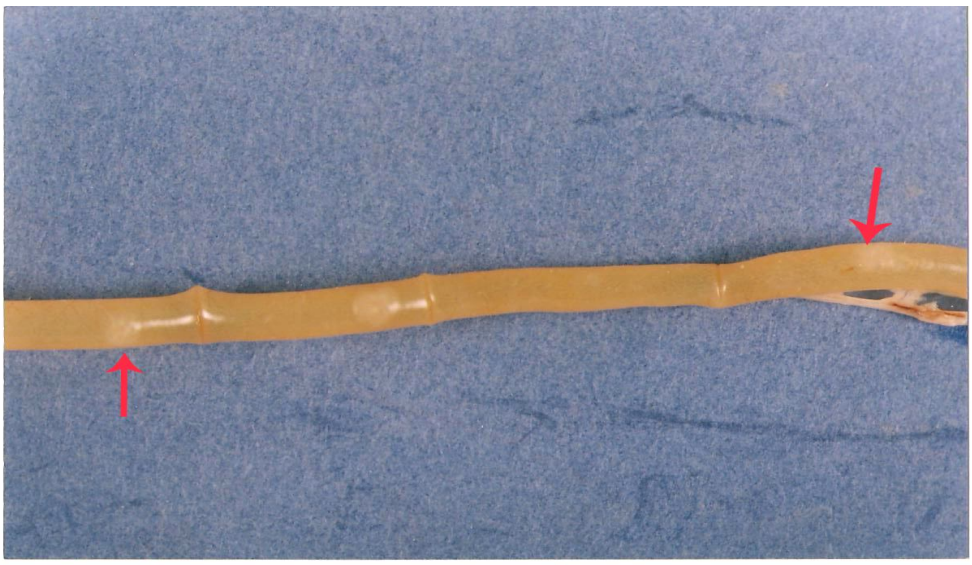
Picture (56) :Local allergic chronic cattahral jejunitis.
Vasculitis with fibrinoid necrosis.
41 days post oral allergen H&E X 25.



Picture (57): Local allergic chronic cattahral jejunitis.
Diffuse and sever thrombosis of serosal blood vessel.
38 days post oral allergen H&E X 10 .

Dexamethasone and omega -3 treated jejunum

Grossly both treatments caused relative subsiding of hyperemia and lymphoid follicles in the jejunum; **picture (58&59).**



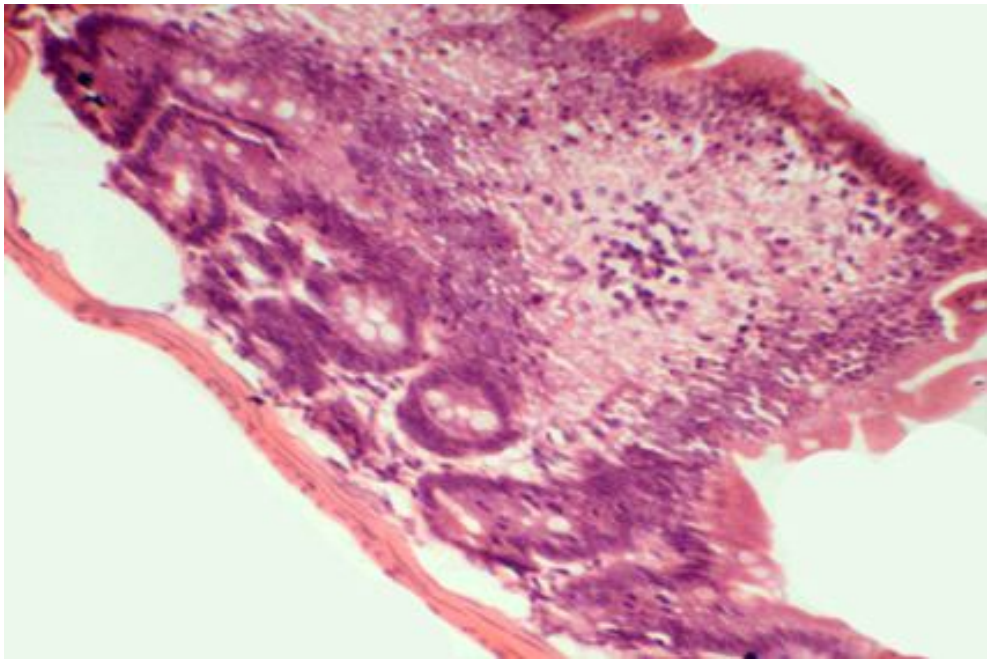
Picture (58): Dexamethasone treated local allergic jejunitis.

Subsiding of hyperemia and depletion of lymphoid follicles (➔).

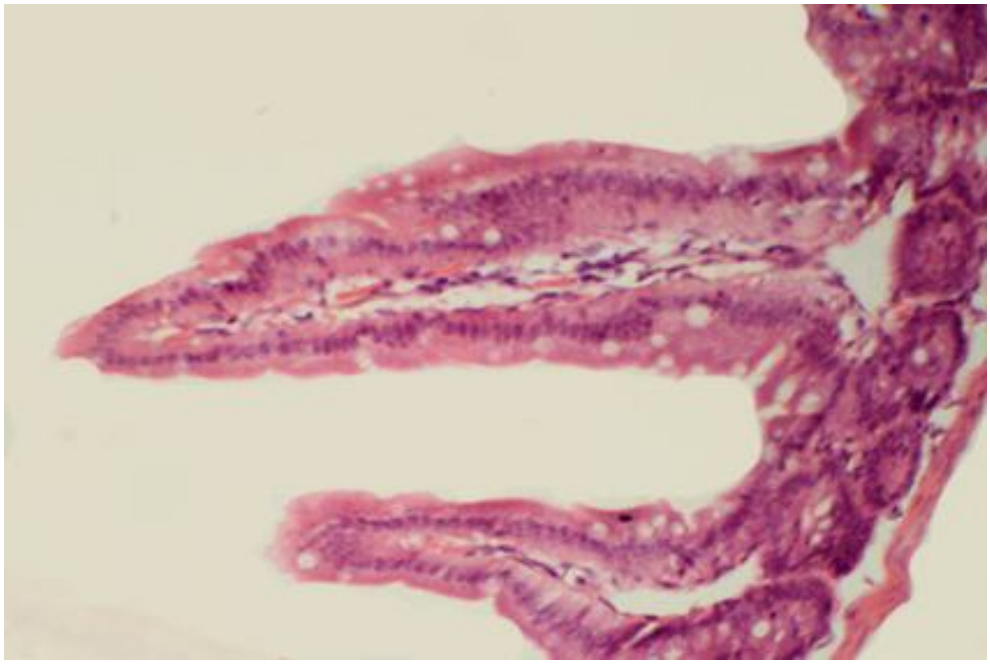
Picture (59): Omega-3 treated local allergic jejunitis.

Subsiding of hyperemia and depletion of lymphoid follicles.

Dexamethasone treatment corrected significantly ; from the day 4 the epithelial damage, the increase of **IELs** and the inflammatory cells in the core of the jejunal villi **;picture (60)** to be decreased to reached to the control level at the day 25**;picture (61). Omega-3 treatment** corrected significantly; from the day 4; the epithelial damage, the increase of **IELs** and inflammatory cells in the villi core of the jejunal villi but to a lesser degree**; picture (62)** and reached to normality latter on the day 32**;picture (63).** The counting of **IELs** confirmed the relative subsiding of inflammatory cells**; picture (60&62).**



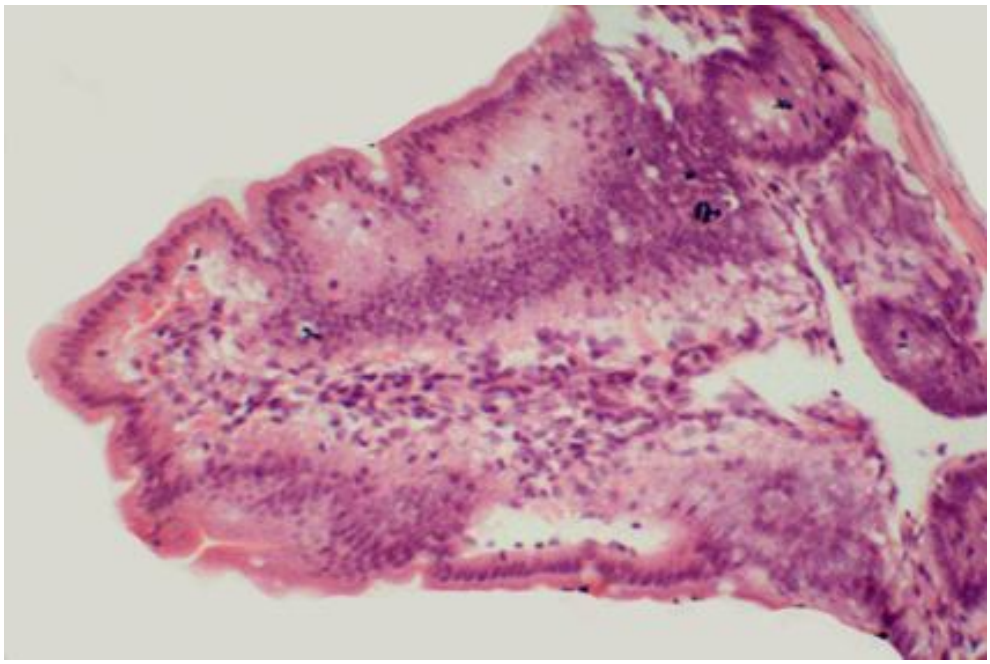
Picture (60): Dexamethasone treated local allergic jejunitis.
Relative subsiding of inflammatory cells in the villi core.
18 days post oral allergen H&E X 10.



Picture (61): Dexamethasone treated local allergic jejunitis.

Nearly normal villi.

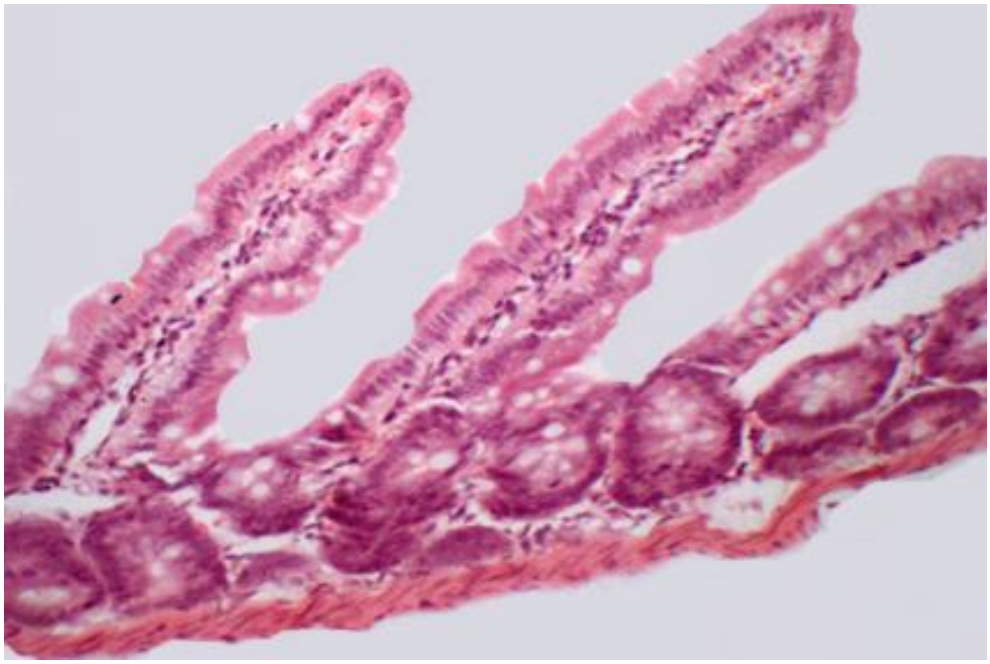
25 days post oral allergen H&E X 10.



Picture (62): Omega -3 treated local allergic jejunitis.

Relative subsiding of inflammatory cells in abnormal shaped villi.

18 days post oral allergen H&E X 10.



Picture (63): Omega -3 treated local allergic jejunitis
More or less normal regenerated villi.
32 days post oral allergen H&E X 10.

Dexamethasone treatment corrected significantly the increase of **IELs** in the jejunal villi from the day 4 (from zero to 3) to be decreased regularly to the day 25 where it reached the control level**; table (9) & figure (13).**

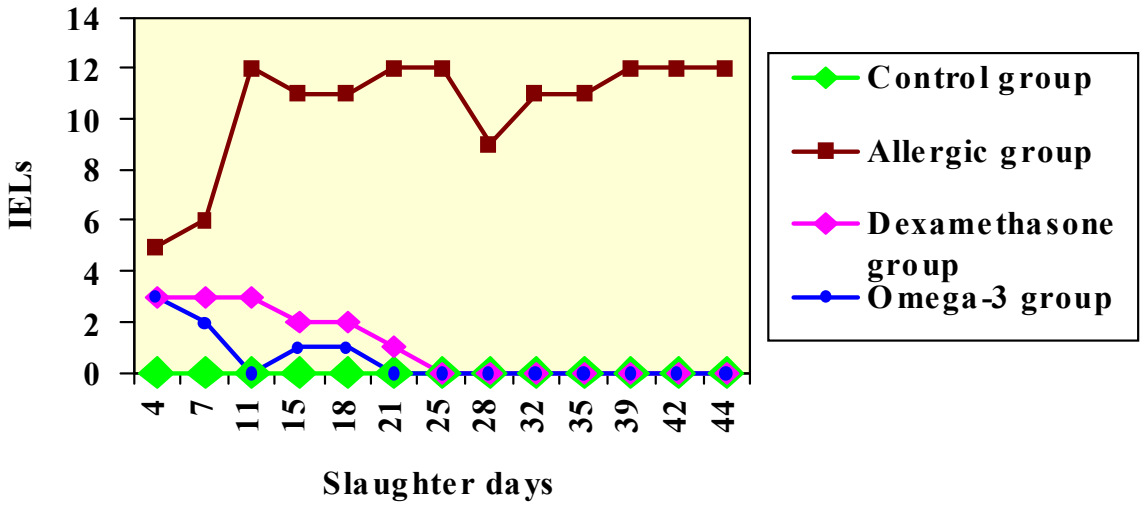


Figure (13): The mean number of intraepithelial lymphocytes per ten villi of control, local allergic, dexamethasone and omega-3 treated jejunum.

Omega-3 treatment corrected significantly the increase of **IELs** in the jejunal villi from the day 4 (from zero to 3)) to be decreased regularly to the day 21; earlier than the correction of the epithelial damage and villi shape ;where it reached to the control level and to the end of the experiment.

Dexamethasone treatment corrected significantly to the control level the decrease in the jejunal villi heights from the day 18 (from 286.14 to 268.73) to the end of the experiment (from 286.14 to 304.23 microns**); table (11) & figure (15).Omega -3 treatment** corrected significantly to the control level the decrease in the jejunal villi heights from the day 7 (from 286.14 to 282.27 microns) to the day 35 to reach 298.52 microns, then became slightly higher to the end of the experiment where it was 327.04 microns**; picture (64) .**

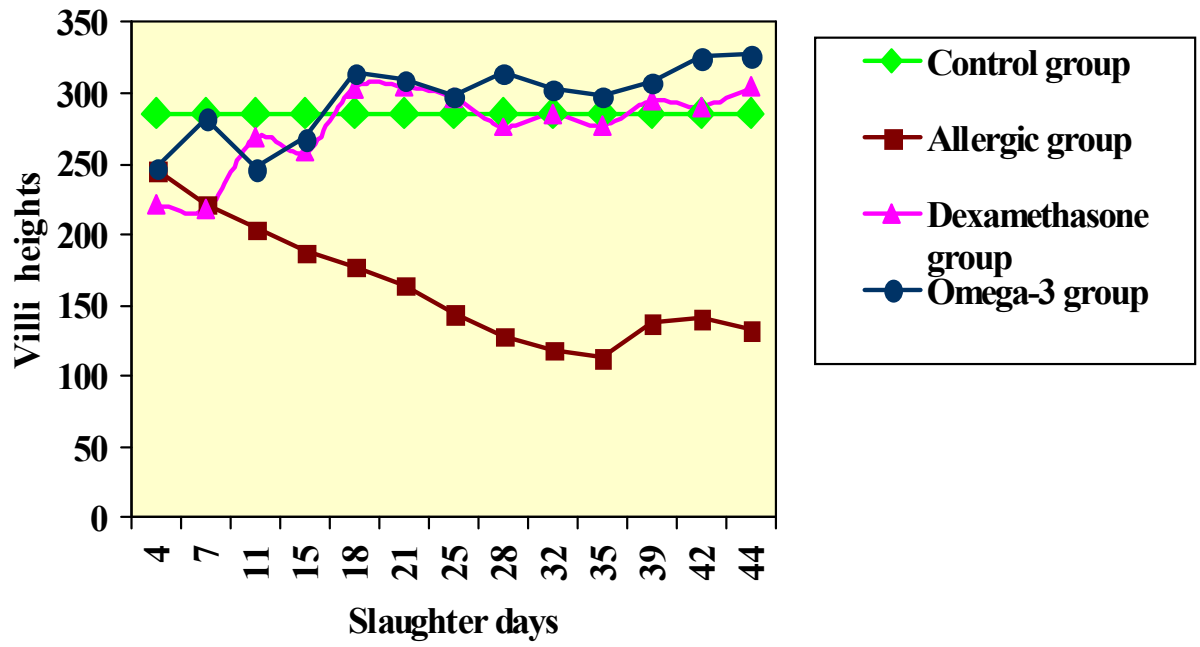
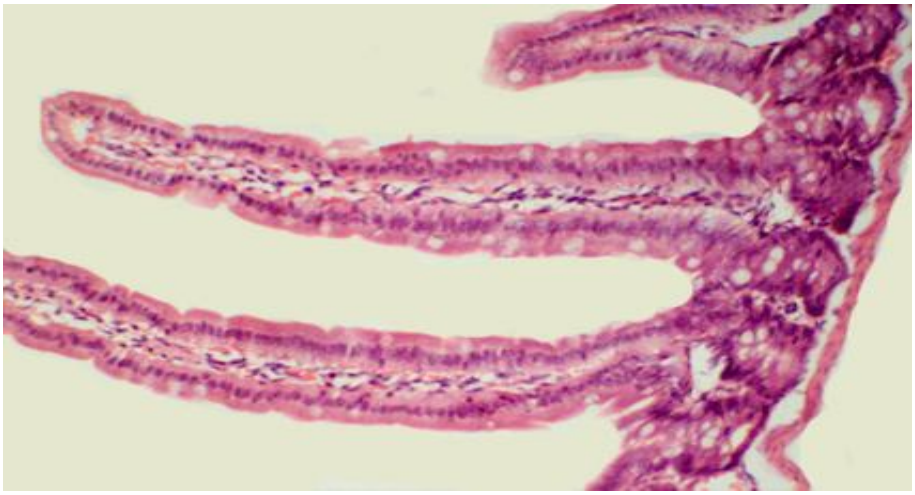


Figure (15): The length of villi heights in microns of the control, local allergic, dexamethasone and omega-3 treated jejunum.



Picture (64): Omega -3 treated local allergic jejunitis.

More or less normal regenerated villi but relatively higher.

35 days post oral allergen H&E X 10.

Dexamethasone treatment corrected significantly the increase of **IELs** in the jejunal crypts from the day 11 (from 0.0 to one).This was in steady level to the day 21 then decreased to the normal at the day 25 and to the end of the experiment**; table (10) & figure (14). Omega -3 treatment** corrected significantly the increase of **IELs** in the jejunal crypts from the day 11 (from zero to one). This was in steady level to the day 15 and then decreased to the normal at the day 18 and to the end of the experiment.

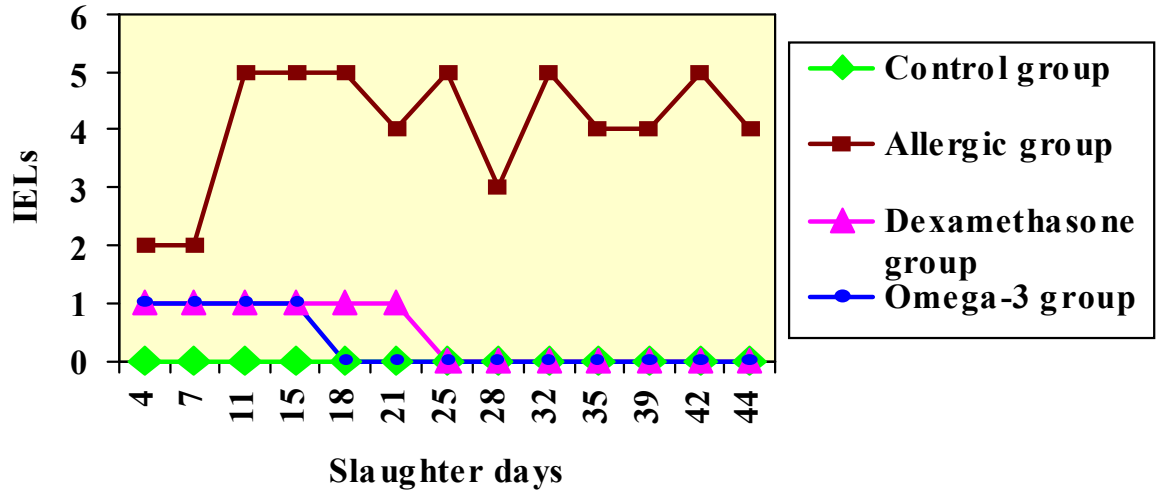


Figure (14): The mean number of intraepithelial lymphocytes per ten crypts of control , local allergic, dexamethasone andomega-3 teated jejunum.

Dexamethasone treatment corrected significantly to the control level the decrease of **the jejunal crypts depths** from the day 11 (from 74.97 to 75.97 microns) and then more or less higher (from 74.97 to 93.70 microns) to the end of the experiment**; table (12) & figure (16).Omega -3 treatment** corrected significantly the decrease of the **jejunal crypts depths** from the day 7 (from 74.97 to 83.76 microns) which was higher than the control level and in the same pattern more or less to the end of the experiment (from 74.97 to 86.43microns) .Although the omega -3 treatment corrected earlier but atypical regeneration was expressed more than in the dexamethasone treated group.

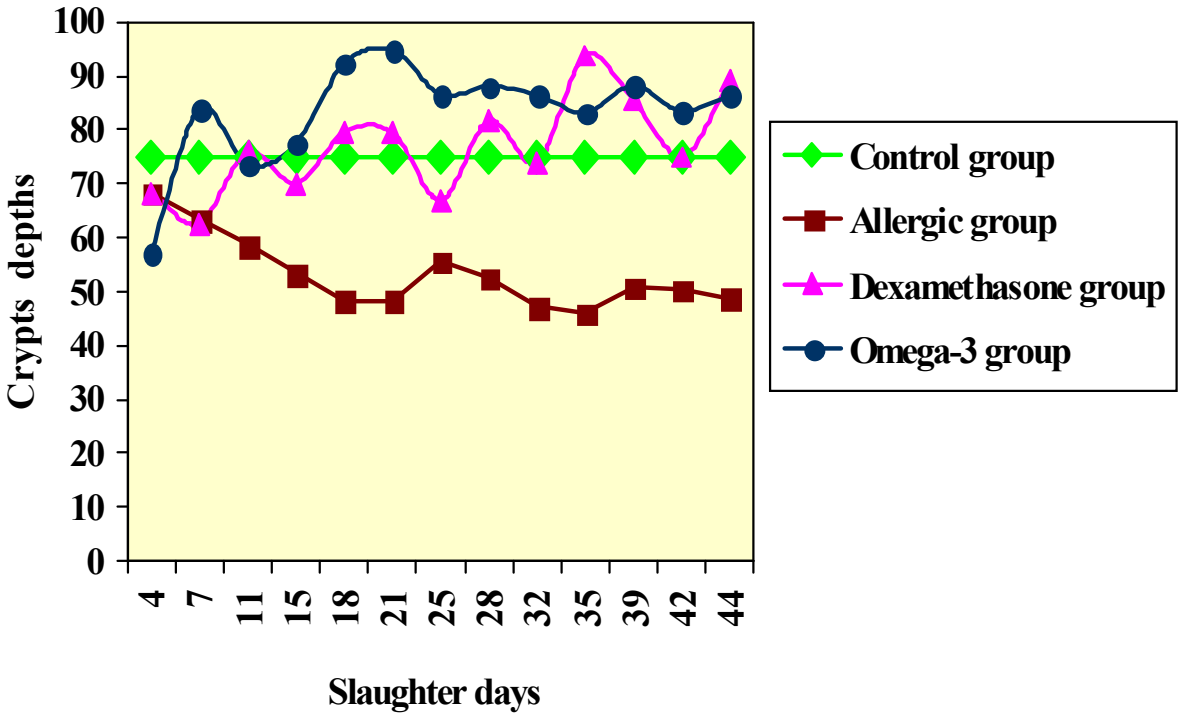
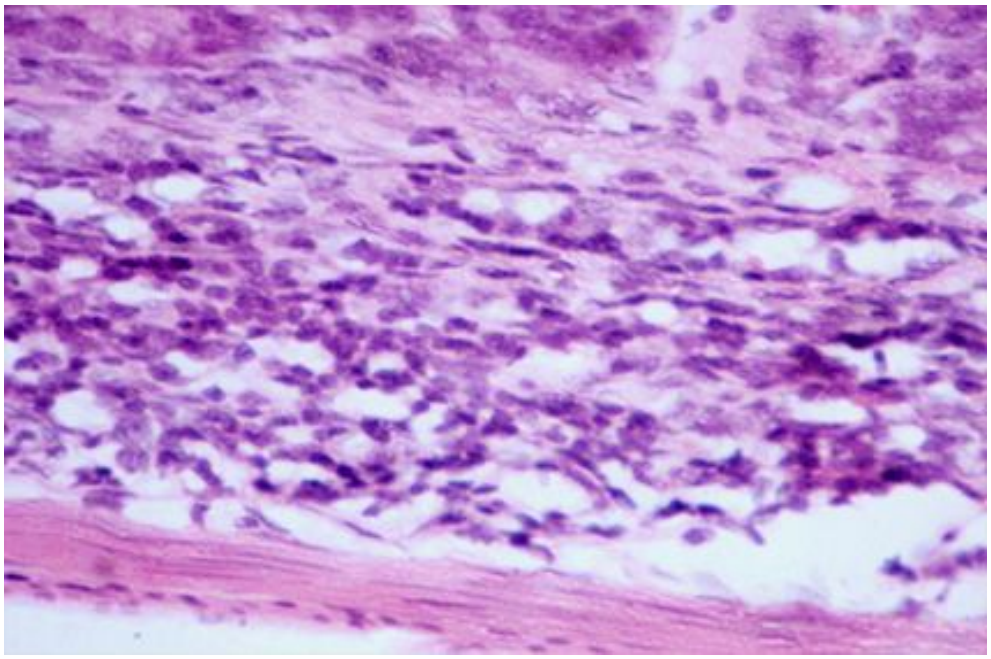


Figure (16): The length of crypts depths in microns of the control, local allergic, dexamethasone and omega-3 and treated jejunum.

Omega-3 treatment was better than dexamethasone in the correction of **IELs** in the jejunal villi because it reached to the control level earlier at the day 21, in the correction of **IELs** in the jejunal crypts because it reached to the control level earlier at the day 18 and in the correction of jejunal **villi heights** because it reached to the control level 11 days earlier. **Dexamethasone**

treatment was better than the omega -3 treatments in the correction of the jejunal **crypts depths** because atypical regeneration was expressed in the omega -3 treated group more than in the dexamethasone treated group although the omega -3 correction was earlier at the day 7.

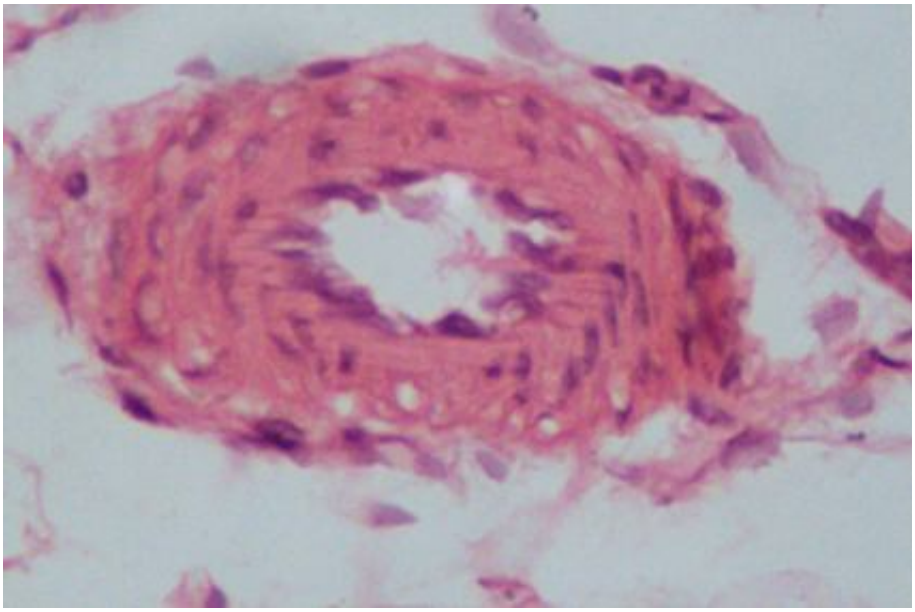
In dexamethasone treated jejunum, although the normality of the intestine was more or less reached, the submucosal lymph follicles demonstrated the picture of resting follicles until the day 25. After the day 25 the lymphocytes were severely exhausted**; picture (65). In omega-3 treated jejunum** no exhaustion was recorded.



Picture (65): Dexamethasone treated local allergic jejunitis.
Lymphoid depletion in the submucosa.
25 days post oral allergen H&E X 25.

Allergic acute serous ileitis

Differential for the ileum was the appearance of allergic vasculitis early in the acute phase at the day 5. The arterioles showed endothelial damage and proliferation and the necrosed wall with infiltration by inflammatory cells**; picture (66)**.



Picture (66): Local allergic acute serous ileitis.
Vasculitis with partial destruction and proliferation of the endothelium and infiltration of the necrosed wall by Inflammatory cells.
5 days post oral allergen H&E X40.

IELs of the ilial villi in the allergic group, increased significantly from the day 4 (from zero to 5) and was more or less steady to the day 21 (5) then raised to the highest peak at the day 29 (20) and more or less high to the end of the experiment **; table (13) & figure (17).The reaction** was more or less the same between the three intestinal segments in that the raising passed more or less in steady period and then reach to a peak which was late in the ileum as the antigen physiologically reached this segment at the end of the digestion.

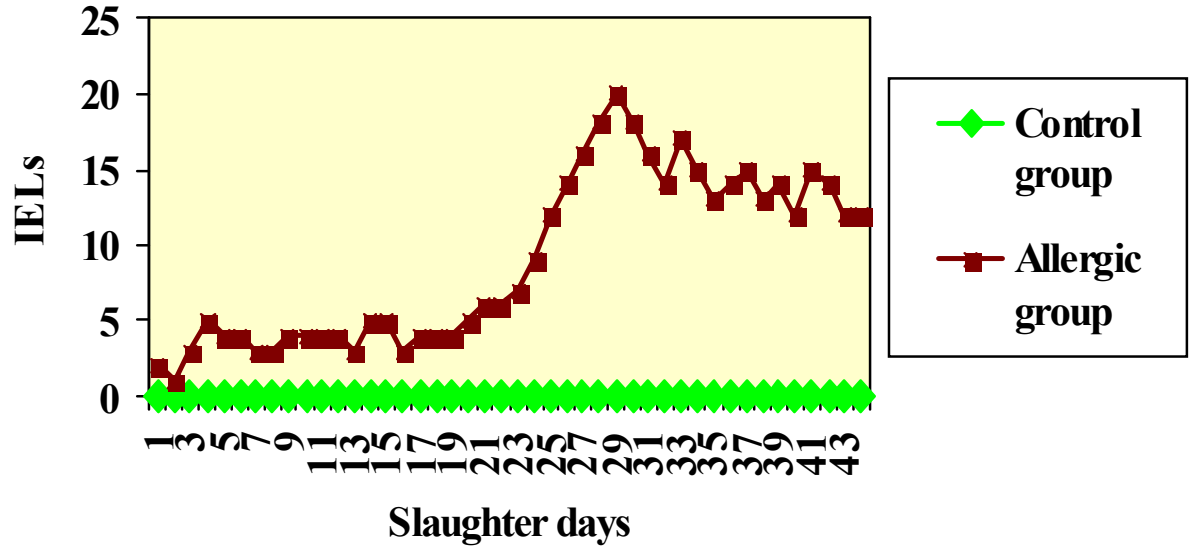


Figure (17): The mean number of intraepithelial lymphocytes per ten villi of control and local allergic ileum.

In the allergic group, the ileal **villi heights** decreased significantly than the control from the day 4 (from 202.72 to 170.79 microns) regularly to the end of the experiment**; table (14) & figure (18).** This reaction was more or less the same to the other intestinal segments, the duodenum and jejunum.

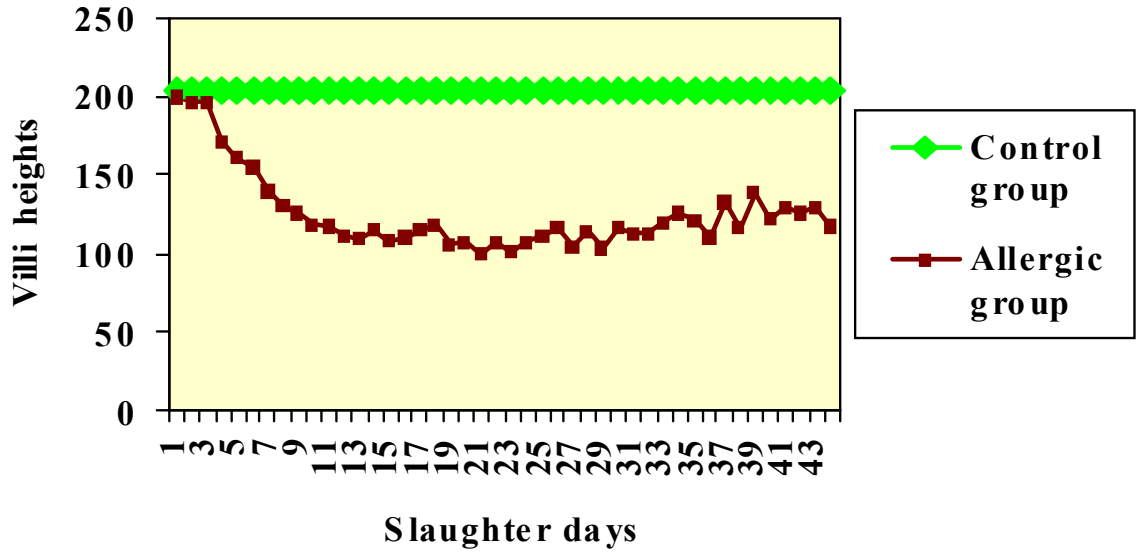


Figure (18) The length of villi heights in microns of control and local allergic ileum.

The IELs of the ileal crypts in the allergic group started to raise significantly at the day 4 (from 0.0 to 2).The increase was more or less steady to the day 24 (5) then raising abruptly to a higher peak more or less to the day 41 & 42 (7) **;table (13)&figure(19).The jejunum rising of the crypts IELs** was at the day 10 earlier than the raising of the crypts IELs in the duodenum at the day 21 and of the ileum at the day 24. This probably may be explained by the time for the antigen exposure and presentation to the cells.

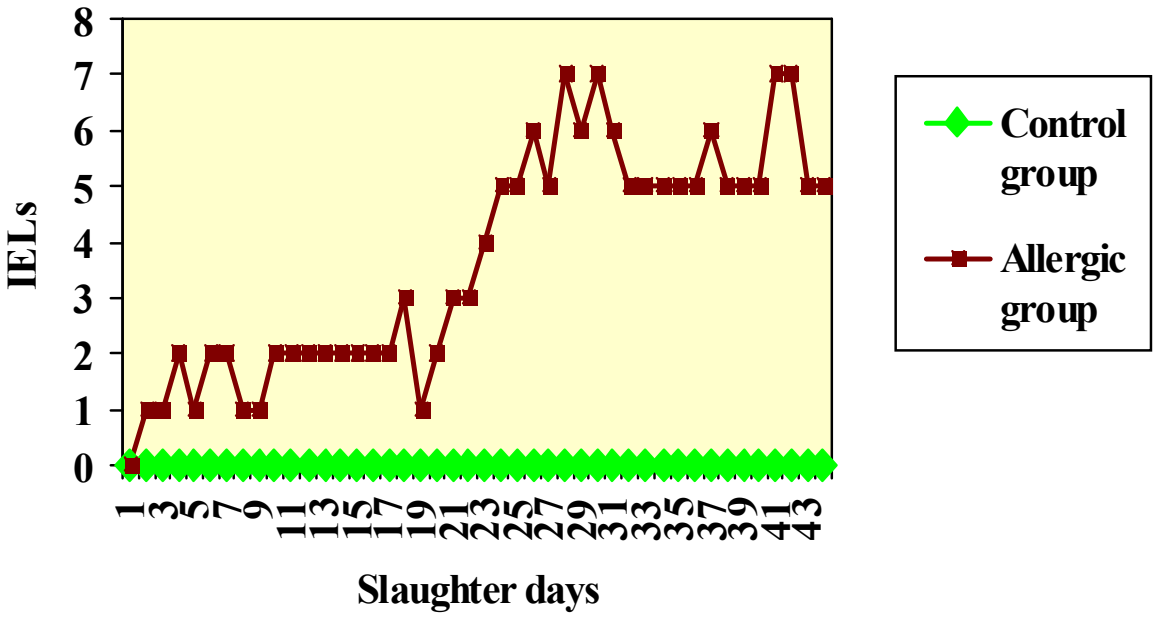


Figure (19): The mean number of intraepithelial lymphocytes per ten crypts of control and allergic ileum.

In allergic group, the decrease of the ileal **crypts depths** significantly stared from the day 4 (from 71.30 to 60.47 microns) and then regularly to the end of the experiment**; table (14) & figure (20).** This reaction was more or less the same to the other small intestinal segments the duodenum and jejunum.

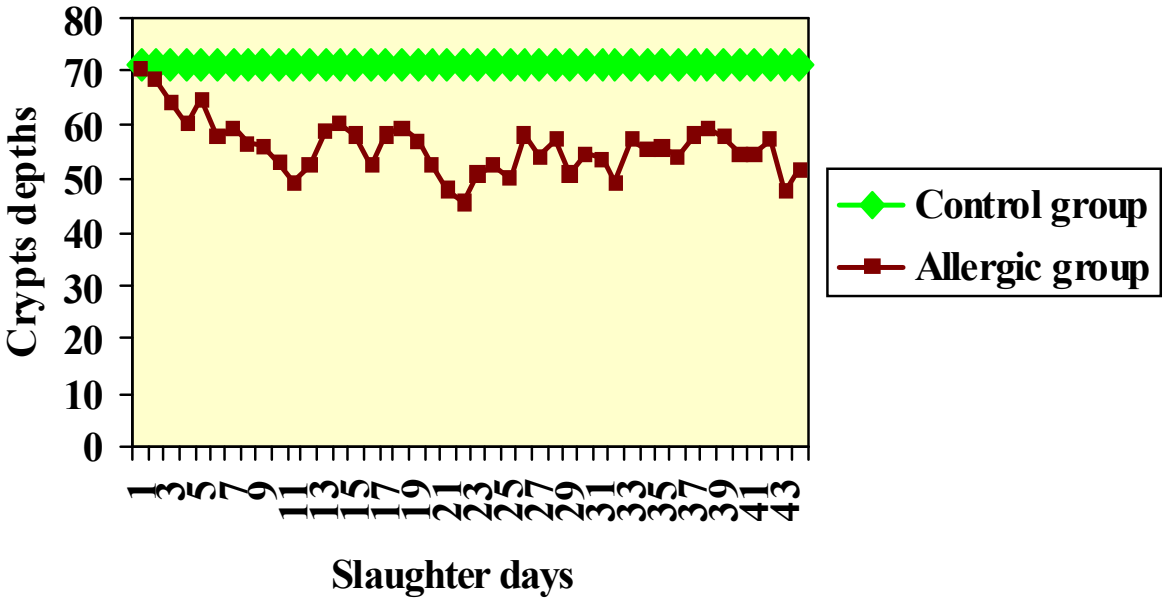


Figure (20): The length of crypts depth in microns of the control and local allergic ileum.

Allergic subacute serocatarral ileitis and chronic catarrhal ileitis.

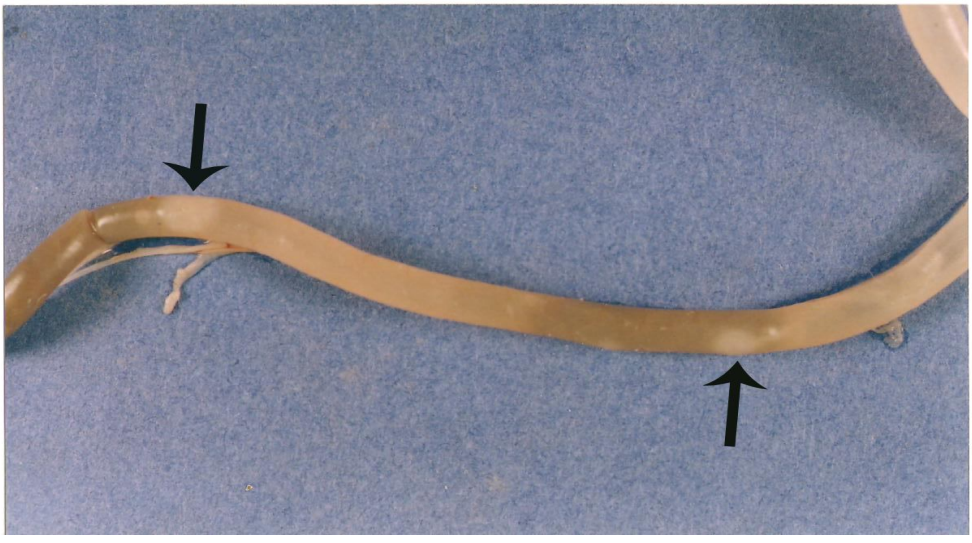
The pathological picture was more or less the same as the other small intestinal segment.

Dexamethasone and omega -3 treated ileum

Grossly both treatments caused relative subsiding of hyperemia and lymphoid follicles in the ileum; **picture (67& 68).**

Picture (67): Dexamethasone treated local allergic ileitis.

Subsiding of hyperemia and depletion of lymphoid follicles (➔).



Picture (68): Omega-3 treated local allergic ileitis.

Subsiding of hyperemia and depletion of lymphoid follicles (➔).

Both dexamethasone and omega -3 treatments had corrected the increase in the IELs of the ileal villi to reach to the control level without any significant difference between the two drugs all over the experimental period**; table (15) & figure (21).**

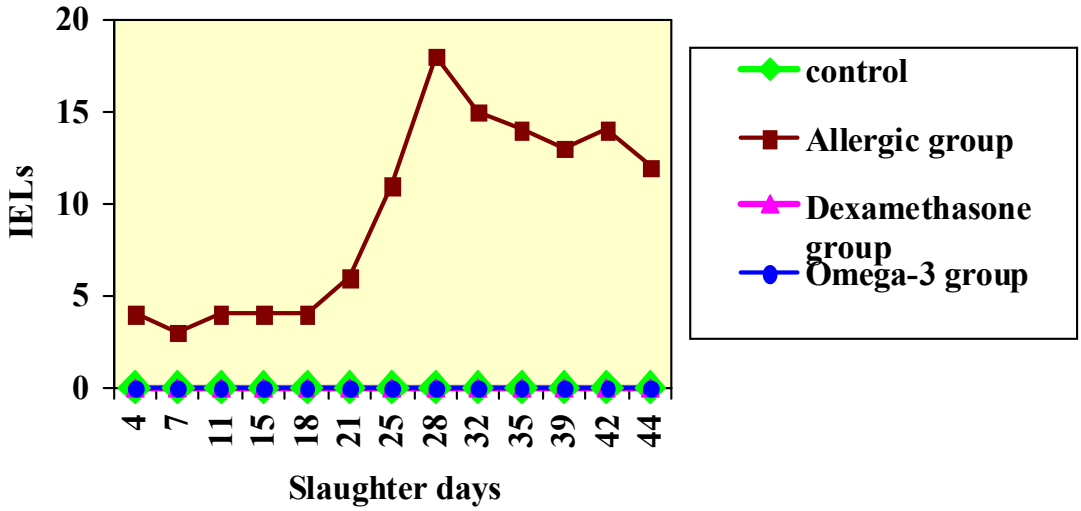


Figure (21): The mean number of intraepithelial lymphocytes per ten villi of control, local allergic, dexamethasone and omega-3 treated ileum.

Comparing the ileum with the two small intestinal segments duodenum and jejunum we found that it coincided with the duodenum that the correction was like the control level. But the jejunum was different as there was a period from the beginning of the experiment where the decrease was retarded to the day 21 for the omega -3 treatment and the day 25 for the dexamethasone treatment. Trying to explain the phenomena, we proposed that the number of the villi IELs was higher during these periods in the jejunum. To verify this supposition we made the following table from**; tables (1, 7 & 15).**

IELs in local allergic villi	Duodenum	Jejunum	ileum
Day 7	4	6	3
Day 11	5	12	4
Day 15	6	11	4
Day 18	5	11	4
Day 21	5	11	6

The dexamethasone treatment started to correct the decrease in the ileal **villi heights** to approach the control level at two periods from the day 18 to 21 and from the day 39 to 42**; picture (69&70)** and **table (16) & figure (22).**

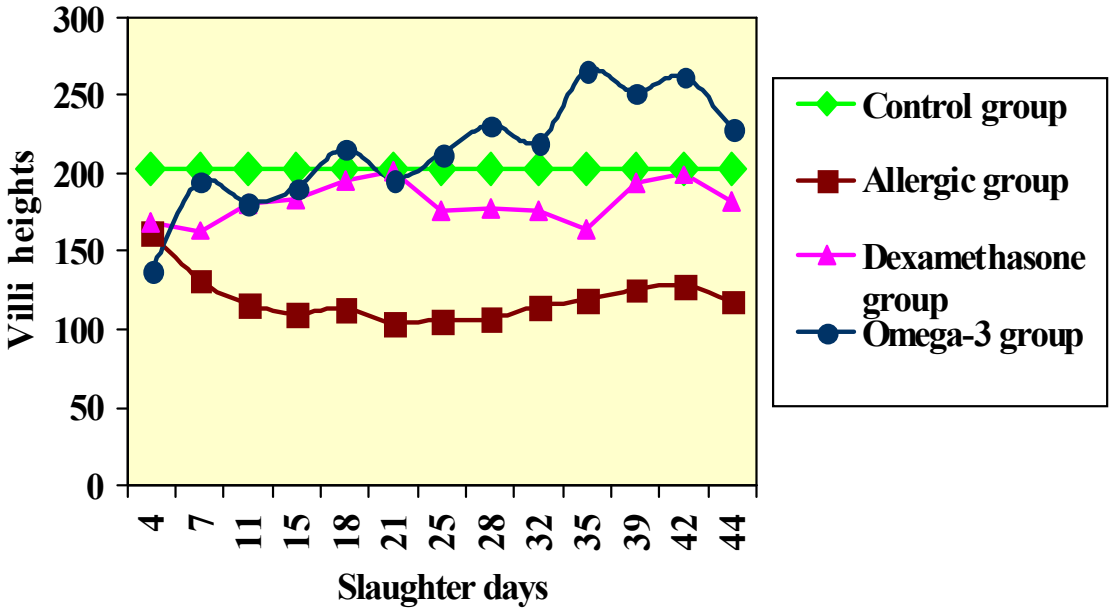
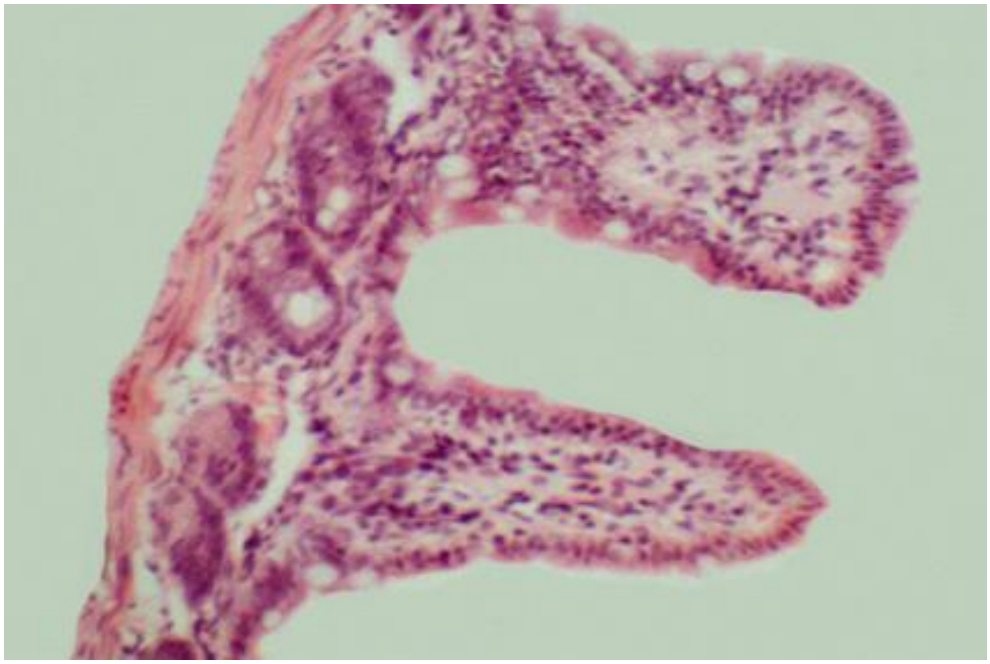
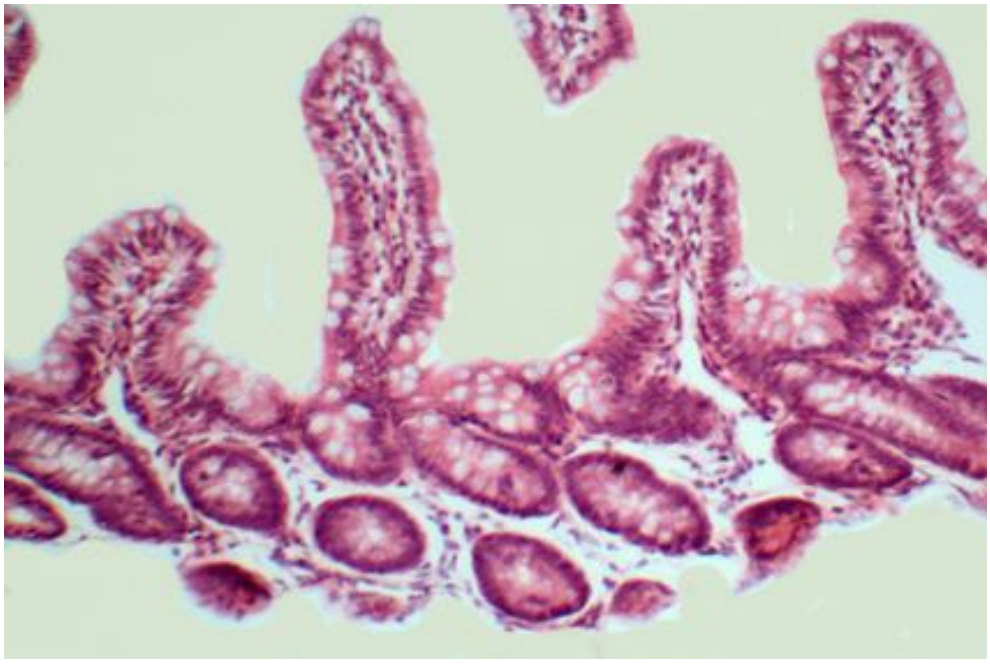


Figure (22): The length of villi heights in microns of the control, local allergic, dexamethasone and omega-3 and treated ileum.



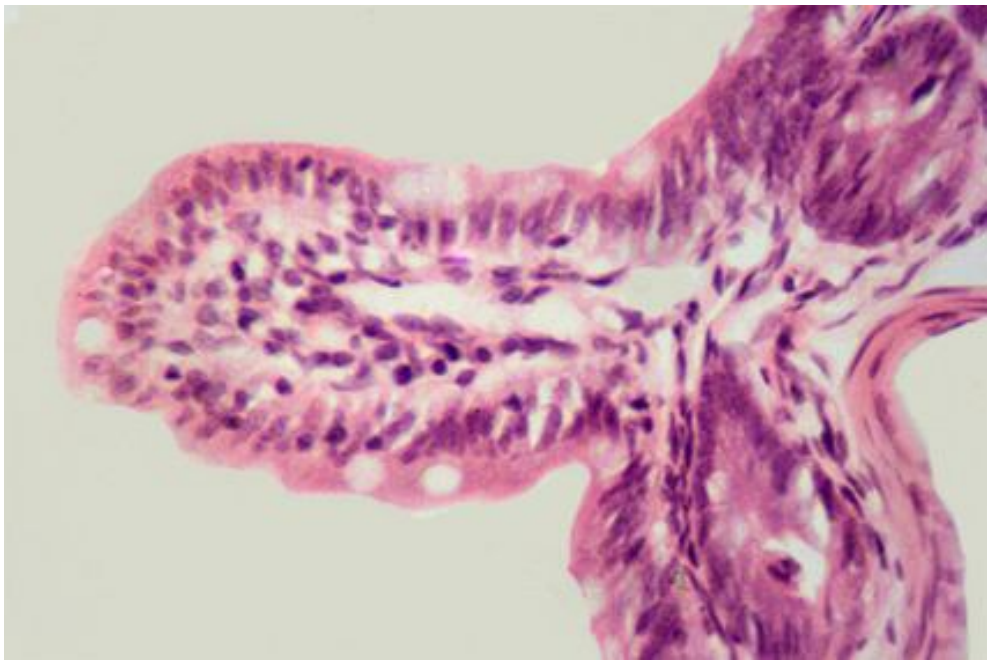
Picture (69): Dexamethasone treated local allergic ileitis.
Relative subsiding of inflammatory cells in the villi core.
18 days post oral allergen H&E X 10.



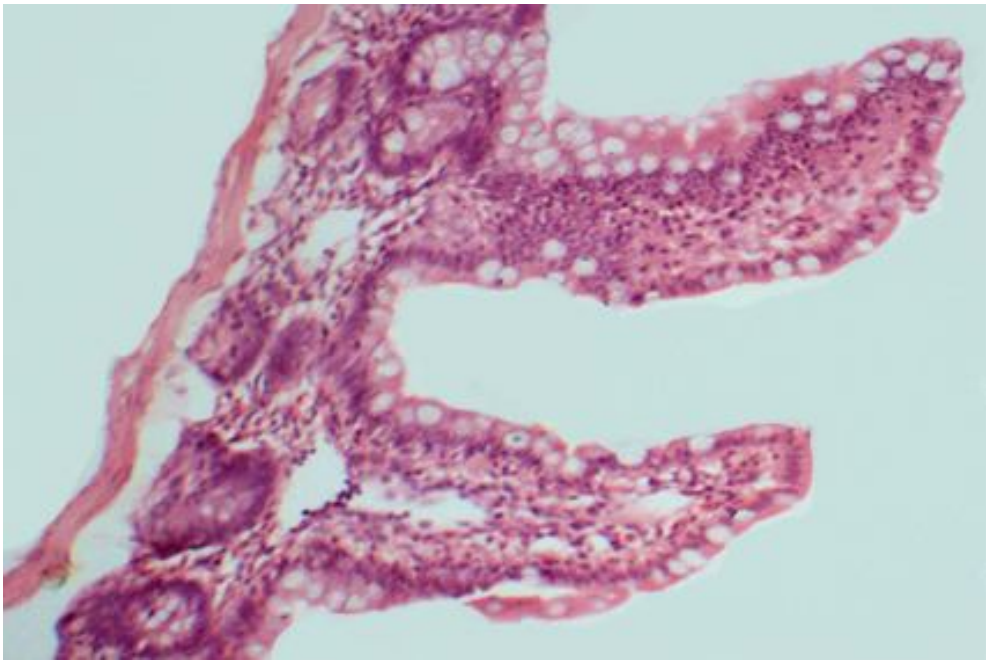
Picture (70) : Dexamethasone treated local allergic ileitis.
Normalizing both exudation and regeneration.
32 days post oral allergen H&E X 10.

Comparing the three small intestinal segments, dexamethasone blocked exudation and gave complete regeneration**; picture (71).** In the jejunum the reaction to **dexamethasone** was more or less like the control, that is to say normalizing both exudation and regeneration. In the duodenum; as the first intestinal segment receiving the treatment; **dexamethasone** although controlling exudation but the regeneration was atypical.

Omega -3 treatment caused approaching to the control level at the day 18 to 21, but the villi heights raised above the control from the day 25 to the end of the experiment on the expense of more expression of atypical regeneration**; picture (72&73).Omega-3treatment** decreased exudation but expressing atypical regeneration**; picture (72).**There was no difference in the three small intestinal segments in response to omega-3 treatment, as omega -3 did not normalize the regeneration on the expense of more atypism**; picture (74).**



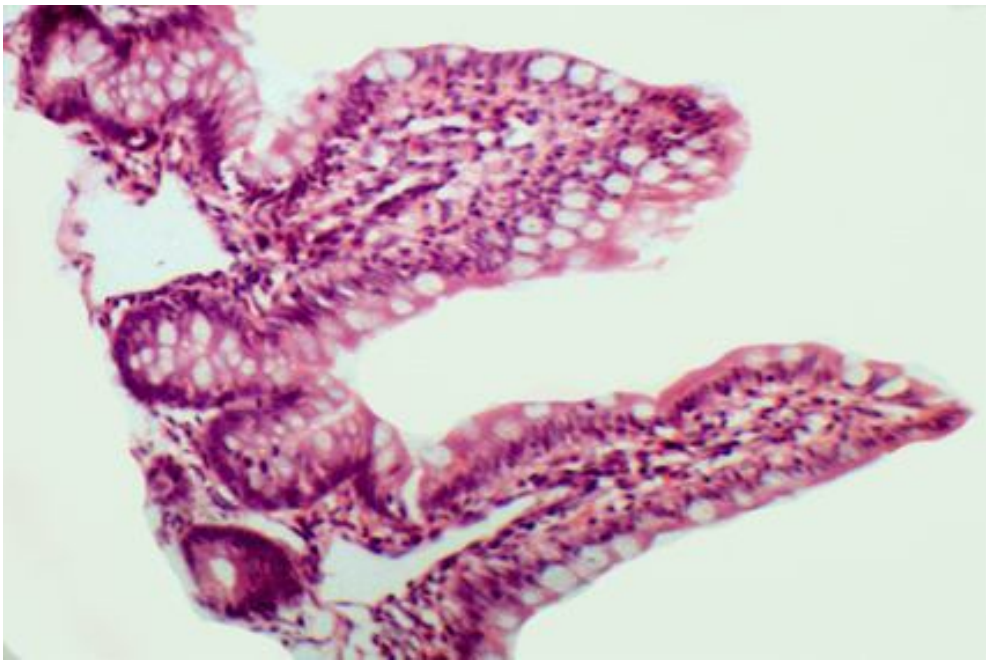
Picture (71): Dexamethasone treated local allergic ileitis.
Blocking both exudation and atypical regeneration.
25 days post oral allergen H&E X 25.



Picture (72): Omega-3 treated local allergic ileitis.

Normalizing exudation but still expressing atypical regeneration.

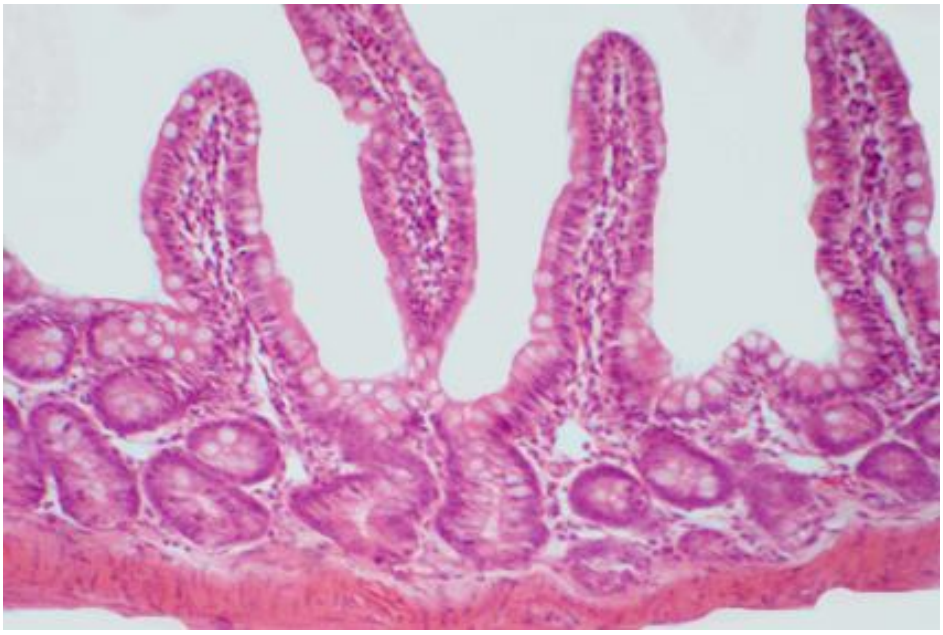
21 days post oral allergen H&E X 10.



Picture (73): Omega-3 treated local allergic ileitis.

Decreased exudation but expressing atypical regeneration.

25 days post oral allergen H&E X 10.



Picture (74): Omega-3 treated local allergic ileitis.

More or less regenerated villi with decreased exudation but still expressing atypical regeneration.

35 days post oral allergen H&E X 10.

Both dexamethasone and omega -3 treatment had corrected the increase of **IELs** in the ileal crypts to reach to the control level without any significant difference between the two drugs allover the experimental period **; table (17) & figure (23) .**

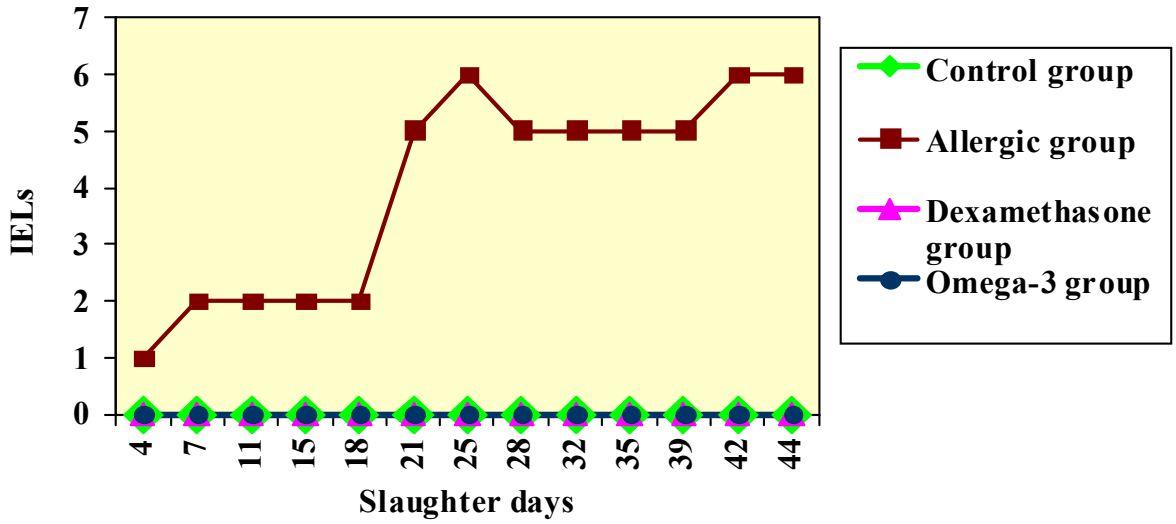


Figure (23): The mean number of intraepithelial lymphocytes per ten crypts of control, local allergic, dexamethasone and omega-3 treated ileum.

Comparing the IELs in the ileal crypts with the two small intestinal segments duodenum and jejunum, we found that it coincided with the duodenum that the correction was like the control, but jejunum was different as there was a period from the beginning of the experiment where the decrease was retarded to the day 18 for omega -3 treatment and the day 21 for dexamethasone treatment. Trying to explain the phenomena we proposed that the number of the crypts IELs was higher during these periods in the jejunum. To verify this supposition we made the following table from **tables 1, 7 &15.**

IELs in local allergic crypts	**Duodenum**	**Jejunum**	**ileum**
Day 7	1	2	2
Day 11	1	5	2
Day 15	2	5	2
Day 18	2	5	2
Day 21	2	4	5

Dexamethasone treatment corrected the decrease in the ileal crypts depths more or less regularly and significantly to reach the control level at the day 32 and to the end of the experiment by normalizing both exudation and regeneration**; table (18) & figure (24).Omega -3 treatment** corrected the decrease in ileal crypts depths significantly to reach normality at the day 7 and to rise up from the same day to be above normal to the end of the experiment by expressing more atypical regeneration. **Comparing** the three intestinal segments the crypts depths confirmed the same conclusion as the villi heights.

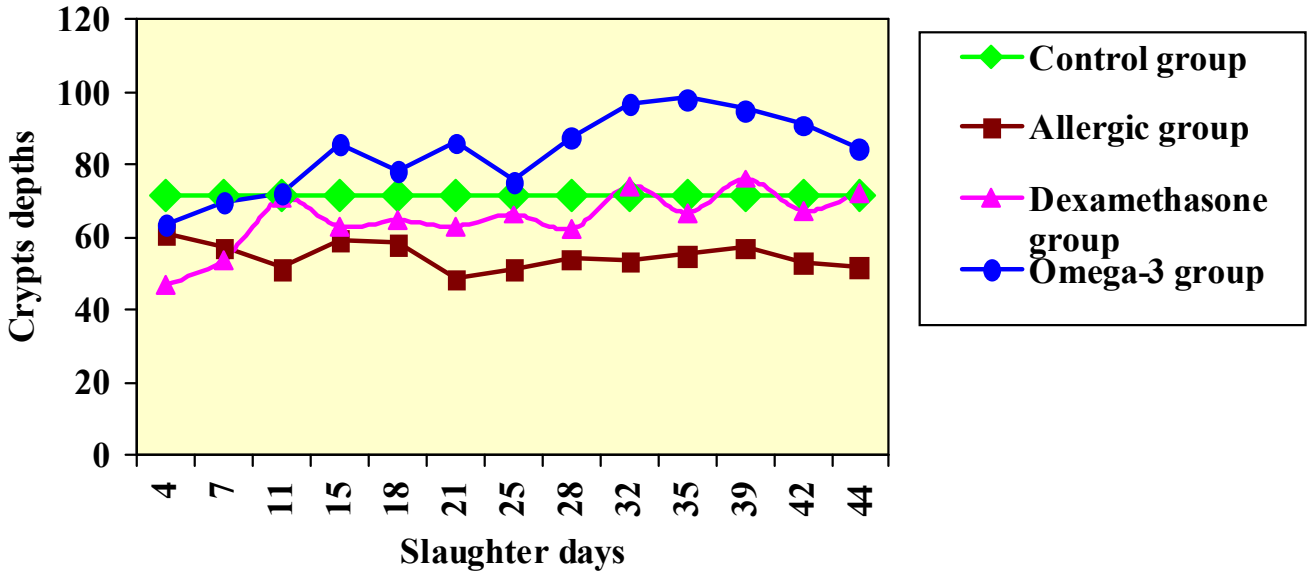
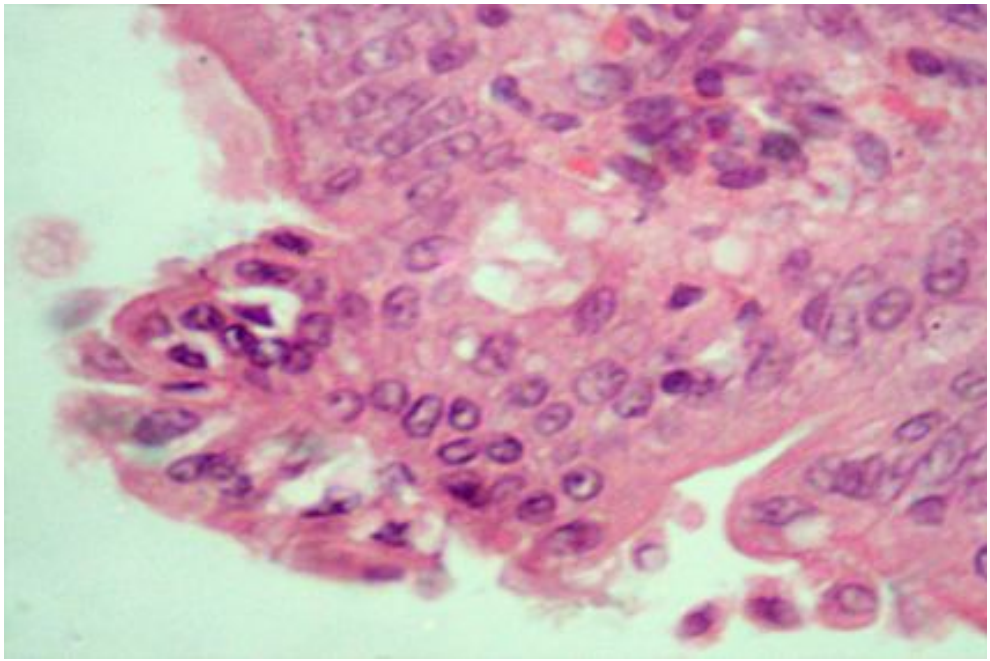


Figure (24): The length of crypts depths in microns of the control, local allergic dexamethasone and omega-3 treated ileum.

B-Systemic food allergy

Systemic allergic duodenitis

The lining epithelial changes of the duodenal villi and crypts showed no differences between systemic allergic group and local allergic one, in both acute and subacute stages. In chronic catarrhal systemic duodenitis, the villi lining epithelium showed diffuse pyknosis, rim pyknosis, cell vaculation and karyolysis**; picture (75).**



Picture (75): Systemic allergic chronic cattrahal duodenitis.
Diffuse necrobiosis involving villi lining epithelium including pycnosis, rim pycnosis, cell vaculation and karyolysis.
21 days post oral allergen H&E X 40.

The number of IELs in the allergic duodenal villi at the 4th day was very higher than control (from 1 to 11), as it was previously sensitized 15 days before**; picture (76), table (19) & figure (25).** From the day 4, it started to increase and reached higher level at the day 7 of the oral dosing (15) and (16) at the day 25. From the day 28 to the end of the experiment, it was relatively lower as the same level of the increase at the day 4. Comparing with the number of IELs of the duodenal villi in local food allergy, it sharply raised to higher level from the day 25 where it was (12) confirming the fact of competency.

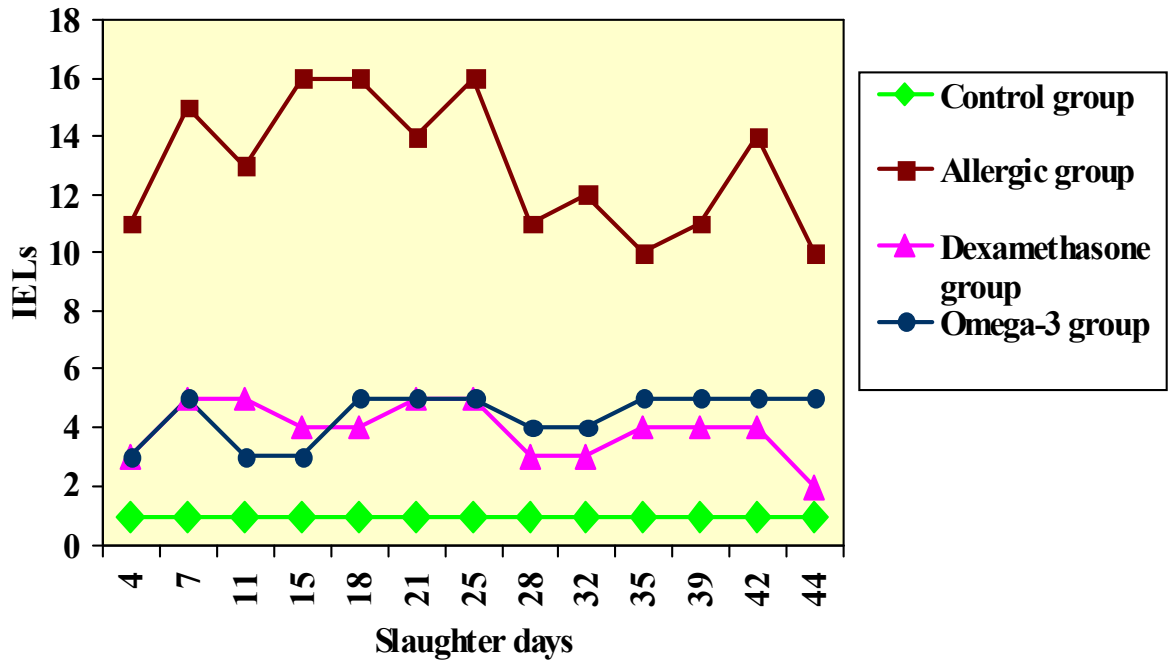
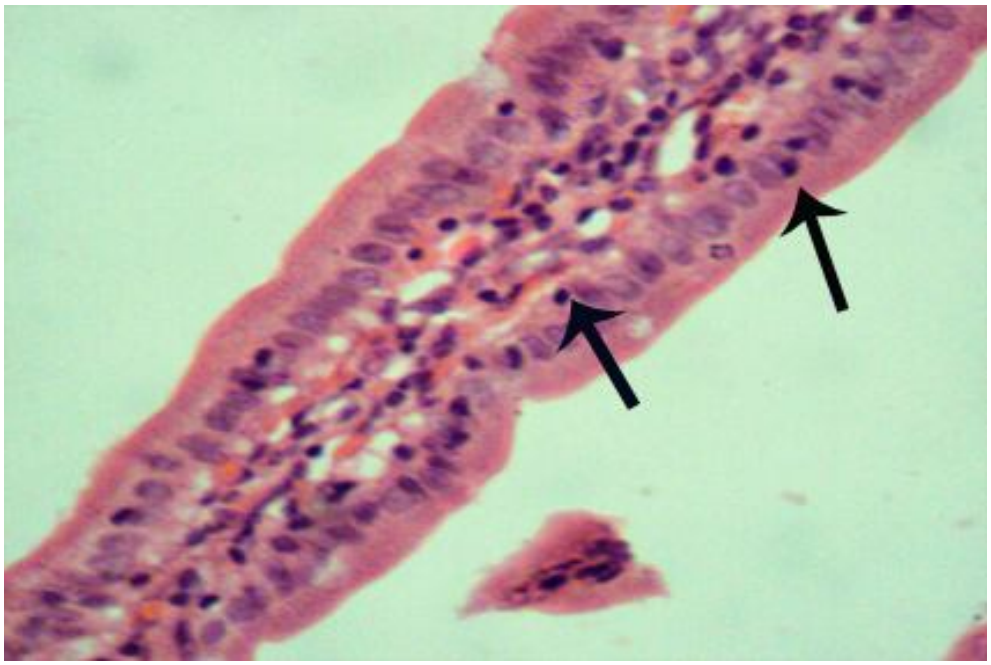
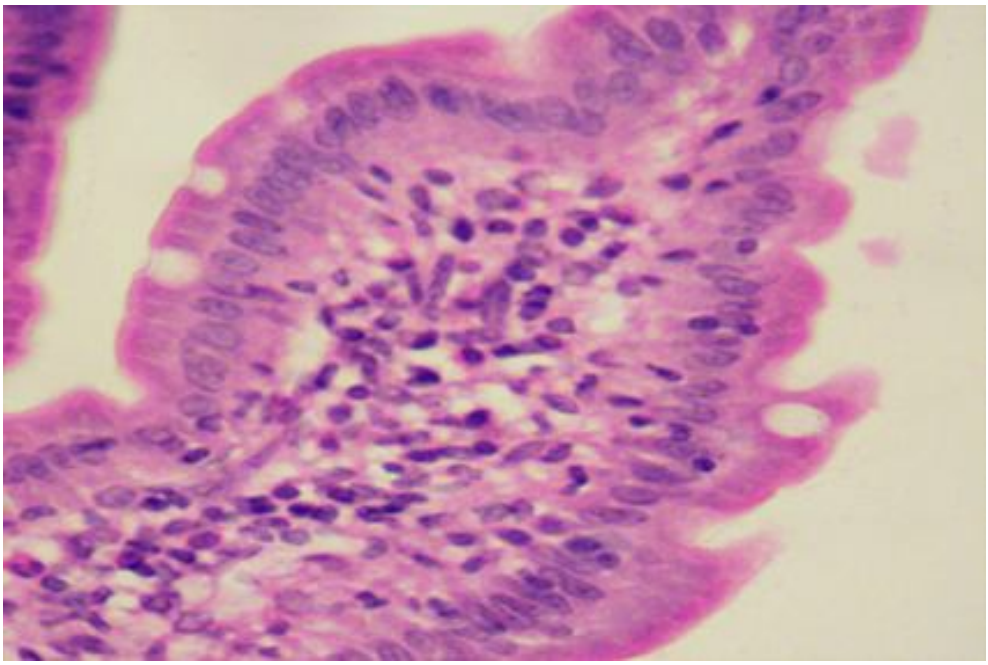


Figure (25): The mean number of intraepithelial lymphocytes per ten villi of control, systemic allergic, dexamethasone and omega-3 treated duodenum.

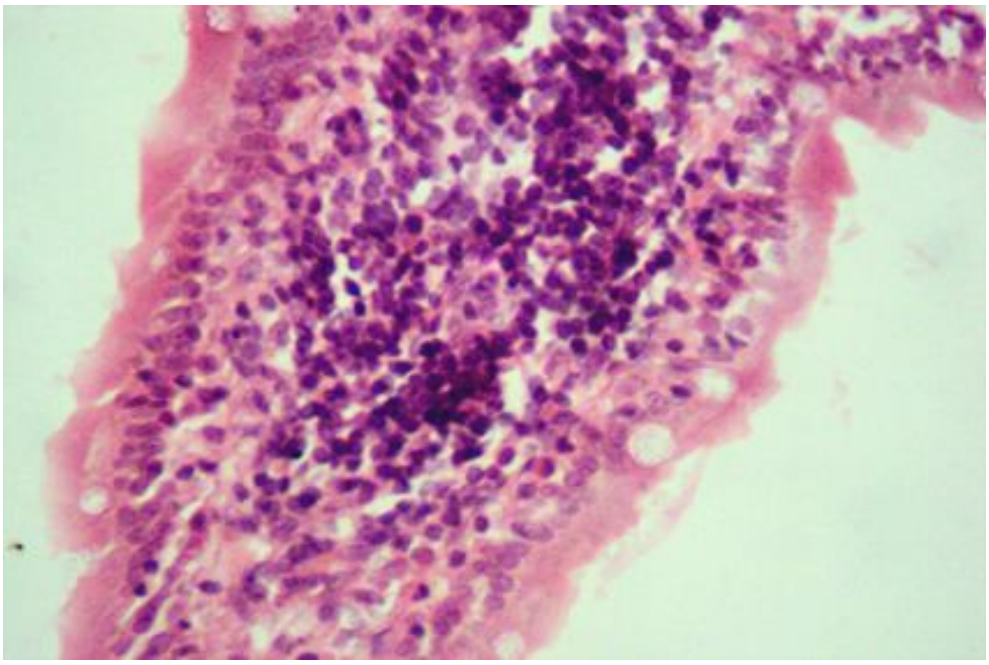


Picture (76): Systemic allergic acute serous duodenitis.
Hyperemia in villi cores with IELs (➔).
4 days post oral allergen H&E X 25.

The changes observed in the duodenal villi cores in systemic allergic group was the already early appearance of mature lymphocytes infiltration beside few macrophages as early as 4 days post oral allergen ; as there was a previous sensitization **; picture (77).** In the subacute duodenitis, the dense aggregation of mature lymphocytes in the villi cores was contrasting the moderate one in local food allergy**; picture (78).**



Picture (77): Systemic allergic subacute serocattrahal duodenitis.
Moderate lymphoid cells infiltrating villi core.
4 days post oral allergen H&E X 40.



Picture (78): Systemic allergic subacute serocattrahal duodenitis.
Dense lymphocytic cells infiltrating villi core with IELs.
15 days post oral allergen H&E X 40.

In the allergic group, the duodenal villi heights decreased significantly under the control level (from 348.26 to 263.08 microns) to the end of the experiment to reach 258.61 microns**; table (20) & figure (26).**

Comparing with local food allergy, the duodenal villi heights started to decrease steadily and significantly from the day 7 (269.43 microns) to reach 193.14 microns at the end of the experiment; table **(4) &figure (6).** The magnitude of the decrease in the duodenal villi heights in local food allergy was higher (193.14 microns at the day 44) than in the systemic food allergy (258.61 microns at the day 44).

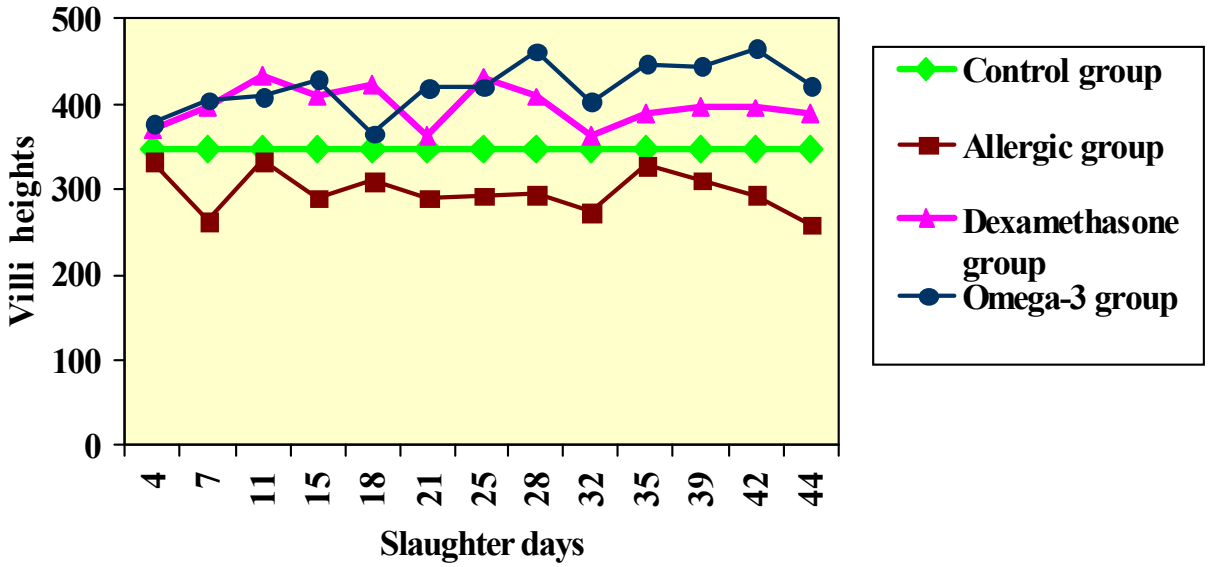


Figure (26): The length of villi heights in microns of the control, systemic allergic, dexamethasone and omega-3 treated duodenum.

The number of IELs in the crypts was statistically higher than the control at the 4th day (from 1 to 5); as it was previously sensitized 15 days before; **table (20) & figure (26).** From the day 4, it started to increase and reached (7) at the day 7 and a peak of 8 at the day 25. Vise versa to the number of IELs in duodenal the villi, the number of IELs in the crypts decreased more or less to the same level at the day 42 & 44 and were lower than that in the villi.

Comparing with the number of IELs of the duodenal crypts in local food allergy, it sharply raised to very high level at the days 25 (5), 28 (7), 32 (7) and the end of the experiment (8) confirming the fact of competency.

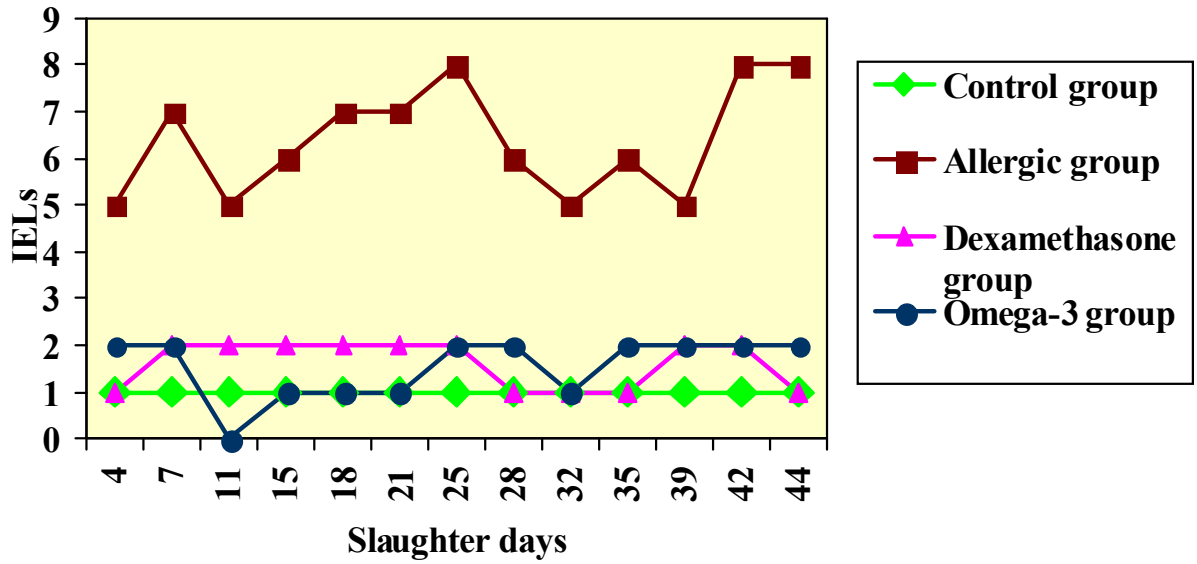


Figure (27): The mean number of intraepithelial lymphocytes per ten crypts of control, systemic allergic, dexamethasone and omega-3 treated duodenum.

The duodenal crypts depths in systemic food allergy decreased significantly from the day 7 (from 105.25 to 85.67 microns) in more or less in steady level to the end of the experiment to reach 82.93 microns**; table (22) & figure (28). The magnitude of the decrease** in the duodenal crypts depths length was lower in systemic food allergy (from 105.25 to 82.93) microns at the end of the experiment) than in local food allergy which reaches to 70.57 microns.

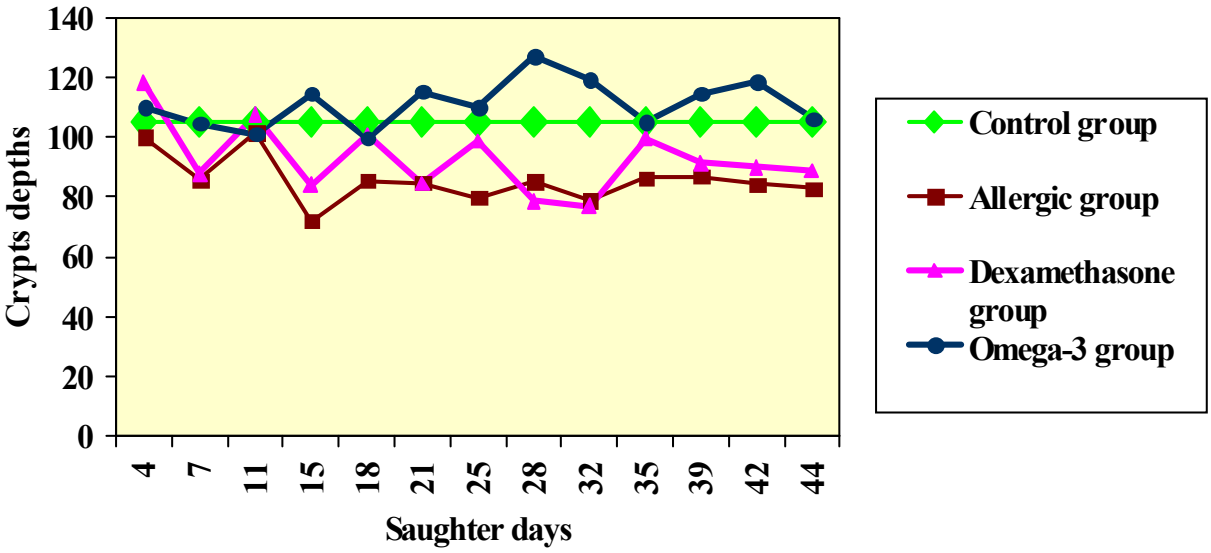
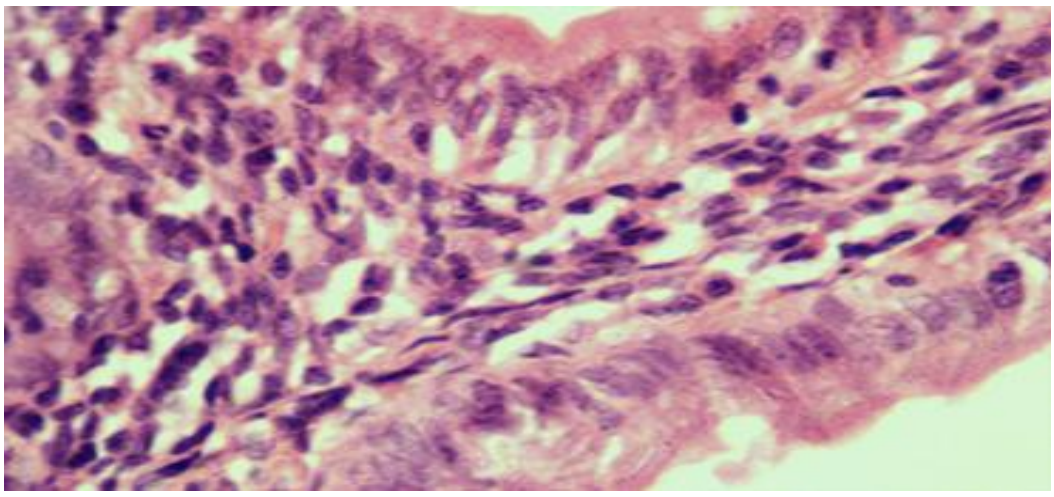


Figure (28): The length of the crypts depths in microns of the control, systemic allergic, dexamethasone and omega-3 treated duodenum.

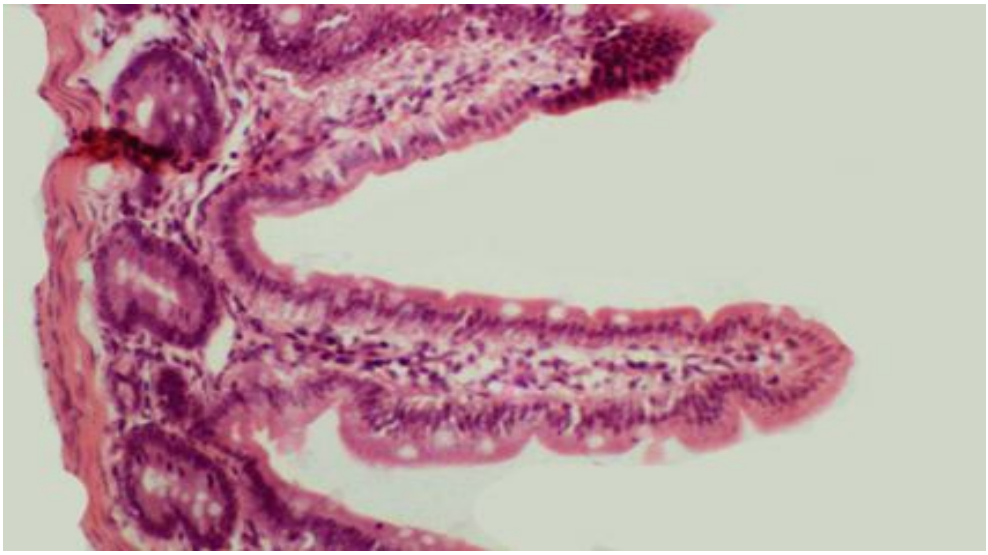
Another difference related to previous sensitization was the early germinating submucosal lymphoid follicles appearing in acute systemic serous duodenitis. The appearance of mature fibrocytes was observed in the subacute stage**; picture (79).**



Picture (79): Systemic allergic subacute serocattrahal duodenitis.
Fibrocytic cells infiltrating villous cores.
15 days post oral allergen H&E X 40.

Dexamethasone and omega -3 treated duodenum

The curative effect of dexamethasone treatment of systemic allergic duodenitis started at the 7 day**; picture (80)** vise versa to local treated group which started at the day 18.The duodenal villi reached the complete normality at the day 32 in systemic allergic dexamethasone treated duodenitis while it was at the day 28 in local allergic treated group. **In omega-3 treated systemic allergic duodenitis** the curative effect of omega -3started at the day 7 vise versa to the local allergic omega -3 treatment which started at the day 18. The duodenal villi reached to complete normality at the day 25 in both allergic groups.



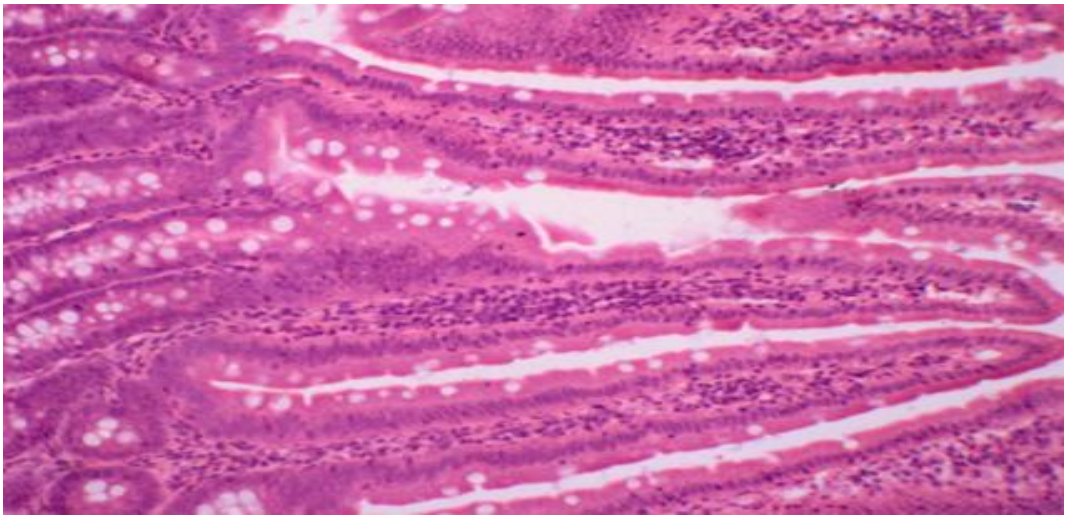
Picture (80): Dexamethasone treated systemic allergic duodenitis .
Unilatera metaplasia with relative subsiding of inflammatory cells .
7 days post oral allergen H&E X10.

Both dexamethasone and omega -3 treatments had treated the increase of **IELs** of duodenal villi in the allergic group to a large extent. At the 4^{th} day, both treatments decreased **IELs** of duodenal villi from 11 to 3. At the 15^{th} day dexamethasone decreased from 16 to 4 and omega -3 decreased from 16 to 3. At the day 25, both treatments decreased from 16 to 5. At the end of the experiment, dexamethasone decreased from 10 to 2 and omega -3 decreased

from 10 to 5**; table (19) & figure (25). In dexamethasone treated group,** the number of **IELs** increased than control from the day 4 and more or less coincided the increase in the systemic allergic group.

Comparing the duodenal villi **IELs** of dexamethasone treated systemic allergic group **with** the dexamethasone treated local allergic group, where it decreased statistically to the control level allover the experiment preventing the production of IELs in the duodenal villi. **Omega -3 treatment** as dexamethasone treatment in systemic food allergy did not completely prevent the production of **IELs** in the duodenal villi as it was higher than the control level allover the experimental period.

Dexamethasone treatment increased significantly the duodenal villi heights from the day 7 (from 348.27 to 397.46 microns) above the control level reaching higher level at the day 25 (432.00 microns) **;picture (81)** and in more or less steady level to the end of the experiment **; table (20) & figure (26) .Dexamethasone correction** was better in systemic allergy than in local allergy as it started from the day 7 higher than the control level.



Picture (81): Dexamethasone treated systemic allergic duodenitis.

Regenerated villi of very long length although of more or less normal appearance.

25 post oral allergen H&E X 10.

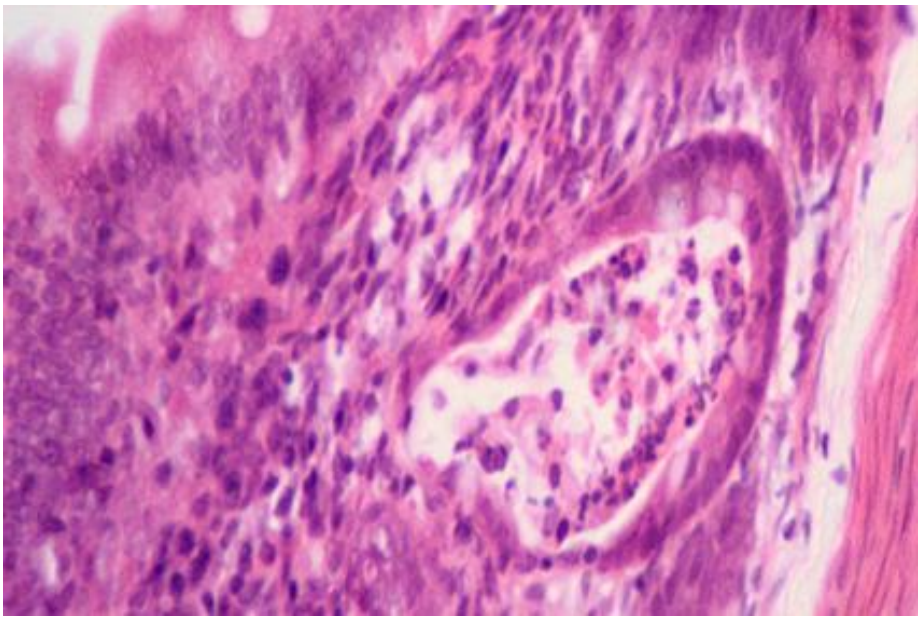
Omega -3 treatment increased the duodenal villi heights significantly from the day 7 (397.46 microns) above the control level to reach a higher point at the day 28 (461.83 microns) and continued more or less in the same level to reach 465.75 microns at the day 42 and to the end of the experiment. **Omega -3 treatment** was in higher magnitude in systemic allergy (465 microns at the day 42) than in local allergy (398.05 microns at the day 42).

Both dexamethasone and omega -3 treatments had corrected the increased number of **IELs** of the duodenal crypts in the allergic group to a large extent .At the 4day, it decreased (from 5 to 1&2), at the day 7 it decreased (from 7 to 2), at the day 25, it decreased (from 8 to 2) and at the end of the experiment, it decreased (from 8 to 2)**; table (20) & figure (26).** The two drugs completely prevented the production of IELs in the crypts allover the experimental period. The Same phenomenon was in the local food allergy. Vise versa to the duodenal villi where the two drugs decreased the number of IELs but did not completely prevent its production**.**

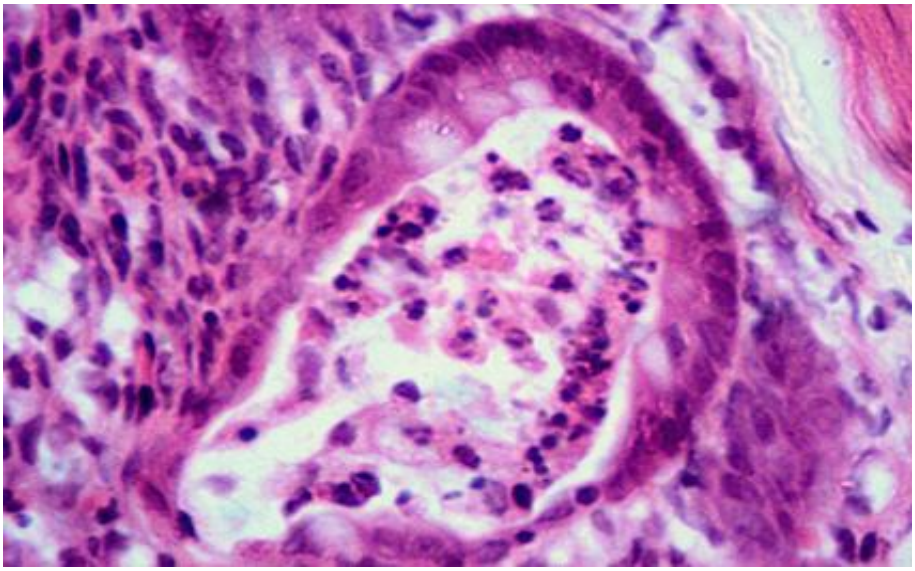
In systemic food allergy, dexamethasone treatment although corrected the decrease in the duodenal crypts depths at interrupted intervals to reach to the control level at the days 11, 25 and 35 it never exceeded and was under the control allover the experimental period**;picture (82&83).Comparing with local food allergy**, **dexamethasone** treated the decrease in the **crypts depths** to reach the control at the 15th day and then, it was higher than the control level during the rest of the experiment, vise versa to the systemic food allergy where it never exceeded the control and approached the control at interrupted intervals.**Omega -3 treatment** succeeded to correct the decrease in the duodenal **crypts depths** to the control level from the day 7 to the day 25 and it was higher than the control in the rest period allover the experiment. **Omega -3 treatment** was better in systemic food allergy than in local allergy , as it increased duodenal crypts

depths after the day 11 vise versa to local food allergy it increased duodenal crypts depths above control level after the day 18.

In dexamethasone treated systemic allergic duodenitis, the lymphoid exhaustion in the submucosal lymphoid follicles was observed at the day 28 while it was at the day 18 in local allergic treated group.**The diffuse lymphocytic cells** infiltration in the submucosa in **omega -3** treated systemic allergic duodenitis was at the day 28 visa versa it was at the day 18 in local allergic treated group.



Picture (82): Dexamethasone treated systemic allergic duodenitis. Desquamation and necrobiosis of the duodenal crypts. 28 days post oral allergen H&E X 25.



Picture (83): High power of upper figure H&E X 40.

Systemic allergic jejunitis

The changes in the epithelial lining of the villi and crypts showed no difference between systemic allergic and local allergic groups in acute stage. Differential for systemic allergic subacute jejunitis was the necrosis involving both villi and crypts epithelium while this phenomenon only involved the crypts epithelium in chronic stage of local allergic group.

In systemic allergic jejunitis, the IELs in the jejunal villi started to increase significantly from the day 4 and steadily to reach its optimum number at day 32 (from zero to 22) and more or less higher to the end of the experiment where it was 17**; table (23) & figure (29).** The magnitude of the increase of the **villi IELs** number was higher in systemic allergic jejunitis than in local allergic jejunitis .That is probably because of previous sensitization. The behavior of villi **IELs** in the systemic allergic jejunitis was the same as that in systemic allergic duodenitis.

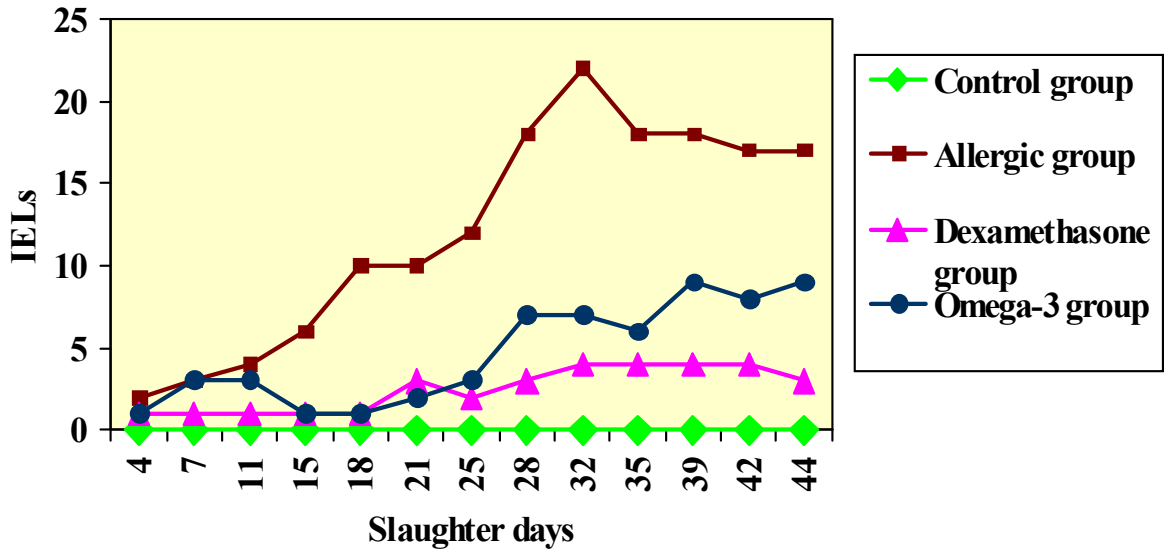
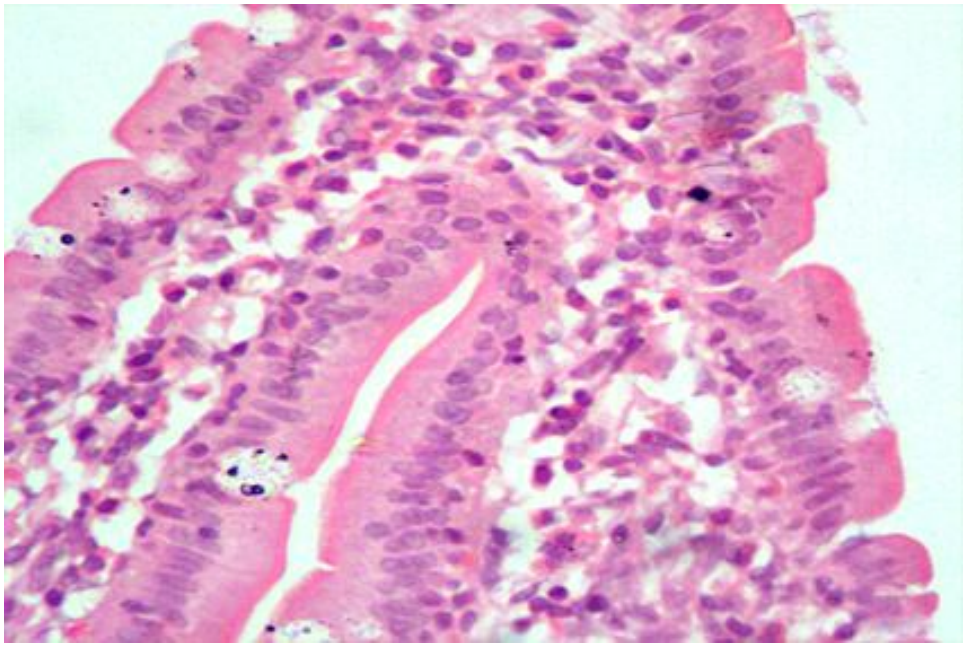


Figure (29): The mean number of intraepithelial lymphocytes per ten villi of control, systemic allergic, dexamethasone and omega-3 treated jejunum.

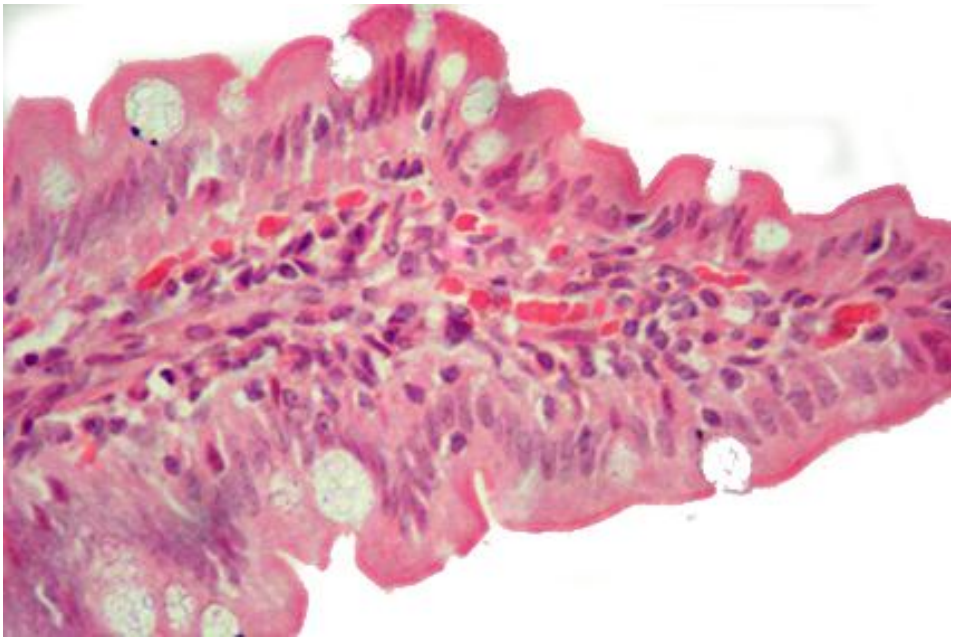
Differential for systemic allergic jejunitis was the presence of hyperemia, eosinophils macrophages and lymphoid cells reaction with regenerated crypt epithelium in the villi core in the acute stage; **picture (84 & 85)**. It appeared in subacute stage of local allergic jejunitis. In subacute stage of systemic allergic jejunitis, chronic inflammatory cells appeared in the villi core earlier than in local allergic jejunitis.



Picture (84): Systemic allergic acute serous jejunitis.

Eosinophils, macrophages and lymphoid cells infiltrating villous core .

7 days post oral allergen H&E X 40.



Picture (85): Systemic allergic acute serous jejunitis.
Hyperemia in villi core.
7 days post oral allergen H&E X 25.

The villi heights in systemic allergic jejunitis were lower significantly than control from the day7 (from 286.13 to 222.15 microns) more or less in regular manner to the end of the experiment to reach 192.37 microns**; table (24) & figure (30).** In local allergic jejunitis, the decrease of the jejunal villi heights started significantly and steadily from the day 4 (245.67 microns) to the end of the experiment to reach 133.32 microns. **Comparing to systemic duodenitis,** the decrease of the jejunal villi heights started significantly from the day 7 and was more or less regularly to the end of the experiment.

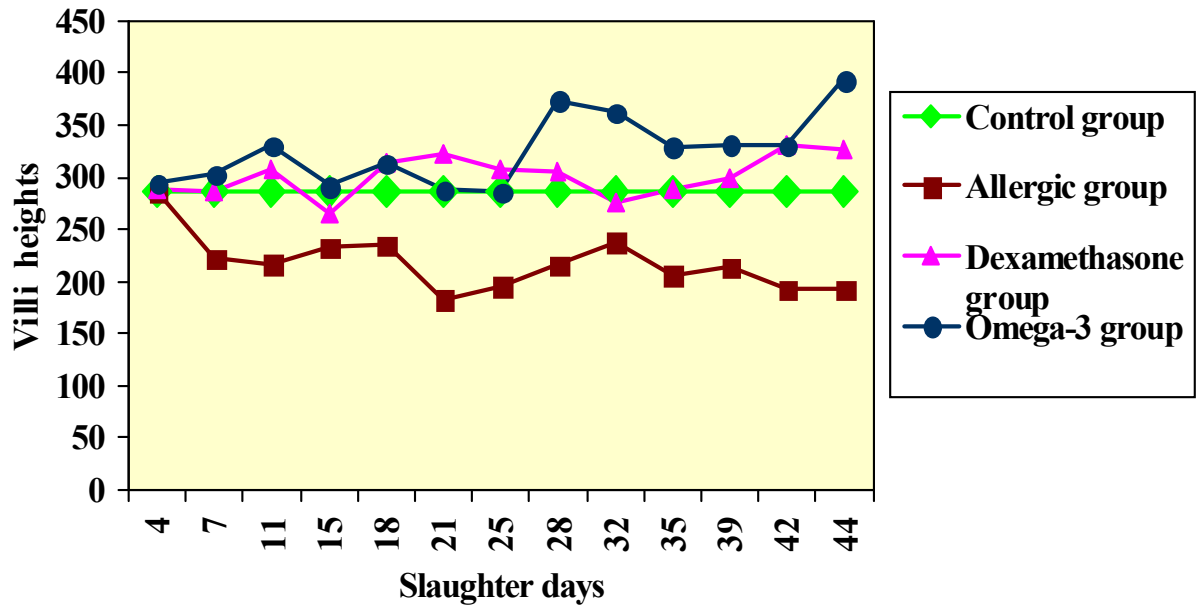


Figure (30): The length of villi heights in microns of the control, systemic allergic, dexamethasone and omega-3 treated jejunum.

The IELs in crypts of systemic allergic jejunitis started to increase significantly from the day 7 and steadily to the end of the experiment to reach 8**; table (25) & figure (31).** In local allergic jejunitis, it started higher significantly from the day 4 (2) and then shot up at a higher level at the day 11 (5) then more or less steadily to the same level to the end of the experiment .In systemic allergic duodenitis **IELs** in the duodenal crypts started earlier at the day 4 and increased more or less steadily to the end of the experiment. The magnitude of the increase of **IELs** in the jejunal crypts was higher in systemic group (9) than in local allergic group (5) nearly double. The number of **IELs** in the villi of the systemic allergic jejunitis was higher than that in the crypts.

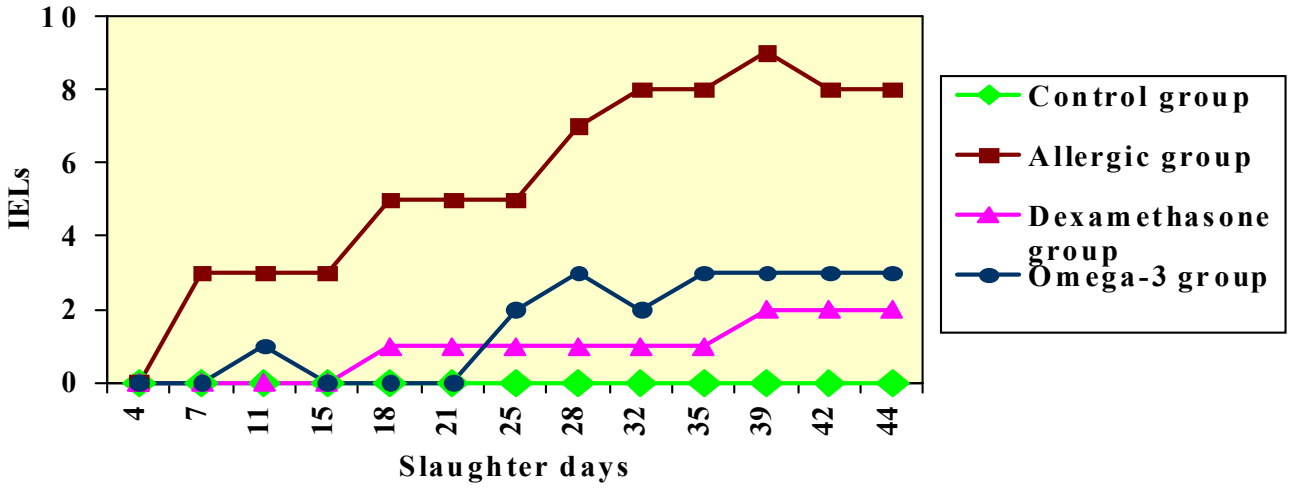


Figure (31): The mean number of intraepithelial lymphocytes per ten crypts of control, systemic allergic, dexamethasone and omega-3 treated jejunum.

In systemic allergic jejunitis, the crypts depths decreased significantly more or less regularly than the control from the day 7 to the end of the experiment; **table (26) & figure (32) .**In local allergic group, it decreased significantly and steadily than the control level from the day 4 to the end of the experiment. There was no difference between systemic allergic duodenitis and jejunitis in the decrease of crypts depths.

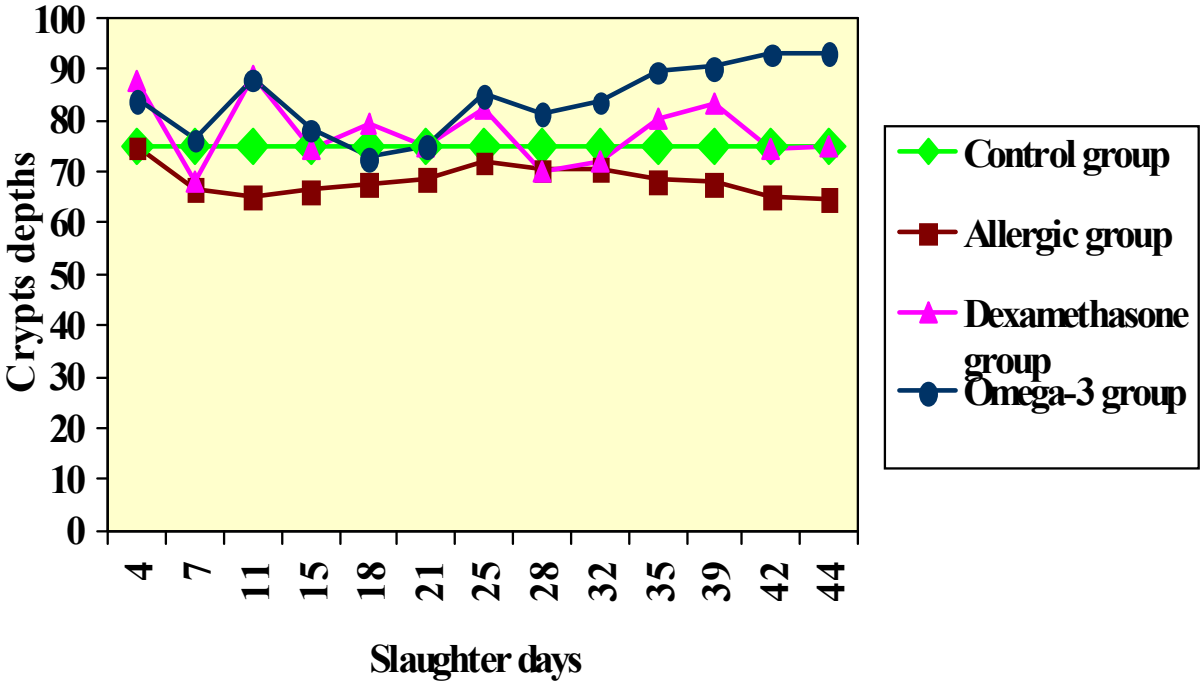
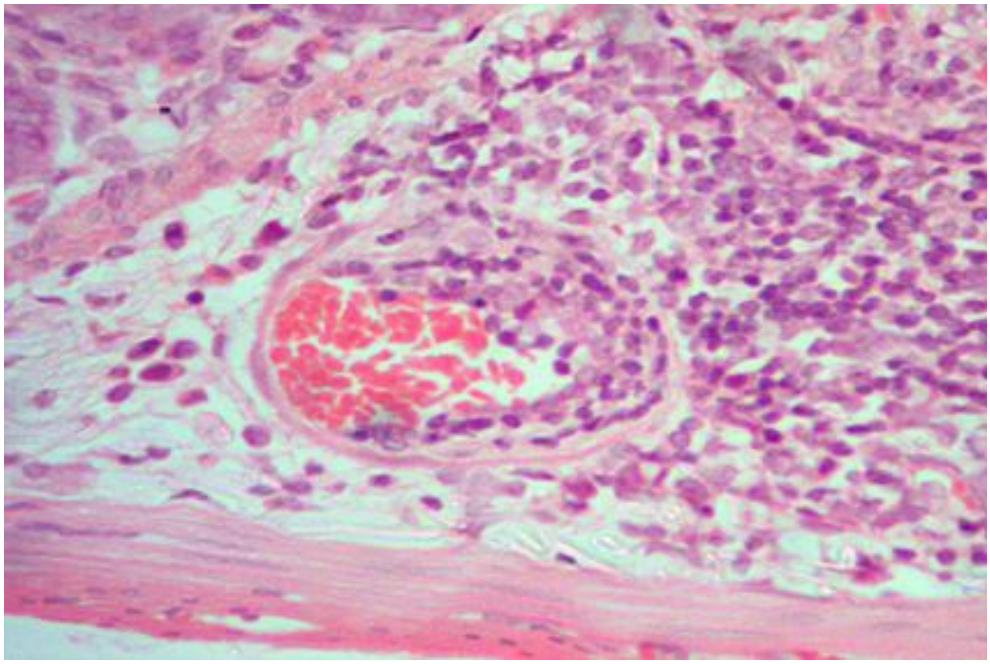


Figure (32): The length of the crypts depths in microns of the control, systemic allergic, dexamethasone and omega-3 treated jejunum.

Another difference related to previous sensitization was the early appearance of submucosal germinating lymphoid follicles in acute stage vise versa to chronic stage of local allergic jejunitis. Thrombosis and vasculitis were the differential pathological pictures appeared in the chronic stage of systemic allergic jejunitis instead of its appearance in subacute stage of local allergic jejunitis.

Differential for systemic allergic jejunitis from duodenitis were vasculitis, thrombosis**; picture (86)** and fibrosis in chronic stage instead of subacute duodenitis.

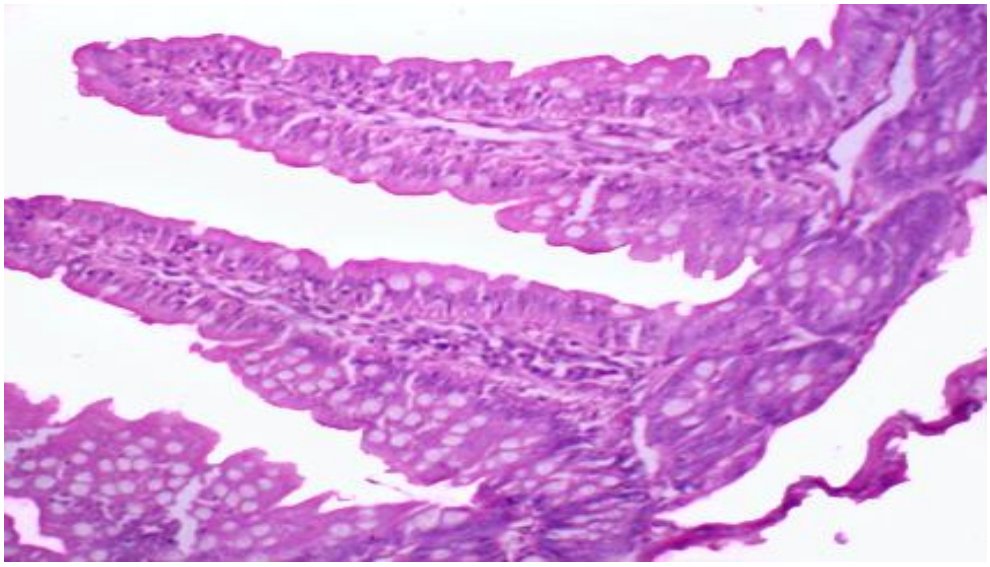


Picture (86): Systemic allergic chronic cattarhal jejunitis. Thrombosis with phlebitis in submucosal blood vessels 42 days post oral allergen H&E X 25.

Dexamethasone and omega -3 treated jejunum

The curative effects of **dexamethasone and omega-3** treatments of systemic allergic jejunitis started at the day 11 vise versa to local allergic jejunitis which started at the day 4 . In **dexamethasone** treated group, the jejunal villi reached the complete normality at the day 32th instead of the day 25 in local allergic jejunitis. In **omega -3** treated, group the villi reached to the complete normality at the day 21 while it was at day 32 in local allergic group. **Omega-3** treatment was better than **dexamethasone** in systemic allergic jejunitis.

Atypical regeneration in the jejunal villi was demonstrated at the day 28 instead of the day 25 in systemic allergic dexamethasone treated duodenitis**;picture (87).**



Picture (87): Dexamethasone treated systemic alleric jejunitis.
Atypical regenerated villi.
28 days post oral allergen H&E X10.

The IELs in the jejunal villi under **dexamethasone** treatment decreased significantly from the day 4 to the end of the experiment .It was the same as control level until the day 18. From the day 21, it started to increase than control

more or less in regular manner to reach (3) at the end of the experiment; **table (23) & figure (29).**The picture of dexamethasone treatment in local allergic jejunitis was controversial as it corrected from the day 4 the increase in the villi IELs and reached to control level at day 25. There was no difference observed in the manner of dexamethasone treatment comparing to systemic allergic duodenitis. **From the 4th day, omega -3** had treated the increase of **IELs** in the jejunal villi to decrease in more or less steady manner until the end of the experiment but the decrease was lower in comparison to dexamethasone treatment. Omega-3 treatment in local allergic jejunitis corrected completely the rise in the number of villi **IELs** to control level at day 21. No difference in the pattern of treatment was observed between the omega-3 treated systemic allergic duodenitis and jejunitis. Dexamethasone treatment was better than omega -3 in the correction of villi IELs in systemic allergic jejunitis.

Dexamethasone treatment corrected significantly the decrease in the jejunal villi heights from the day7 to be more or less higher than the control level in interrupted periods from day 18 to 28 and from day 39 to 44**; table (24) & figure (30) and picture (86)** .The picture explained the phenomena to be due to atypical regeneration . In local allergic jejunitis, dexamethasone corrected the decrease in the jejunal villi heights to reach control relatively at day 18 and was like control allover the experimental period except after the day 18 to day 25.**Dexamethasone** in systemic allergic duodenitis corrected the villi heights significantly from the day 7 more or less regularly to the end of the experimental period. **Omega-3** corrected significantly the decrease in the jejunal villi heights from day 7 to be little higher than the control. The highest correction reached at day 28 to be from 286.14 to 373.85 microns and to the end of the experiment.**Omega-3** was better than **dexamethasone** treatment in the correction of villi heights in systemic allergic jejunitis. **Omega-3** treated significantly the decrease of villi heights in local allergic jejunitis from the day 7 to 15 to reach control then it was more or less higher than control allover the

experimental period. **Omega-3** treated significantly the decrease of villi heights in systemic allergic duodenitis from day 7 and was more or less regular to the end of the experiment.

In systemic allergic jejunitis, dexamethasone corrected significantly the increase of IELs in the crypts to be like the control to the day 35 then it was slightly higher to the end of the experiment**; table (25) & figure (31).**In local allergic jejunitis **dexamethasone** corrected significantly the increase of **IELs** in the crypts allover the experimental period like in systemic allergic duodenitis.**Omega-3** in systemic allergic group corrected to the control level the number of **IELs** in the crypts until the day 21 after that it was higher than the control to the end of the experiment. While in local allergic jejunitis and in systemic duodenitis, it corrected the increase of IELs allover the experimental period. **Dexamethasone treatment** was better than omega -3 in the correction of **IELs in the crypts** of systemic allergic jejunitis.

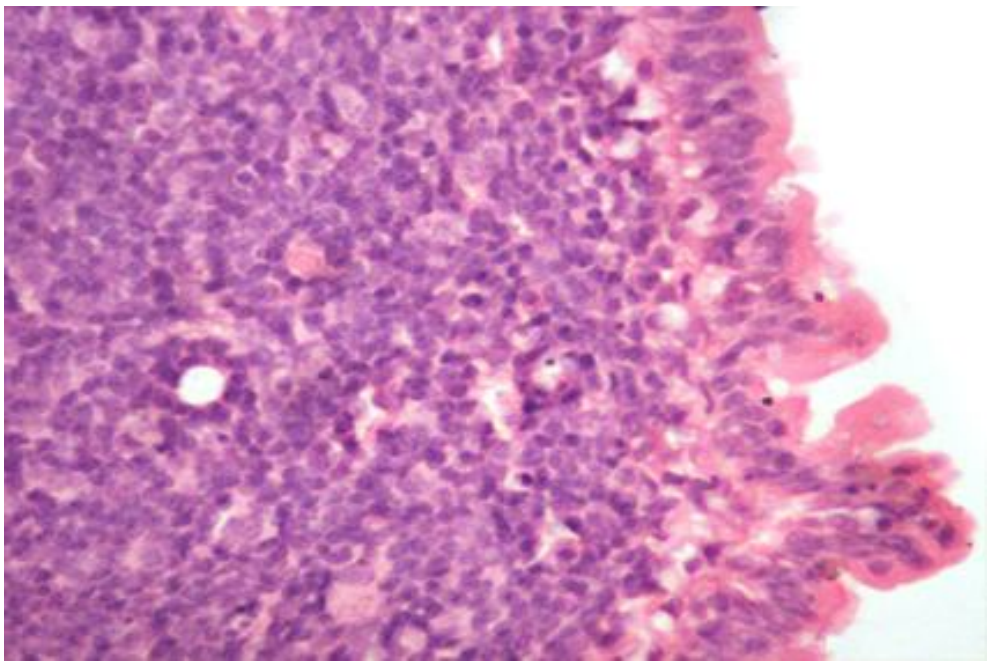
In systemic allergic jejunitis, from day 18 to the end of the experiment **dexamethasone** corrected the decrease of the jejunal **crypts depths** to the control level before that the correction was not complete. **In local allergic dexamethasone treated group**, the decrease of jejunal crypts depths was corrected to the control level from the day 11 to 21 after that the correction was higher than control level. **In systemic allergic dexamethasone treated duodenitis,** the correction was under the control level.**Omega-3 correction** of the decrease **crypts depths** was higher than the control level and better than dexamethasone allover the experimental period in systemic allergic duodenitis and jejunitis .

In dexamethasone treated systemic allergic jejunitis, the submucosal lymphoid follicles showed picture of resting follicle at day 15, while in local allergic treated group it was at day 21. At day 28 the submucosal lymphocytes

were severely exhausted in systemic allergic treated group vise versa to local allergic treated group it was after 25 days. **In omega-3 treated systemic allergic jejunitis** diffuse lymphoid cells infiltrating submucosa were recorded at day 28 instead of the day 21 in local allergic treated jejunitis.

Systemic allergic ileitis

Hyperplasia of the surface lining epithelium was observed in chronic stage of both local and systemic allergic ileitis**; picture (88)**.



Picture (88): Systemic allergic chronic ileitis.
Hyperplasia of surface epithelium
21 days post oral allergen H&E X 40.

The number of **IELs** in the ileal **villi** of systemic allergic group was increased significantly and steadily from the day 4 from 0.0 to 6 to reach 17 at the end of the experiment; **table (27) & figure (33).** Comparing to the local allergic ileitis, the increase of IELs reached a high peak at the day 28 (18) because of the competency was achieved at this time. **The behavior of the villi IELs** in systemic allergic ileitis was the same as that in systemic allergic duodenitis. **Comparing to systemic allergic jejunitis, the villi IELs** reached the higher peak at the day 32 with high magnitude than that in systemic allergic ileitis.

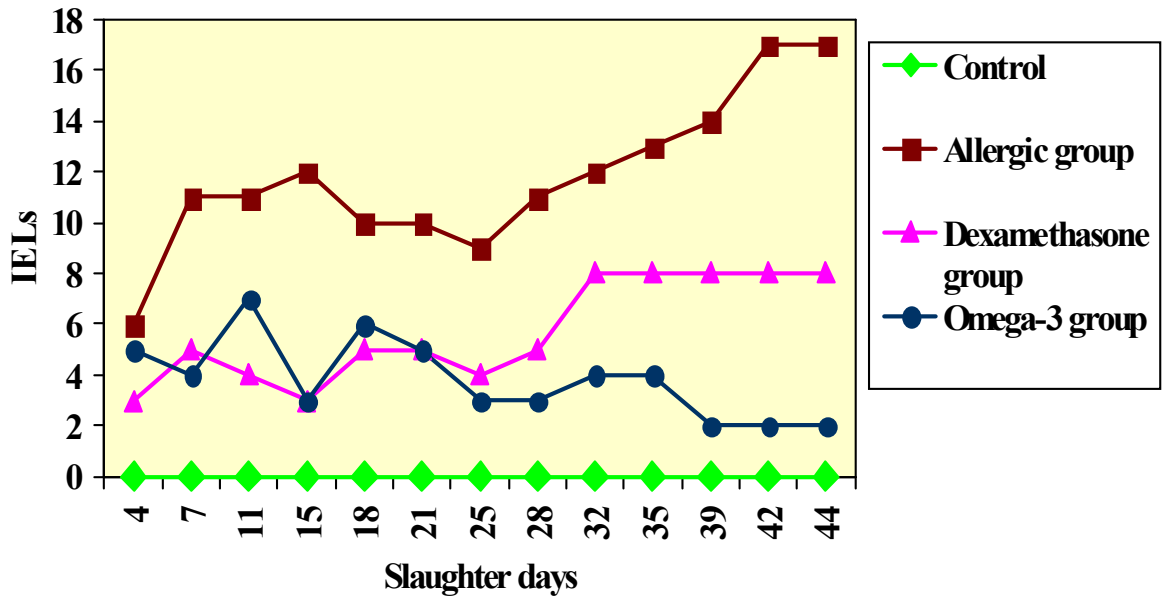
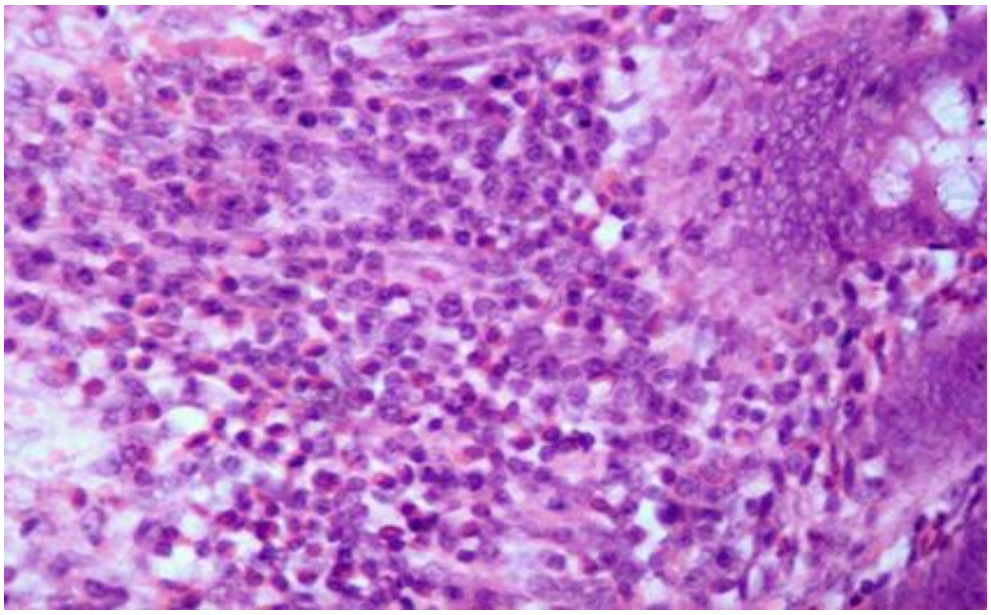


Figure (33): The mean number of intraepithelial lymphocytes per ten villi of control, systemic allergic, dexamethasone and omega-3 treated ileum.

Differential for acute stage of systemic allergic ileitis were hyperemia, eosinophils, macrophages and lymphoid cells infiltrating villi cores with degenerative and necrotic changes in the crypts lining epithelium, **picture (89&90).**This phenomenon was demonstrated in the subacute stage of local allergic ileitis.

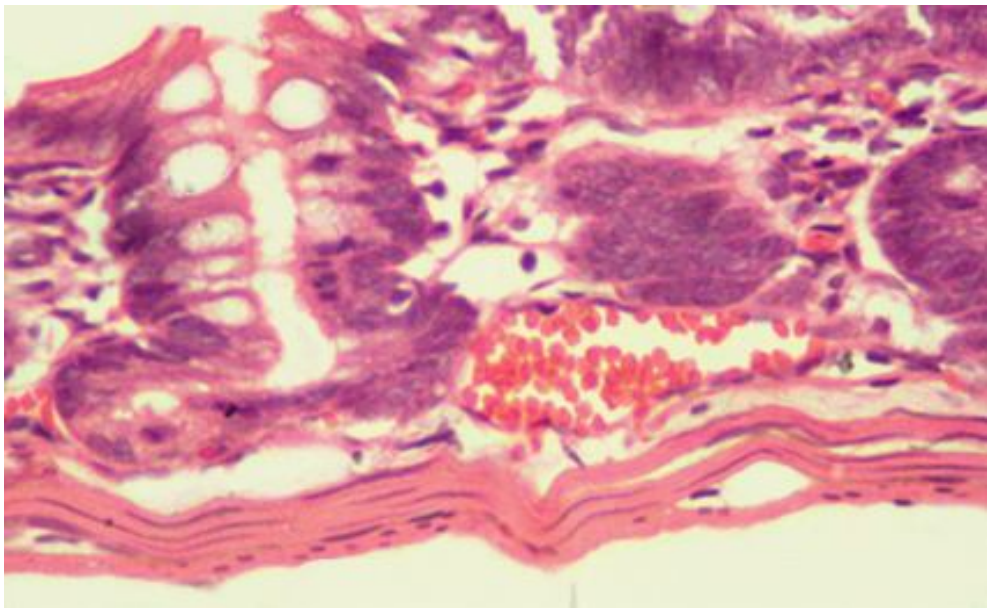
Differential for the subacute stage of systemic allergic ileitis were dense lymphocytic cells with fibroblasts and fibrocytes infiltrating villi core and lamina propria.This pathological picture was observed in chronic stage of local allergic ileitis.



Picture (89): Systemic allergic acute serous ileitis.

Hyperemia, eosinophils, macrophages and lymphoid cells infiltrated villi core .

7 days post oral allergen H&E X 25.



Picture (90): Systemic allergic acute serous ileitis.

Degenerative and necrotic changes in the crypts lining epithelium with thrombosis in lamina propria.

7 days post oral allergen H&E X 25.

The villi heights in systemic allergic ileitis decreased significantly and regularly from the day 4 (from 202.72 to 133.67 microns) to the end of the experiment to reach 115.04 microns**; table (28) & figure (34).** The decrease of ileal villi heights was on the same manner as in systemic allergic duodenitis and jejunitis and in local allergic ileitis.

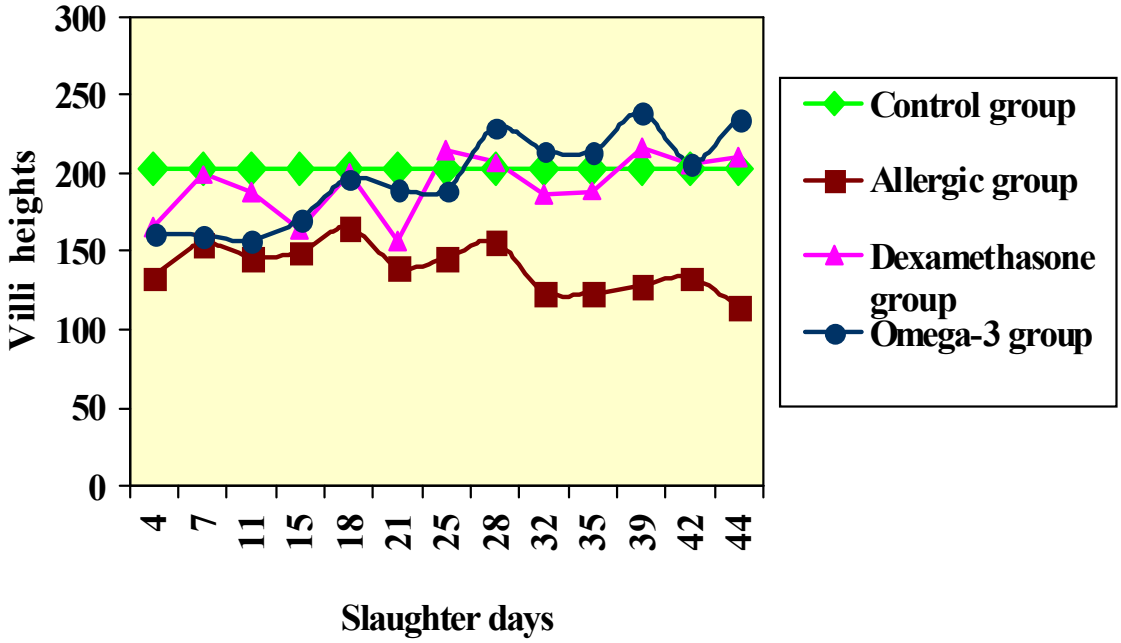


Figure (34): The length of villi heights in microns of the control, systemic allergic, dexamethasone and omega-3 treated ileum.

The number of IELs in crypts in systemic allergic ileitis was increasing significantly and steadily from the day 4 (from 0.0 to 4) to the end of the experiment to reach 10**; table (29) & figure (35). This behavior** was on the same manner as in systemic allergic duodenitis. In systemic allergic jejunitis, the increase of **IEL**s in crypts visualized the higher peak after 25 days as those in local allergic ileitis.

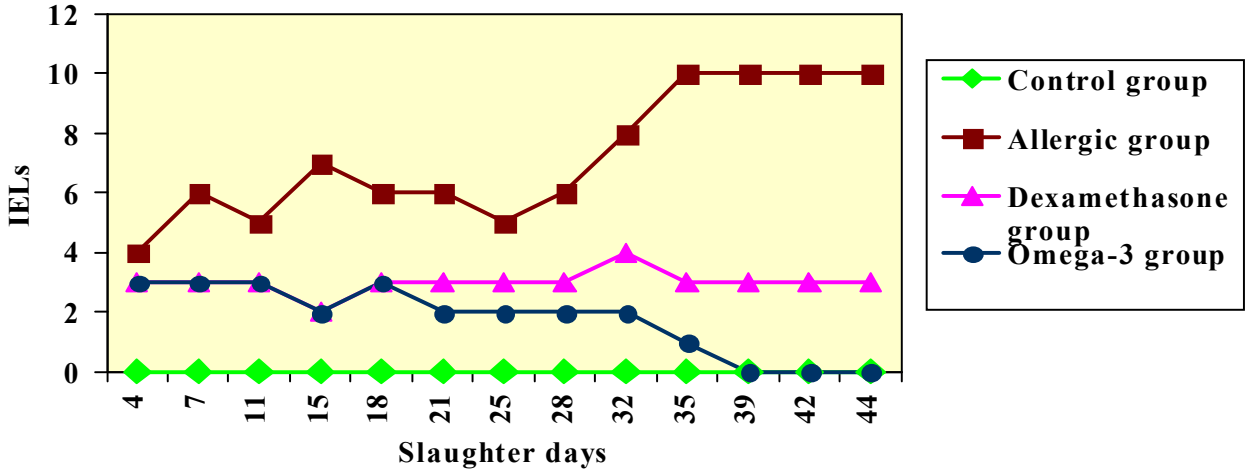


Figure (35): The mean number of intraepithelial lymphocytes per tencrypts of control, systemic allergic, dexamethasone and omega-3 treated ileum .

The **crypt depths** in systemic allergic ileitis were significantly lower than control from the day 4 (from 71.30 to 62.55 microns) and more or less regularly to the end of the experiment; **table (30) & figure (36).**The decrease of ileal crypts depths was on the same manner as in systemic duodenitis and jejunitis and in local allergic ileitis.

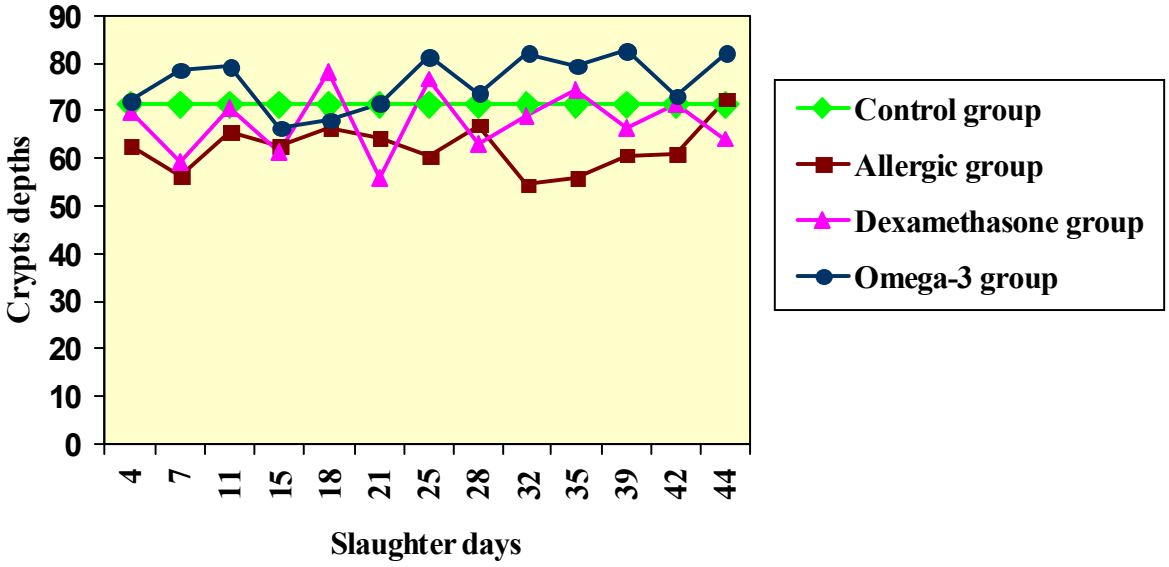


Figure (36): The length of crypts depth in microns of the control, systemic allergic, dexamethasone and omega- 3treated ileum.

Early germination of submucosal lymphoid follicles was observed in acute stage of systemic allergic ileitis instead of its occurrence in chronic stage of local allergic group.

Thrombosis and vasculitis was occurred in the acute stage of systemic allergic ileitis while vasculitis was the only phenomenon in acute stage of local allergic ileitis.

Dexamethasone and omega -3 treated ileum

The curative effect of dexamethasone started early at the day 7 in systemic allergic ileitis while it was at the day 18 in local allergic ileitis. **Dexamethasone** succeeded to normalize both exudation and atypical regeneration at the day 18 instead of the day 21 in local allergic ileitis. Normality of the villi reached earlier at the day 18 in the systemic ilieitis instead of the day 32 in systemic duodenitis and jejuninitis. **In omega-3 treated** group, the normality of the villi was reached at the day 21 in all small intestinal segments in systemic allergic and in local allergic ileitis.

Both treatments corrected significantly the increase of **IELs** in the ileal villi from the day 4 to the end of the experiment**; table (27) & figure (33).** In the two treated groups still the number of **IELs** was higher than the control but in **omeg-3** the correction was better from the day 25. The same manner was observed in the systemic allergic duodenitis and jejunitis. Comparing to local allergic ileitis, both treatments corrected the IELs number to the control level.

The correction of ileal villi heights in both treated groups was more or less approaching the control level until the day 25.**In dexamethasone** treated group, the ileal villi heights were more or less like the control to the end of the experiment .While **in omega-3,** the correction reached a little bit higher level; **table (28) &figure (34).In systemic allergic duodenitis and jejunitis** the correction of the villi heights was more or less higher than the control in both treatments but **omega-3** correction was the highest.**In local allergic ileitis**, **dexamethasone** treatment corrected the ileal villi heights from the day 25 to the end of the experiment. While **omega-3** correction was better than dexamethasone .It reached to the control at the day 21 and was higher than the control to the end of the experiment.

Both treatments corrected significantly the increase of **IELs** in the systemic allergic ileal crypt but the correction in the **omega-3** treated group was better from the day 21 to reach to the control at the day 35th**; table (29) &figure (35).In systemic allergic duodenitis**, the correction of both treatments achieved the control level. Vise versa in systemic allergic jejunitis, the correction of dexamethasone was better than that in omega-3 treated group from the day 25 to the end of the experiment. **In local allergic ileitis**, both treatments corrected the **IELs** to the control level allover the experimental period.

Dexamethasone correction of the crypt depths in systemic allergic ileitis reached the control level more or less allover the experimental period like in systemic allergic jejunitis**; table (30) & figure (36) .**While it failed to do this correction in systemic allergic duodenitis. In local allergic ileitis, dexamethasone correction reached only to the control level at the day 32 and to the end of the experiment. **Omega-3 treatment corrected the ileal crypt depths** and was higher than the control allover the experimental period in the three intestinal segments in systemic allergic group. **In local allergic ileitis, omega-3 correction** reached the control level at the day 7 and from the day11; it was higher than the control and to the end of the experiment.

In dexamethasone treated group, submucosal **lymphoid follicles** were exhausted after the day 28 in all small intestinal segments in systemic allergic group instead of the day 21 in local allergic ileitis. **In omega-3** treated group the **lymph follicles** were transported to complete diffuse infiltration of the submucosa by mature lymphocytes at the day 28 and persist as such to the end of the experiment in all small intestinal segments in systemic allergic group instead of the day 21 in local allergic ileitis.

Table (1): The mean number of intraepithelial lymphocytes per ten villi and crypts of local allergic duodenum.

Case No.	Duodenum	
	Villi	Crypts
1	3	1
2	4	1
3	5*	1
4	5*	2
5	5*	1
Mean	**5***	**1**
6	4*	2
7	4*	1
8	4*	1
Mean	**4***	**2**
9	5*	1
10	5*	1
11	5*	1
12	6*	1
Mean	**5***	**1**
13	5*	1
14	5*	1
15	5*	2
16	7*	2
Mean	**6***	**2**
17	5*	2
18	5*	3*
19	5*	2
Mean	**5***	**2**
20	4*	1
21	4*	2
22	6*	2
Mean	**5***	**1**
23	6*	3*
24	14*	5*

25		12*	5*
26		17*	6*
Mean		**14***	**5***
27		17*	6*
28		16*	8*
29		18*	6*
Mean		**17***	**7***
30		18*	7*
31		17*	7*
32		17*	8*
33		16*	7*
Mean		**17***	**7***
34		16*	6*
35		15*	6*
36		14*	7*
Mean		**15***	**6***
37		13*	8*
38		14*	7*
39		15*	6*
40		18*	6*
Mean		**16***	**6***
41		20*	8*
42		17*	7*
43		18*	7*
Mean		**18***	**7***
44	**1**	20*	8*
	2	16*	8*
	3	15*	8*
	Mean	**17***	**8***

*The decrease was significant in correlation to control.

Table (2): The length of villi heights and crypts depths in microns of the local allergic duodenum.

Case No.	Duodenum	
	Villi heights	**Crypts depths**
1	330.15	100.99
2	328.49	104.33
3	331.70	99.89
4	335.41	102.18
5	300.97	100.99
6	287.60*	90.88*
7	260.64*	95.21*
8	260.05*	93.20*
Mean	**269.43***	**93.10***
9	240.81*	85.33*
10	235.46*	88.66*
11	228.61*	85.15*
Mean	**231.37***	**84.79***
12	230.05*	80.55*
13	236.75*	84.06*
14	214.36*	79.03*
15	228.12*	75.26*
Mean	**221.11***	**77.17***
16	220.84*	77.22*
17	215.89*	72.33*
18	215.35*	71.99*
19	218.90*	74.14*
Mean	**216.71***	**72.82***
20	210.35*	75.55*
21	210.84*	73.64*
22	210.27*	76.90*
Mean	**210.49***	**75.36***
23	199.62*	65.66*
24	189.87*	62.40*

25	173.83*	69.96*
26	180.83*	69.18*
Mean	**181.51***	**67.18***
27	189.27*	63.12*
28	179.84*	66.96*
29	210.98*	65.73*
Mean	**193.36***	**65.27***
30	217.18*	69.72*
31	205.01*	65.75*
32	200.88*	70.00*
33	212.22*	63.33*
Mean	**206.04***	**66.36***
34	218.10*	71.55*
35	205.28*	70.84*
36	220.11*	69.80*
Mean	**214.50***	**70.73***
37	228.11*	70.51*
38	230.86*	65.26*
39	233.58*	67.19*
40	230.37*	67.95*
Mean	**231.60***	**66.80***
41	221.93*	69.38*
42	215.17*	68.15*
43	209.97*	69.11*
Mean	**215.69***	**68.88***
44 1	184.15*	74.33*
2	200.12*	66.94*
3	195.15*	70.44*
Mean	**193.14***	**70.57***

*The decrease was significant in correlation to control.

Table (3): The mean number of intraepithelial lymphocytes per ten villi of control, local allergic, dexamethasone and omega-3 treated duodenum.

Slaughter days	Control group	allergic group	Dexamethasone group	Omega-3 group
4	1	5*	0.0	0.0
7	1	4*	0.0	0.0
11	1	5*	0.0	0.0
15	1	6*	0.0 *	1*
18	1	5*	0.0*	0.0*
21	1	5*	0.0*	0.0*
25	1	14*	0.0*	0.0*
28	1	17*	0.0*	0.0*
32	1	17*	0.0*	1*
35	1	15*	0.0*	1*
39	1	16*	0.0*	1*
42	1	18*	0.0*	1*
44	1	17*	0.0*	1*

*The increase was significant in correlation to control.

*The decrease was significant in correlation to allergic group and reached to control level.

Table (4): The length of villi heights in microns of the control allergic, dexamethasone and omega-3 treated duodenum.

Slaughter days	Control group	Allergic group	Dexamethasone group	Omega-3 group
4	348.26	322.96	327.97	327.81
7	348.26	269.43*	313.18*	381.81*
11	348.26	231.37*	349.10*	369.05*
15	348.26	221.11*	357.36*	387.51*
18	348.26	216.71*	357.92*	362.29*
21	348.26	210.49*	451.47*	383.63*
25	348.26	181.51*	418.76*	396.03*
28	348.26	193.36*	413.92*	405.69*
32	348.26	206.54*	386.49*	344.70*
35	348.26	214.50*	437.80*	406.33*
39	348.26	231.60*	392.55*	424.35*
42	348.26	215.69*	386.78*	398.05*
44	348.26	193.14*	436.30*	414.26*

*The decrease was significant in correlation to control.

*The increase was significant in correlation to allergic group and reached to control level.

*The increase was significant in correlation to allergic group.

Table (5): The mean number of intraepithelial lymphocytes per ten crypts of control, local allergic, dexamethasone and omega-3 treated duodenum.

Slaughter days	Control group	allergic group	Dexamethasone group	Omega-3 group
4	1	1	0.0	0.0
7	1	1	0.0	0.0
11	1	1	0.0	0.0
15	1	2*	0.0 *	1*
18	1	2*	0.0*	0.0*
21	1	2*	0.0*	0.0*
25	1	5*	0.0*	0.0*
28	1	7*	0.0*	0.0*
32	1	7*	0.0*	0.0*
35	1	6*	0.0*	0.0*
39	1	6*	0.0*	1*
42	1	7*	0.0*	1*
44	1	8*	0.0*	1*

*The increase was significant in correlation to control.

*The decrease was significant in correlation to allergic group and reached to control level.

Table (6): The length of crypts depths in microns of the control, local allergic, dexamethasone and omega-3 treated duodenum.

Slaughter days	Control group	Allergic group	Dexametasone group	Omega-3 group
4	105.25	101.02	86.67	87.25
7	105.25	93.10*	85.05	92.15
11	105.25	84.79*	89.07	99.70*
15	105.25	77.17*	85.99	100.73*
18	105.25	72.82*	98.35*	100.77*
21	105.25	75.36*	106.50*	118.70*
25	105.25	67.18*	113.01*	125.27*
28	105.25	65.27*	107.40*	117.61*
32	105.25	66.36*	106.63*	105.26*
35	105.25	70.73*	120.08*	117.89*
39	105.25	66.80*	115.50*	119.37*
42	105.25	68.88*	115.32*	112.38*
44	105.25	70.57*	103.92*	116.92*

*The decrease was significant in correlation to control.

*The increase was significant in correlation to allergic group and reached to control level.

*The increase was significant in correlation to allergic group.

Table (7): The mean number of intraepithelial lymphocytes per ten villi and crypts of local allergic jejunum.

Case No.	Jejunum	
	Villi	Crypts
1	2	1
2	4	2
3	4*	1
4	5*	3*
5	6*	2*
Mean	**5***	**2***
6	6*	2*
7	6*	2*
8	7*	3*
9	7*	4*
Mean	**6***	**2***
10	13*	5*
11	12*	5*
12	10*	5*
Mean	**12***	**5***
13	10*	5*
14	10*	5*
15	13*	5*
16	10*	5*
Mean	**11***	**5***
17	9*	4*
18	11*	5*
19	12*	5*
Mean	**11***	**5***
20	11*	4*
21	13*	5*
22	12*	4*
Mean	**12***	**4***
23	10*	5*
24	13*	5*
25	12*	4*

26	12*	5*
Mean	**12***	**5***
27	9*	4*
28	9*	3*
29	8*	3*
Mean	**9***	**3***
30	10*	5*
31	11*	5*
32	12*	4*
33	11*	5*
Mean	**11***	**5***
34	12*	6*
35	10*	4*
36	12*	3*
Mean	**11***	**4***
37	12*	4*
38	13*	4*
39	13*	5*
40	10*	4*
Mean	**12***	**4***
41	13*	4*
42	12*	5*
43	12*	5*
Mean	**12***	**5***
44 1	12*	4*
	13*	5*
3	12*	3*
Mean	**12***	**4***

*The decrease was significant in correlation to control.

Table (8): The length of villi heights and crypts depths in microns of local allergic jejunum.

Case No.	Jejunum	
	Villi heights	**Crypts depths**
1	285.35	74.11
2	280.04	74.96
3	250.92*	69.49
4	240.03*	66.62*
5	246.05*	68.89*
Mean	**245.67***	**68.33***
6	220.58*	60.87*
7	220.49*	65.39*
8	225.43*	63.68*
Mean	**222.17***	**63.31***
9	220.58*	60.87*
10	215.12*	60.20*
11	200.47*	59.37*
12	197.72*	55.82*
Mean	**204.44***	**58.46***
13	190.11*	56.49*
14	180.77*	55.92*
15	197.64*	54.36*
16	185.65*	49.48*
Mean	**188.02***	**53.25***
17	180.65*	51.52*
18	182.92*	47.87*
19	170.65*	45.61*
Mean	**178.07***	**48.33***
20	165.89*	51.64*
21	162.29*	49.75*
22	165.41*	43.50*
Mean	**164.53***	**48.30***
23	155.47*	51.04*

24	150.22*	54.61*
25	143.63*	58.73*
26	140.92*	53.43*
Mean	**144.92***	**55.59***
27	133.64*	57.58*
28	129.11*	50.37*
29	124.20*	49.57*
30	117.61*	50.26*
31	121.62*	51.74*
32	125.19*	43.74*
33	110.08*	45.83*
Mean	**118.96***	**47.10***
34	105.13*	45.80*
35	116.24*	46.44*
36	118.86*	45.62*
Mean	**113.41***	**45.95***
37	120.75*	50.11*
38	139.58*	48.45*
39	127.42*	54.48*
40	147.98*	49.47*
Mean	**138.33***	**50.80***
41	138.58*	44.97*
42	138.95*	50.97*
43	145.62*	54.87*
Mean	**141.05***	**50.27***
44 1	148.64*	46.07*
2	119.74*	45.51*
3	131.57*	54.47*
Mean	**133.32***	**48.68***

*The decrease was significant in correlation to control.

Table (9): The mean number of intraepithelial lymphocytes per ten villi of control, local allergic, dexamethasone and omega-3 treated jejunum.

Slaughter days	Control group	Allergic group	Dexamethasone group	Omega-3 group
4	Zero	5*	3*	3*
7	Zero	6*	3*	2*
11	Zero	12*	3*	Zero*
15	Zero	11*	2*	1*
18	Zero	11*	2*	1*
21	Zero	12*	1*	Zero*
25	Zero	12*	Zero*	Zero*
28	Zero	9*	Zero*	Zero*
32	Zero	11*	Zero*	Zero*
35	Zero	11*	Zero*	Zero*
39	Zero	12*	Zero*	Zero*
42	Zero	12*	Zero*	Zero*
44	Zero	12*	Zero*	Zero*

*The increase was significant in correlation to control.

*The decrease was significant in correlation to allergic group and reached to control level.

Table (10): The length of villi heights in microns of the control, local allergic dexamethasone and omega-3 treated jejunum.

Slaughter days	Control group	Allergic group	Dexamethasone group	Omega-3 group
4	286.14	245.67*	220.70	247.71
7	286.14	222.17*	218.40	282.27*
11	286.14	204.44*	268.73*	247.18*
15	286.14	188.02*	258.19*	268.17*
18	286.14	178.07*	303.57*	314.60*
21	286.14	164.53*	304.76*	309.85*
25	286.14	144.92*	297.04*	298.31*
28	286.14	128.99*	276.33*	314.30*
32	286.14	118.96*	285.11*	302.97*
35	286.14	113.41*	276.33*	298.52*
39	286.14	138.33*	294.36*	308.23*
42	286.14	141.05*	290.43*	325.50*
44	286.14	133.32*	304.23*	327.04*

*The decrease was significant in correlation to control.

*The increase was significant in correlation to allergic group and reached to control level.

*The increase was significant in correlation to allergic group.

* The increase was significant in correlation to allergic group.

Table (11): The mean number of intraepithelial lymphocytes per ten crypts of control, local allergic, dexamethasone and omega-3 treated jejunum.

Slaughter days	Control group	Allergic group	Dexamethasone group	Omega-3 group
4	Zero	2*	1	1
7	Zero	2*	1	1
11	Zero	5*	1*	1*
15	Zero	5*	1*	1*
18	Zero	5*	1*	Zero*
21	Zero	4*	1*	Zero*
25	Zero	5*	Zero*	Zero*
28	Zero	3*	Zero*	Zero*
32	Zero	5*	Zero*	Zero*
35	Zero	4*	Zero*	Zero*
39	Zero	4*	Zero*	Zero*
42	Zero	5*	Zero*	Zero*
44	Zero	4*	Zero*	Zero*

*The increase was significant in correlation to control.

*The decrease was significant in correlation to allergic group and reached to control level.

Table (12): The length of crypts depths in microns of the control, local allergic, dexamethasone and omega-3 and treated jejunum.

Slaughter days	Control group	Allergic group	Dexametasone group	Omega-3 group
4	74.97	68.33*	68.17	57.21
7	74.97	63.31*	62.57	83.76*
11	74.97	58.46*	75.97*	73.49*
15	74.97	53.25*	70.04*	77.45*
18	74.97	48.33*	79.51*	92.29*
21	74.97	48.30*	79.45*	94.73*
25	74.97	55.59*	66.97*	86.56*
28	74.97	52.51*	81.67*	88.54*
32	74.97	47.15*	73.88*	86.35*
35	74.97	45.95*	93.70*	83.20*
39	74.97	50.80*	85.51*	88.21*
42	74.97	50.27*	74.91*	83.40*
44	74.97	48.68*	89.81*	86.43*

*The decrease was significant in correlation to control.

*The increase was significant in correlation to allergic group and reached to control level.

*The increase was significant in correlation to allergic group.

* The increase was significant in correlation to allergic group

Table (13): The mean number of intraepithelial lymphocytes per ten villi and crypts of local allergic ileum.

Case No.	Ileum	
	Villi	Crypts
1	2	Zero
2	1	1
3	3*	1
4	5*	2*
5	4*	1*
Mean	4*	1*
6	4*	2*
7	3*	2*
8	3*	1*
Mean	3*	2*
9	4*	1*
10	4*	2*
11	4*	2*
12	4*	2*
Mean	4*	2*
13	3*	2*
14	5*	2*
15	5*	2*
Mean	4*	2*
16	3*	2*
17	4*	2*
18	4*	3*
19	4*	1*
Mean	4	2*
20	5*	2*

21	6*	3*
22	6*	3*
Mean	6*	3*
23	7*	4*
24	9*	5*
25	12*	5*
26	14*	6*
Mean	12*	5*
27	16*	5*
28	18*	7*
29	20*	6*
Mean	18*	6*
30	18*	7*
31	16*	6*
32	14*	5*
33	17*	5*
Mean	16*	5*
34	15*	5*
35	13*	5*
36	14*	5*
Mean	14*	5*
37	15*	6*
38	13*	5*
39	14*	5*
40	12*	5*
Mean	13*	5*
41	15*	7*
42	14*	7*
43	12*	5*

Mean		14*	6*
44	**1**	11*	6*
	2	13*	5*
	3	14*	6*
	Mean	12*	6*

*The decrease was significant in correlation to control.

Table (14): The length of villi heights and crypts depths in microns of local allergic ileum.

Case No	Ileum	
	Villi heights	**Crypts depths**
1	199.68	70.44
2	195.65	68.64
3	196.57*	64.29*
4	170.79*	60.47*
5	160.75*	64.80*
Mean	**162.23***	**61.08***
6	155.15*	57.97*
7	140.08*	59.31*
8	129.82*	56.80*
Mean	**131.78***	**57.37***
9	125.44*	56.01*
10	118.56*	52.89*
11	117.69*	49.06*
12	111.44*	52.57*
Mean	**115.89***	**51.51***
13	109.40*	59.20*
14	114.49*	60.11*
15	108.16*	58.37*
16	110.25*	52.38*
Mean	**110.68***	**59.23***
17	114.58*	58.14*
18	118.86*	59.46*
19	106.20*	57.11*
Mean	**113.21***	**58.24***
20	106.43*	52.40*

21	100.00*	48.00*
22	107.36*	45.70*
Mean	**104.60***	**48.70***
23	100.61*	50.99*
24	107.16*	52.69*
25	110.94*	50.19*
26	116.03*	58.21*
Mean	**106.24***	**51.29***
27	103.93*	54.26*
28	114.31*	57.50*
29	102.98*	50.89*
Mean	**107.07***	**54.22***
30	115.76*	54.44*
31	112.24*	53.78*
32	112.87*	49.43*
33	119.38*	57.64*
Mean	**114.83***	**53.62***
34	125.46*	55.39*
35	121.28*	55.94*
36	110.04*	54.23*
Mean	**118.93***	**55.19***
37	132.87*	58.44*
38	116.68*	59.46*
39	138.90*	57.66*
40	121.65*	54.54*
Mean	**125.74***	**57.22***
41	128.54*	54.47*

42		125.50*	57.33*
43		129.66*	47.53*
Mean		**127.90***	**53.11***
44	**1**	104.99*	51.90*
	2	118.01*	52.09*
	3	131.61*	46.38*
	Mean	**118.59***	**51.84***

*The decrease was significant in correlation to control.

Table (15): The mean number of intraepithelial lymphocytes per villi of control, local allergic, dexamethasone and omega-3 treated ileum.

Slaughter days	Control group	Allergic group	Dexamethasone group	Omega-3 group
4	Zero	4*	Zero*	Zero*
7	Zero	3*	Zero*	Zero*
11	Zero	4*	Zero*	Zero*
15	Zero	4*	Zero*	Zero*
18	Zero	4*	Zero*	Zero*
21	Zero	6*	Zero*	Zero*
25	Zero	12*	Zero*	Zero*
28	Zero	18*	Zero*	Zero*
32	Zero	16*	Zero*	Zero*
35	Zero	14*	Zero*	Zero*
39	Zero	13*	Zero*	Zero*
42	Zero	14*	Zero*	Zero*
44	Zero	11*	Zero*	Zero*

*The increase was significant in correlation to control.

*The decrease was significant in correlation to allergic group and reached to control level.

Table (16): The length of villi heights in microns of the control, local allergic, dexamethasone and omega-3 and treated ileum.

Slaughter days	Control group	Allergic group	Dexamethasone group	Omega-3 group
4	202.72	162.23*	169.19	137.91
7	202.72	131.78*	163.25*	195.07*
11	202.72	115.89*	181.06*	181.50*
15	202.72	110.68*	183.46*	190.99*
18	202.72	113.21*	195.75*	216.12*
21	202.72	104.60*	201.33*	196.38*
25	202.72	106.24*	175.59*	212.04*
28	202.72	107.07*	177.66*	231.16*
32	202.72	114.83*	175.90*	219.87*
35	202.72	118.93*	163.58*	265.85*
39	202.72	125.74*	193.41*	252.02*
42	202.72	127.90*	199.18*	262.40*
44	202.72	118.59*	182.41*	229.02*

*The decrease was significant in correlation to control.

*The increase was significant in correlation to allergic group and reached to the control level.

*The increase was significant in correlation to allergic group.

* The increase was significant in correlation to allergic group.

Table (17): The mean number of intraepithelial lymphocytes per ten crypts of control, local allergic, dexamethasone omega-3 treated ileum.

Slaughter days	Control group	Allergic group	Dexamethasone group	Omega-3 group
4	Zero	1*	Zero*	Zero*
7	Zero	2*	Zero*	Zero*
11	Zero	2*	Zero*	Zero*
15	Zero	2*	Zero*	Zero*
18	Zero	2*	Zero*	Zero*
21	Zero	5*	Zero*	Zero*
25	Zero	6*	Zero*	Zero*
28	Zero	5*	Zero*	Zero*
32	Zero	5*	Zero*	Zero*
35	Zero	5*	Zero*	Zero*
39	Zero	5*	Zero*	Zero*
42	Zero	6*	Zero*	Zero*
44	Zero	6*	Zero*	Zero*

*The increase was significant in correlation to control.

*The decrease was significant in correlation to allergic group and reached to control level

Table (18): The length of crypts depth in microns of the control, local allergic dexamethasone and omega-3 treated ileum.

Slaughter days	Control group	Allergic group	Dexamethasone group	Omega-3 group
4	71.30	61.08*	46.89	63.64
7	71.30	57.37*	53.68	69.80*
11	71.30	51.51*	70.55*	72.18*
15	71.30	59.23*	62.94*	85.80*
18	71.30	58.24*	64.47*	78.50*
21	71.30	48.70*	62.96*	86.17*
25	71.30	51.29*	66.27*	75.48*
28	71.30	54.22*	62.21*	87.69*
32	71.30	53.62*	74.06*	97.04*
35	71.30	55.19*	66.72*	98.30*
39	71.30	57.22*	76.08*	95.22*
42	71.30	53.11*	67.33*	91.12*
44	71.30	51.84*	72.29*	84.55*

*The decrease was significant in correlation to control.

*The increase was significant in correlation to allergic group and reached to control level.

*The increase was significant in correlation to allergic group.

*The increase was significant in correlation to allergic group.

Table (19): The mean number of intraepithelial lymphocyte per ten villi of control systemic allergic, dexamethasone and omega-3 treated duodenum.

Slaughter days	Control group	allergic group	Dexamethasone group	Omega-3 group
4	1	11*	3*	3*
7	1	15*	5*	5*
11	1	13*	5*	3*
15	1	16*	4*	3*
18	1	16*	4*	5*
21	1	14*	5*	5*
25	1	16*	5*	5*
28	1	11*	3*	4*
32	1	12*	3*	4*
35	1	10*	4*	5*
39	1	11*	4*	5*
42	1	14*	4*	5*
44	1	10*	2*	5*

*The increase was significant in correlation to control.

*The decrease was significant in correlation to allergic group and reached to control level.

*The decrease was significant in correlation to allergic group but above control

Table (20): The length of villi heights in microns of the control, systemic allergic, dexamethasone and omega-3 treated duodenum.

Slaughter days	Control group	allergic group	Dexamethasone group	Omega-3 group
4	348.26	332.90	369.80	377.73
7	348.26	263.08*	397.46*	405.01*
11	348.26	333.32	434.01	408.79
15	348.26	289.85*	409.70*	429.30*
18	348.26	309.85*	423.57*	365.88*
21	348.26	290.30*	362.75*	419.66*
25	348.26	292.46*	432.00*	420.45*
28	348.26	294.19*	408.63*	461.83*
32	348.26	273.57*	363.49*	402.94*
35	348.26	328.10	390.06	447.63
39	348.26	310.95*	396.53*	445.11*
42	348.26	293.81*	395.65*	465.75*
44	348.26	258.61*	389.23*	422.09*

*The decrease was significant in correlation to control.

*The increase was significant in correlation to allergic group and reached to control level.

*The increase was significant in correlation to allergic group but above control.

Table (21): The mean number of intraepithelial lymphocytes per ten crypts of control, systemic allergic, dexamethasone and omega-3 treated duodenum.

Slaughter days	Control group	allergic group	Dexamethasone group	Omega-3 group
4	1	5*	1*	2*
7	1	7*	2*	2*
11	1	5*	2*	0.0*
15	1	6*	2*	1*
18	1	7*	2*	1*
21	1	7*	2*	1*
25	1	8*	2*	2*
28	1	6*	1*	2*
32	1	5*	1*	1*
35	1	6*	1*	2*
39	1	5*	2*	2*
42	1	8*	2*	2*
44	1	8*	1*	2*

*The increase was significant in correlation to control.

*The decrease was significant in correlation to allergic group and reached to control level

Table (22): The length of the crypts depths in microns of the control, systemic allergic, dexamethasone and omega-3 treated duodenum.

Slaughter days	Control group	Allergic group	Dexamethasone group	Omega-3 group
4	105.25	100.08	118.39	110.16
7	105.25	85.67*	87.96	104.78*
11	105.25	101.75	107.57	101.24
15	105.25	71.96*	83.98	114.64*
18	105.25	85.48*	100.65*	99.75*
21	105.25	84.72*	84.61	115.39*
25	105.25	79.97*	98.83*	110.11*
28	105.25	85.10*	78.76*	126.91*
32	105.25	78.87*	76.98	119.39*
35	105.25	86.43*	99.71*	105.21*
39	105.25	86.98*	91.46	114.70*
42	105.25	84.21*	89.94	118.41*
44	105.25	82.93*	88.82 *	106.33*

* The decrease was significant in correlation to control.

* The decrease was significant in correlation to control and allergic group.

*The increase was significant in correlation to allergic group and ached to control level.

*The increase was significant in correlation to allergic group but above control.

*The increase was significant in correlation to allergic group and below control.

Table (23): The mean number of intraepithelial lymphocytes per ten villi of control, systemic allergic, dexamethasone and omega-3 treated jejunum.

Slaughter days	Control group	Allergic group	Dexamethasone group	Omega-3 group
4	Zero	2*	1*	1*
7	Zero	3*	1*	3
11	Zero	4*	1*	3*
15	Zero	6*	1*	1*
18	Zero	10*	1*	1*
21	Zero	10*	3*	2*
25	Zero	12*	2*	3*
28	Zero	18*	3*	7*
32	Zero	22*	4*	7*
35	Zero	18*	4*	6*
39	Zero	18*	4*	9*
42	Zero	17*	4*	8*
44	Zero	17*	3*	9*

*The increase was significant in correlation to control.

*The decrease was significant in correlation to allergic group and reached to control level.

*The decrease was significant in correlation to allergic group but above control.

Table (24): The length of villi heights in microns of the control systemic allergic, dexamethasone and omega-3 treated jejunum.

Slaughter days	Control group	Allergic group	Dexamethasone group	Omega-3 group
4	286.14	286.131	288.36	294.67
7	286.14	222.15*	286.70*	302.86*
11	286.14	217.01*	307.76*	331.16*
15	286.14	232.78*	265.39*	291.84*
18	286.14	235.05*	313.59*	313.64*
21	286.14	182.97*	322.50*	288.01*
25	286.14	195.21*	307.13*	286.16*
28	286.14	216.28*	305.72*	373.85*
32	286.14	238.08*	276.00*	362.42*
35	286.14	205.76*	289.15*	329.59*
39	286.14	213.55*	299.30*	331.51*
42	286.14	193.10*	330.57*	330.54*
44	286.14	192.37*	326.79*	393.93*

*The decrease was significant in correlation to control.

*The increase was significant in correlation to allergic group and reached to control

level.

*The increase was significant in correlation to allergic group but above control.

* The increase was significant in correlation to allergic group and below control.

Table (25): The mean number of intraepithelial lymphocytes per ten crypts of control, systemic allergic, dexamethasone and omega-3 treated jejunum.

Slaughter days	Control group	Allergic group	Dexamethasone group	Omega-3 group
4	Zero	Zero	Zero	Zero
7	Zero	3*	Zero	Zero
11	Zero	3*	Zero*	1*
15	Zero	3*	Zero*	Zero*
18	Zero	5*	1*	Zero*
21	Zero	5*	1*	Zero*
25	Zero	5*	1*	2*
28	Zero	7*	1*	3*
32	Zero	8*	1*	2*
35	Zero	8*	1*	3*
39	Zero	9*	2*	3*
42	Zero	8*	2*	3*
44	Zero	8*	2*	3*

*The increase was significant in correlation to control.

*The decrease was significant in correlation to allergic group and reached to control level.

*The decrease was significant in correlation to allergic group but above control.

Table (26): The length of the crypts depths in microns of the control, systemic allergic, dexamethasone and omega-3 treated jejunum.

Slaughter days	Control group	Allergic group	Dexamethasone group	Omega-3 group
4	74.97	74.95	87.66	84.00
7	74.97	66.75*	68.23	76.32*
11	74.97	65.20*	88.71*	88.06*
15	74.97	66.45*	74.30	78.38*
18	74.97	67.62*	79.44*	72.79*
21	74.97	68.65	74.87	75.10
25	74.97	71.90	82.33	85.03
28	74.97	70.57	70.22	81.42
32	74.97	70.59	71.81	83.76
35	74.97	68.35*	80.52*	89.50*
39	74.97	67.81*	83.28*	90.44*
42	74.97	65.19*	74.54*	93.08*
44	74.97	64.85*	74.78*	93.22*

*The decrease was significant in correlation to control.

*The increase was significant in correlation to allergic group and reached to control

level.

*The increase was significant in correlation to allergic group but above control.

Table (27): The mean number of intraepithelial lymphocytes per ten villi of control, systemic allergic, dexamethasone and omega-3 treated ileum.

Slaughter days	Control group	Allergic group	Dexamethasone group	Omega-3 group
4	Zero	6*	3*	5*
7	Zero	11*	5*	4*
11	Zero	11*	4*	7*
15	Zero	12*	3*	3*
18	Zero	10*	5*	6*
21	Zero	10*	5*	5*
25	Zero	9*	4*	3*
28	Zero	11*	5*	3*
32	Zero	12*	8*	4*
35	Zero	13*	8*	4*
39	Zero	14*	8*	2*
42	Zero	17*	8*	2*
44	Zero	17*	8*	2*

*The increase was significant in correlation to control.

*The decrease was significant in correlation to allergic group and reached to control level.

*The decrease was significant in correlation to allergic group but above control.

Table (28): The length of villi heights in microns of the control, systemic allergic, dexamethasone and omega-3 treated ileum.

Slaughter days	Control group	Allergic group	Dexamethasone group	Omega-3 group
4	202.72	133.67*	165.57*	161.65*
7	202.72	155.47*	199.21*	160.34
11	202.72	146.50*	187.85*	157.28
15	202.72	149.76*	164.74*	171.03*
18	202.72	165.69*	199.62*	196.50*
21	202.72	140.48*	156.48*	190.28*
25	202.72	146.03*	214.26*	189.40*
28	202.72	156.75*	206.73*	229.56*
32	202.72	124.11*	186.75*	214.47*
35	202.72	123.50*	188.70*	213.92*
39	202.72	128.35*	215.82*	239.53*
42	202.72	133.49*	206.16*	206.62*
44	202.72	115.04*	210.36*	235.28*

*The decrease was significant in correlation to control.

*The increase was significant in correlation to allergic group and reached to control

level.

*The increase was significant in correlation to allergic group but above control.

* The increase was significant in correlation to allergic group and below control.

Table (29): The mean number of intraepithelial lymphocytes per ten crypts of control, systemic allergic, dexamethasone and omega-3 treated ileum.

Slaughter days	Control group	Allergic group	Dexamethasone group	Omega-3 group
4	Zero	4*	3	3
7	Zero	6*	3*	3*
11	Zero	5*	3*	3*
15	Zero	7*	2*	2*
18	Zero	6*	3*	3*
21	Zero	6*	3*	2*
25	Zero	5*	3*	2*
28	Zero	6*	3*	2*
32	Zero	8*	4*	2*
35	Zero	10*	3*	Zero*
39	Zero	10*	3*	Zero*
42	Zero	10*	3*	Zero*
44	Zero	10*	3*	Zero*

*The increase was significant in correlation to control.

*The decrease was significant in correlation to allergic group and reached to control level.

*The decrease was significant in correlation to allergic group but above control.

Table (30): The length of the crypts depths in microns of the control, systemic allergic, dexamethasone and omega-3treated ileum.

Slaughter days	Control group	Allergic group	Dexamethasone group	Omega-3 group
4	71.30	62.55*	69.88*	72.11*
7	71.30	56.31*	59.18	78.56*
11	71.30	65.56*	70.73	79.29*
15	71.30	62.54*	61.51	66.44*
18	71.30	66.32*	78.05*	68.01
21	71.30	64.36*	55.79*	71.57*
25	71.30	60.35*	76.68*	81.34*
28	71.30	67.01	62.94	73.71*
32	71.30	54.50*	68.83*	82.14*
35	71.30	55.91*	74.54*	79.41*
39	71.30	60.69*	66.47*	82.59*
42	71.30	60.90*	71.50*	73.13*
44	71.30	72.41	64.11	82.10

*The decrease was significant in correlation to control.

*The decrease was significant in correlation to control and allergic group.

*The increase was significant in correlation to allergic group and reached to control

level.

*The increase was significant in correlation to allergic group but above control.

* The increase was significant in correlation to allergic group and below control.

DISCUSSION

In both local and systemic food allergic experiments, administration of **ovalbumin (OVA)** induced **allergic enteritis** in the duodenum, jejunum and ileum. These findings coincide with D'Inca et al., 1990; Crowe et al., 1993; Scudamore et al., 1995, Ohtsuka et al., 1996; Hogan et al., 2000; Ogawa et al., 2002; Brandt et al., 2003; Saavedra and Vergara, 2004; Ogawa et al., 2004; Nakaiima-Adachi et al., 2006; Vaali et al., 2006; Fujitani et al., 2007; Forbes et al., 2008; Yeun et al., 2008 ; Pali-Scholl et al., 2008 and Valeur et al., 2009. This was in incomplete agreement with Dobbins, 1991; Oberhuber, 2000; and Meijer et al., 2003 who recorded **allergic enteritis** only in the duodenum and jejunum and **no enteropathy** was seen in the ileum.

This inflammation could be classified into: **A- Acute serous enteritis. B-Subacute sero-catarrhal enteritis. C-Chronic catarrhal enteritis**. The components of inflammation were:

Alteration: 1-Degenerative and necrobiotic changes in the lining epithelium of villi and crypts which were non significant in the acute phase and prominent in the subacute and chronic phases. **2-**Thrombosis in the blood vessels in the three phases.

Exudation: 1-Intraepithelial lymphocytosis in both villi and crypts. **2-**Inflammatory exudate was infiltrating villi cores and lamina propria. **3-**Vasculitis

Proliferation: 1–Villi and crypts hyperplasia and goblet cell metaplasia of the lining epithelium in the subacute phase. **2-**Fibrocytic cells proliferation was infiltrating villi cores and lamina propria in the subacute and chronic phases. **3-** Germination of submucosal lymphoid follicles.

These inflammatory reactions lead to changes in the shapes of villi and crypts and decrease of villi heights and crypts depths.

In local food allergy, the lining epithelium of the villi and crypts were suffering from **necrobiosis and desquamations** in subacute duodenitis. **Massive areas of coagulative necrosis** involving many villi with **degenerated upnormal shaped Brunner's glands** were observed in chronic duodenitis. In subacute jejunitis, degenerative and necrobiotic changes were observed in the villi lining epithelium**.** In chronic jejunitis, these changes extended deeply to involve the jejunal crypts. In the ileum, degenerative and necrobiotic changes were observed in both villi and crypts lining epithelium in subacute and chronic stages.

In systemic food allergy, the **degenerative and necrobiotic** changes were observed in both villi and crypts lining epithelium in the acute ileitis, subacute jejunitis and chronic duodenitis.

The degeneration and necrosis of the crypt epithelium and **the desuamation** of the villi lining epithelium were resembled to those detected by Miller et al., 1983; King and Miller, 1984 and Scudamore et al., 1995 in the rat during intestinal anaphylaxis. In piglets similar results were described by Helm et al., 2002 and Helm et al., 2003 during peanut allergy.

These changes may be due immunologic injury to the enterocytes caused by the toxic cationic proteins released from the lytic or intact eosinophils (Gleich and Adolphson, 1986; Dvorak et al., 1991 and Weller, 1991) and by increased cytotoxic intraepithelial and lamina propria lymphocytes (Dobbins, 1991 and Nagata et al., 1995). These activated T cells decrease epithelial proliferation and cause enterocytes injury from increased apoptosis via the tumor necrosis factor α , Fas/FasL and perforin / granzyme pathways leading to apoptotic enterocytes loss and villous architectural upnormalities (O'Farrelly, 2000; Ciccocioppo et al ., 2001; Lionetti,2002 and Merger et al., 2002).

The degenerated upnormal shaped Brunner's glands observed in chronic duodenitis were nearly similar to that recorded by Robert et al., 2000; Cellier et

al., 2000 and Vakani et al., 2010 in collagenous sprue ,celiac disease and milk intolerance.

On the other hand, this finding disagreed with Jones et al., 1984 who found **Brunner's glands hyperplasia** associated with celiac disease as a manifestation of peptic duodenitis and gastric hypersecretion.

In both local and systemic food allergy, **hemorrhages** in lamina propria, between intestinal crypts, in the submucosa and serosa was found in the three small intestinal segments in subacute and chronic stages. This finding was in line with that described by Lin et al., 2002; Helm et al., 2002; Helm et al., 2003 and Westerholm-Ormio,2004) in food allergy. This pathological alteration was due to degeneration in the blood vessels pointing to type III reaction (Parish, 1983 and Suen and Gordan, 2003).

Thrombosis started to be observed in the subacute phase in jejunum and ileum in local food allergy and was postponed to the chronic phase of duodenum inflammation. This fact pointed to the local mechanism of antigenic vasculitis as the duodenum which is the first segment receiving antigen was postponed to the late chronic stage.

In systemic food allergy, **thrombosis** was observed in acute phase of ileal inflammation, subacute phase of duodenal inflammation and chronic phase of jejunitis. This fact can be explained only by the systemic antigenic vasculitis.

In both local and systemic food allergy, **Vasculitis** was observed in the acute ileitis, subacute jejunitis, subacute and chronic duodenitis. **Serous arteritis** was demonstrated by proliferation of endothelial cells and inflammatory cells infiltration in the muscular wall and periartetiolar. In chronic jejunitis, **type III allergic vasculitis** which was manifested in the form of diffuse fibrinoid necrosis of the wall with inflammatory cells infiltration. The prescence of vasculitis agreed with that described in type III mediated hypersensitivity (Arseculeratne et al.,

1980), which initiated by establishment of immune coplexes in the wall of blood vessels in tissues and organs and activation of complement system (Suen and Gordan, 2003).

In local food allergy, the increase **IELs** in both **villi** and **crypts** was more or less the same between the three intestinal segments in that the raising passed more or less in steady period and then reached to a peak which was early in the jejunum and late in the ileum. This probably may be explained by the time for the antigen exposure and presentation to the cells.

In systemic food allergy, the increase of **villi IELs** and **crypts** was higher than in local food allergy in the three small intestinal segments. That is probably because of previous sensitization. The behavior of the **villi IELs** was the same in the three intestinal segments. The increase of **IELs in crypts** started earlier in systemic allergic duodenitis and ileitis than in systemic allergic jejunitis.

Similar findings to the increase of **IELs** were recorded in mice and rats by Ohtsuka et al., 1996, Ogawa et al., 2004.

Data supporting these findings in human were reported by Corazza et al., 1984; Hwang and Kim, 1998; Goldstein and Underllhill, 2001; Wahab, 2002; Green and Jabri, 2003; Biagi et al., 2004; Jarvinen et al., 2004 and Collin et al., 2005. But these findings were partly similar with those observed by Paajanen, 2005 who found an elevation of **intraepithelial $\gamma\delta^+$ T cells** without mononuclear cells infiltration in the lamina propria of the duodenum and ileum with cow milk allergy.

Most of **IELs** in food sensitive enteropathy were suppressor cytotoxic $CD8^+$cells. These findings confirm the importance of cell mediated immunity and lymphocytes toxicity in this condition (Nagata et al., 1995).

In local food allergy, **serous exudates** rich in eosinophils and macrophages were increasing the width of villi cores and infiltrating the lamina propria,

submucosa and serosa in the acute stage in the three intestinal segments**.** In subacute stage, the **serous exudates** became rich in lymphoid cells and widened between the muscle fibers of the muscularis where lymphocytes were permeating**.** There was a **diffuse lymphocytic reaction** allover the submucosa**.** Finally **serous serositis** was also found. These changes lead to upnormalities in the shape, length and width of the villi. In chronic stage, the dense lymphocytic reaction widened the villi cores.

In systemic food allergy; as there was a previous sensitization**, early appearance of mature lymphocytes** infiltration beside hyperemia, eosinophils, macrophages and lymphoid cells reaction in the villi cores and lamina propria was observed in the acute stage in the three intestinal segments. In subacute stage, **dense aggregation of mature lymphocytes** appeared in the villi cores and lamina propria earlier than that in local food allergy.

Data on **exudates** were nearly similar with those observed by Hogan et al., 2000; Yang et al., 2001 and Chen et al., 2011 in rats and mice allergy. But were in disagreement with those detected by Nakaiima-Adachi et al., 2006 and Pali-Scholl et al., 2008 ,as there was non significant inflammatory infiltration which indicating moderate degree of inflammation under mucosal repair.

In local food allergy, **germination of submucosal lymphoid follicles** was observed in chronic stage in the three small intestinal segments. In systemic food allergy, early germination of the submucosal lymphoid follicles was recorded in acute stage in the three small intestinal segments due to previous sensitization.

This data was partly resembled to that described by Kokkonen, 1999; Kokkonen et al., 2000; Kokkonen et al., 2001 and Turunen et al., 2004 in delayed cow milk allergy. These changes were not accompanied by either villous atrophy or the increase of mononuclear cells infiltration in lamina propria. Nearly similar data was described by Paajanen, 2005 who mentioned that **germinating lymphoid follicles** with **elevation** of the denisity **intraepithelial γ δ^+ T** cell were the only characteristic findings in delayed cow milk allergy.

In local food allergy, **hyperplasia and metaplasia** of the villi and crypts lining epithelium started to appear in the subacute and chronic phases in the three small intestinal segments. **In systemic food allergy,** these changes were observed in acute jejunitis ,subacute duodenitis and in chronic ileitis .

These data were partly similar to those described by Chen et al., 2011 in rice allergy in mice.

In both local and systemic food allergy, both **villi heights and crypts depths** were significantly decreased. In local food allergy, both **duodenal villi heights and crypts depths** were decreased significantly from the day 6 to the end of the experiment. In the jejunum and ileum, the decrease of **villi heights and crypts depths** was significant from the day 4 to the end of the experiment earlier than the duodenum. In systemic food allergy, the decrease of **villi heights and crypts depths** was significant from the day 7 to the end of the experiment in the duodenum and jejunum. In the ileum, it was earlier at the 4^{th} day.

These findings partly agreed with Ogawa et al., 2002, Ogawa et al., 2004; Nakaiima-Adachi et al., 2006 and Pali-Scholl et al., 2008 who detected **increased crypts depths** with significant **reduction in villi heights**. The **crypts elongation** was owing to the decrease in the villi heights (Walker-Smith et al., 1978 and Maluenda et al., 1984).

These data disagreed with Wakefield et al., 2000 and Veres et al., 2003 who recorded lacking of **villous atrophy** and or the mononuclear cells infiltration in the lamina propria in delayed type food allergy.

The **villous atrophy** may be the result of the inflammatory reaction and the increase of immunoglobulin-containing cells in the lamina propria (Perkkio et al., 1981) and may be due to mucosal T-cells activation (MacDonald and Spencer, 1988 and Ciccocioppo et al., 2002), but loss of ileal villi was recorded in T-cell deficient mice (Dohi et al., 2003).

Dexamethasone and omega-3 treatments

In both local and systemic food allergy, the two drugs repaired the **pathological alterations** in the villi and crypts epithelium in the three small intestinal segments after 25 days. This data was in coordination with Nagafuchi al., 2000; Nagura et al., 2002; and Takano et al., 2004 and Kaminogawa and Nanno, 2004 who stated that **dexamethasone** and **omega-3** are potent widely used anti-inflammatory and anti-allergic drugs.

Omega-3 treatment was better and earlier than dexamethasone in repairing the **degenerative** and **necrotic changes** in the villi and crypts lining epithelium in the three small intestinal segments in both local and systemic food allergy. Surveying the available to us literature through the internet, no similar data were found in animals and human.

This result may be due to the effect of **omega-3** in lowering the production of the most powerful arachidonic acid metabolite; leukotriene B1, thromboxane A2 and leukotriene-B4 (Lee et al., 1985; Rampton and Collins, 1993 and Seibold, 2005). **Omega-3** was promoting the formation of less inflammatory series prostaglandins and thromboxanes (Belluzzi et al., 1996), modulating eicosanoid synthesis and inhibiting the pro-inflammatory cytokine IL-1 (James et al., 2000; Jones and Papamand-Jaris, 2001 and Simopoulos, 2002). In addition to the effects of **omega-3** in attenuating intestinal mucosal damage (Yamashiro et al., 1994) and reducing the incidence of intestinal necrosis (Caplan et al., 2001). Omega-3 affected intestinal cell differentiation (Alessandri et al., 1995) and formation of tight junction (Jaing et al., 1998).

In both local and systemic allergic groups, the **two drugs** prevented **vasculitis** and **thrombosis** after the day 25 in the three small intestinal segments. No similar data were found in animals and human.

Omega-3 caused an increase in thromboxane A3 (a weak platelet aggregator and a weak vasoconstrictor) and an increase in prostacyclin (PG13; an active vasodilator and inhibitor of platelet aggregation). It caused an increase in leukotriene B5 (a weak inducer of inflammation and a weak chemotactic agent (Weber et al., 1986 and Lewis et al., 1986). **Omega-3** decreased intestinal platelets activating factor (PAF) and leukotriene concentrations (Akisu et al., 1998). O**mega-3** led to decrease in thromboxane A2 (a potent platelets aggregator and vasoconstriction (Teitelbaum and Walker, 2001) and decrease in leukotriene B4 formation (an inducer of inflammation and a powerful inducer of leukocyte chemotaxis and adherence).

In local food allergy, **both treatments** completely prevented the **IELs** in the villi and crypts of the three small intestinal segments. **Omega-3** was better than dexamethasone as the correction was exactly as the control. **Comparing the ileum** with the other two small intestinal segments, the **jejunum** was different as the decrease was retarded to the day 21 for the omega-3 treatment and the day 25 for the dexamethasone treatment. **Comparing the IELs** in the **ileal crypts** with the other two small intestinal segments, it coincided with duodenum. The jejunum was different as the decrease was retarded to the day 18 for **omega-3** treatment and the day 21 for **dexamethasone** treatment. No similar data were found in animals and human.

Glucocorticoids affected cell mediated immunity by inhibiting the proliferation of lymphoid tissue, reducing the chemo-attraction of lymphocytes, modulating lymphotoxin production and preventing accumulation of macrophages (Eyre, 1980). **Dexamethasone** is routinely used to modulate cells migration into sites of inflammation and this action is accomplished in part by a potent effect on the synthesis of pro-inflammatory cytokines and chemokines (Schleimer, 1990) and reducing the degree of leucocytes responsiveness (Mancuso et al., 1995). **Dexamethasone** reduced endogenous transforming factor-B1 synthesis (TGF-B1); which is involved in the homing mechanism of cells to endothelial venules;

markedly altering enterocytic antigen presentation, and reducing the aberrant state of activation of mucosal immune cells (Ruemmele et al., 1999).

Omega-3 decreased the level of major histocompitapility complex class II (MHCII) expression on the surface of peripheral blood monocytes (Hughes et al., 1996) and thereby affected T-cell proliferative response to antigen. **Omega-3** inhibited the proliferation of lymphocytes (Jeffery et al., 1996; Jeffery et al., 1997a&b) through surface markers involved in T cell proliferation (Sasaki et al., 1999). Furthermore, **omega-3** can suppress the production of IL-2; which is necessary for the lymphocytes proliferation and regulation of function of cytotoxic lymphocytes, natural killer, B cells and macrophages; (Calder et al., 1992; Das, 1994 and Devi and Das, 1994). **Omega-3** suppressed excessive activation of T cells (Fujikawa et al., 1992 and Hughes and Pinder, 2000). **Omega-3 fatty acids**-rich diets were associated with a lower percentage of activated T and B- cells (Robinson and Field, 1998).**Omega-3** can decrease the lymphocyte proliferation through its effects on glucose and glutamine utilization; which are essential for lymphocytes proliferative capacity; (Teitelbaum and Walker, 2001).

In systemic food allergy**, both dexamethasone and omega-3 treatments** decreased the **IELs** of duodenal villi in the allergic group from the 4^{th} day. **Comparing** with local allergic treated group, both treatments decreased **IELs** in the duodenal villi statistically to the control level allover the experiment and prevented its production. No similar data were found in animals and human.

In systemic food allergy**, both dexamethasone and omega-3 treatments** completely prevented the production of **IELs** in the duodenal crypts allover the experimental period. The Same phenomenon was in the local food allergy. No similar data were found in animals and human.

In systemic food allergy the **IELs** in the jejunal **villi** under **dexamethasone** treatment decreased significantly from the day 4 to the end of the experiment .It was the same as control level until the day 18. From the day 21, it started to

increase than control more or less in regular manner to the end of the experiment. The picture of **dexamethasone** treatment in local allergic jejunitis was controversial as it corrected from the day 4 the increase in the villi **IELs** and reached to control level at day 25. There was no difference observed in the manner of dexamethasone treatment comparing to systemic allergic duodenitis.

Omega-3 had treated; from the 4^{th} day; the increase of **IELs** in the jejunal villi to decrease in more or less steady manner until the end of the experiment but the decrease was lower in comparison to **dexamethasone** treatment.

Omega-3 treatment in local allergic jejunitis corrected completely the rise in the number of villi **IELs** to control level at day 21. No difference in the pattern of treatment was observed between the omega-3 treated systemic allergic duodenitis and jejunitis.

Dexamethasone treatment was better than **omega-3** in systemic allergic jejunitis. No similar data were found in animals and human.

In systemic allergic jejunitis, **dexamethasone** corrected significantly the increase of **IELs** in the crypts to be like the control to the day 35 then it was slightly higher to the end of the experiment**.** In local allergic jejunitis **dexamethasone** corrected significantly the increase of **IELs** in the crypts allover the experimental period like in systemic allergic duodenitis.

Omega-3 in systemic allergic group corrected to the control level the number of **IELs** in the crypts until the day 21 after that it was higher than the control to the end of the experiment. While in local allergic jejunitis and in systemic duodenitis, it corrected the increase of **IELs** allover the experimental period. **Dexamethasone treatment** was better than omega-3. No similar data were found in animals and human.

Both dexamethasone and omega-3 treatments corrected significantly the increase of **IELs** in the ileal **villi** from the day 4 to the end of the experiment**.** In

the two treated groups still the number of **IELs** was higher than the control but in **omeg-3** treated group the correction was better from the day 25. The same manner was observed in the systemic allergic duodenitis and jejunitis. Comparing to local allergic ileitis, both treatments corrected the **IELs** number to the control level. No similar data were found in animals and human.

Both treatments corrected significantly the increase of **IELs** in the systemic allergic **ileal crypts** but the correction in the **omega-3** treated group was better from the day 21 to reach to the control at the day 35. In systemic allergic duodenitis, the correction of **both treatments** achieved to reach to the control level. Vise versa in systemic allergic jejunitis, the correction of **dexamethasone** was better than that in **omega-3** treated group from the day 25 to the end of the experiment. In local allergic ileitis, **both treatments** corrected the **IELs** to the control level allover the experimental period. No similar data were found in animals and human.

Dexamethasone induced apoptosis of IELs (Brunner et al., 2001 and Norrman et al., 2003), depressed CD8+ T cells function (Lo et al., 2005) and reduced number of $\gamma\ \delta^{+}$ T cells (Menge and Dean-Nystrom,2008).

Both dexamethasone and omega-3 treatments repaired the villous abnormalities; including hyperemia, edema, infiltration of eosinophils and macrophages and proliferation of lymphoid cells, lymphocytes , fibroblasts and fibrocytes; where most of the villi were completely normal after the day 25 in the three small intestinal segments in both local and systemic food allergy.

Steroids are immunosuppressant and have inhibitory action on fibroblasts (Grieco and Ushman, 1970). All **glucocorticoids** suppress all aspects of inflammation including early responses (vasodilatation, edema, and leucocytes migration), later events (collagen deposition, fibroblast and capillary proliferation) and finally scar formation irrespective of the cause; physical chemical or immunological trauma; (Eyre, 1980). **Glucocorticoids** effectively suppressed the

late allergic responses $CD4^+$ T cells and eosinophils infiltration (Durham and Kay, 1985). An immediate blood eosinopaenia induced by glucocorticoids may be due to inhibition of tissue and circulating eosinophil responses to granulocyte-macrophage colony stimulating factor; GM-CSF; (Lamas et al., 1991) or mediated by sequestration of leucocytes to lymphoid organs and inhibition of the release of cells from bone marrow (Schleimer and Bochner 1994). **Dexamethasone** inhibited eosinophils accumulation in mice (Das et al., 1997).This effect may be due to induction of apoptosis (Kawabori, et al., 1991) or inhibition of eosinophil production in rat bone marrow (Pasquale et al., 1999). **Dexamethasone** is routinely used to modulate cells migration into sites of inflammation and this action is accomplished in part by a potent effect on the synthesis of pro-inflammatory cytokines and chemokines (Schleimer, 1990) and reducing the degree of leucocytes responsiveness (Mancuso et al., 1995). **Dexamethasone** reduced endogenous transforming factor-B1 synthesis (TGF-B1); which involving in the homing mechanism of cells to endothelial venules,markedly alter enterocytic antigen presentation and reducing the aberrant state of activation of mucosal immune cells (Ruemmele et al., 1999). **Dexamethasone** inhibited the synthesis of IL-9 which involving mast cells proliferation, eosinophils function, IgE production and in stimulation of mucus production (Holz et al., 2005).

In contrast, **glucocorticoids** were found to enhance bone eosinopoiesis through glucocorticoids receptors, in normal and allergic murine model (Maria et al., 2000).

Omega-3 regulated or modulated the immune response by specifically impairing T cell responses (Erickson et al., 1980; Chandra, 1980 and Beisel et al., 1981). Furthermore, it increased thromboxane A3, prostacyclin (PG13) and leukotriene B5 (Weber et al., 1986 and Lewis et al., 1986). **Omga-3** competed with arachadonic acid (AA) for prostaglandin and leukotriene synthesis at the cyclooxygenase and lipoxygenase level (Lands, 1992) and partially replaced the AA in cell membranes including the membranes of platelets, erythrocytes,

neutrophils, monocytes and hepatocytes so that the ingestion of **omega-3** led to decrease prostaglandin E2 production (Teitelbaum and Walker, 2001), decrease in thromboxane A2 and decrease in leukotriene B4 formation. **Fish oil** could diminish the antigen presenting cell activity of dendritic cells migrating from the gut (Sanderson et al., 1997).

In local food allergy, **dexamethasone** could normalize the regeneration in the jejunum and ileum. **But in the duodenum** it did not control the atypical regeneration. **Omega-3** did not normalize the regeneration on the expense of more atypism. No similar data were found in animals and human.

In systemic food allergy, **dexamethasone** could normalize regeneration in the ileum, while in the **duodenum and jejunum;** it did not control the atypical regeneration.

Omega-3 could normalize the atypical regeneration in the three small intestinal segments. No similar data were found in animals and human.

In both local and systemic food allergy, **dexamethasone** caused **lymphoid exhaustion** in the submucosal lymphoid follicles of the three small intestinal segments. This reaction was lated in systemic food allergy than in local allergic treated group. In systemic food allergy the lymphoid depletion occurred after 28 days in the three segments. While in local food allergy, it was earlier in the duodenum than in the jejunum and ileum. No similar data were found in animals and human.

Glucocorticoids can inhibit the proliferation of lymphoid tissue (Eyre, 1980). **Glucocorticoids** can acceletate apoptosis of lymphocytes in lymphoid tissue including peyer's patches (Ruiz-Santana et al., 2001; Goya et al., 2003; Pearse, 2006 and Totini et al., 2006) and suppressing the proliferative capacity of lymphocytes in lymphoid follicles (Norrman et al., 2003 and Menge and Dean-Nystrom,2008).

Dexamethasone induced lymphocytes apoptosis and thymus atrophy through inhibition of antioxidant enzymes activity and increasing reactive oxygen species (ROS) and (Orzechowski and Ostasewski, 2002 and Kis, 2010).

In both local and systemic **omega-3** treated groups, the submucosal **lymphoid follicles** were transformed to complete diffuse infiltration of the submucosa by mature lymphocytes and persisted as such to the end of the experiment. **In systemic allergic treated group,** this reaction was after 28 days in the three segments and appeared later than in local omega-3 treated ones. **In local food allergy,** the reaction appeared earlier in the duodenum than in the jejunum and ileum. No similar data were found in animals and human.

Dietary **omega-3** able to attenuate T-cell mediated inflammation. The suppressive effects on T cell may result from either reducing lymphocytes proliferation or enhanced apoptosis of activated T cells or both (Switzer et al., 2004).

In local food allergy ,**both dexamethasone and omega-3 treatments** corrected the decrease in the duodenal **villi heights** in the **local allergic group** at the same time at the day 11 but the villi heights in **omega-3** treated group were nearer to the control than the **dexamethasone** treated one. No similar data were found in animals and human.

Both treatments corrected the decrease in the duodenal **crypts depths** in local food allergy. But **omega-3** corrected the duodenal crypts depths 7 days earlier than **dexamethasone** treatment and the regeneration was more or less the same in both groups. No similar data were found in animals and human.

Both dexamethasone and omega-3 treatments corrected significantly the decrease in the jejunal **villi heights** in the local allergic group. But **omega-3** correction was better than dexamethasone because it reached to the control level 11 days earlier. No similar data were found in animals and human.

Both treatments corrected the decrease in the jejunal **crypts depths** in local food allergy. But **dexamethasone** treatment was better than the **omega-3** treatment in the correction of the jejunal **crypts depths** because atypical regeneration was expressed in the **omega-3** treated group more than in the **dexamethasone** treated group although the **omega-3** correction was earlier at the day 7. No similar data were found in animals and human.

Comparing the three small intestinal segments**, dexamethasone** blocked exudation in the ileum and gave complete regeneration. In the **jejunum** the reaction to **dexamethasone** was more or less like the control, that is to say normalizing both exudation and regeneration. **In the duodenum**; as the first intestinal segment receiving the treatment; **dexamethasone** although controlling exudation but the regeneration was atypical. No similar data were found in animals and human.

In systemic food allergy, **omega-3 treatment** caused approaching to the control level at the day 18 to 21, but the **villi heights** raised above the control from the day 25 to the end of the experiment on the expense of more expression of atypical regeneration. **Omega-3treatment** decreased exudation but expressing atypical regeneration in the three intestinal segments. No similar data were found in animals and human.

In local food allergy, **both treatments** repaired significantly the decrease of ileal **crypts depths**. **Dexamethasone treatment** reached to the control level later at the day 32 and to the end of the experiment by normalizing both exudation and regeneration. While **omega-3** correction reached normality earlier at the day 7 and rose up from the same day to be above normal to the end of the experiment by expressing more atypical regeneration. **Comparing** the three intestinal segments the **crypts depths** confirmed the same conclusion as the villi heights. No similar data were found in animals and human.

In systemic food allergy, **both dexamethasone and Omega-3 treatments** increased significantly the duodenal **villi heights** from the day 7 above the control level. **Dexamethasone correction** was better in systemic allergy than in local allergy, as it started to correct **villi heights** from the day 7 higher than the control level. **Omega-3 treatment** was in higher magnitude in systemic allergy. No similar data were found in animals and human.

In systemic food allergy, **dexamethasone** treatment although corrected the decrease in the **duodenal crypts depths** at interrupted intervals to reach to the control level at the days 11, 25 and 35, it never exceeded and was under the control allover the experimental period**.** Comparing with local food allergy, **dexamethasone** treated the decrease in the **crypts depths** to reach the control at the 15th day and then, it was higher than the control level during the rest of the experiment. **Omega-3 treatment** succeeded to correct the decrease in the duodenal **crypts depths** to the control level from the day 7 to the day 25 and it was higher than the control in the rest period allover the experiment. **Omega-3 treatment** was better and earlier. No similar data were found in animals and human.

In systemic food allergy**, dexamethasone** treatment corrected significantly the decrease in the jejunal **villi heights** from the day7 to be more or less higher than the control level in interrupted periods from day 18 to 28 and from day 39 to 44. This phenomenon may be due to atypical regeneration. **Omega-3** corrected significantly the decrease in the jejunal **villi heights** from day 7 to the end of the experiment to be little higher than the control. **Omega-3** was better than **dexamethasone** treatment. No similar data were found in animals and human.

From the **day 18** to the end of the experiment, **dexamethasone** corrected the decrease of the jejunal **crypts depths** to the control level before that the correction was not complete in systemic food allergy. **In local allergic dexamethasone treated group**, the decrease of jejunal **crypts depths** was

corrected to the control level from the day 11 to 21 after that the correction was higher than control level. **In systemic allergic dexamethasone treated duodenitis,** the correction of the decrease **crypts depths** was under the control level. **Omega-3 correction** of the decrease **crypts depths** was higher than the control level and **better** than dexamethasone allover the experimental period in systemic allergic duodenitis and jejunitis and in local allergic jejunitis. No similar data were found in animals and human.

In systemic food allergy, the correction of ileal **villi heights** in both treated groups was more or less approaching to the control level until the day 25. **In dexamethasone** treated group, the ileal villi heights were more or less like the control to the end of the experiment .While **in omega-3,** the correction reached a little bit higher level. **In systemic allergic duodenitis and jejunitis** the correction of the villi heights was more or less higher than the control in both treatments but **omega-3** correction was the highest. **In local allergic ileitis**, **dexamethasone** treatment corrected the ileal villi heights from the day 25 to the end of the experiment. While **omega-3** correction was better than dexamethasone. It reached to the control at the day 21 and was higher than the control to the end of the experiment. No similar data were found in animals and human.

Dexamethasone correction of **the crypt depths** in systemic allergic **ileitis** reached to the control level more or less allover the experimental period like in systemic allergic **jejunitis.** While it failed to do this correction in systemic allergic **duodenitis**. **In local allergic ileitis, dexamethasone** correction reached only to the control level at the day 32 and to the end of the experiment. **Omega-3 treatment** corrected the ileal **crypt depths** and was higher than the control allover the experimental period in the three intestinal segments in systemic allergic group. **In local allergic ileitis, omega-3 correction** reached the control level at the day 7 and from the day 11, it was higher than the control and to the end of the experiment. No similar data were found in animals and human.

Dexamethasone could repair the intestinal mucosal lesion through stimulation of enterocytes proliferation and migration (Nobili et al., 1997) .Thus it was capable to increase the villi heights and crypts depths (Iordache et al., 2005).

Omega–3 could increase villi heights and crypts depths via increasing cell proliferation, inhibiting enterocytes apoptosis and decreasing intestinal mucosal injury (Rosa et al., 2010; Sukhotnik et al., 2010 and Sukhotnik et al., 2011).

CONCLUSION

In both local and systemic food allergic experiments, administration of **ovalbumin (OVA)** induced **allergic enteritis** in the duodenum, jejunum and ileum. This inflammation could be classified into: **A-Acute serous enteritis. B-Subacute sero-catarrhal enteritis. C-Chronic catarrhal enteritis**. The components of inflammation were:

Alteration: 1-Degenerative and necrobiotic changes in the lining epithelium of villi and crypts, non significant in the acute phase and prominent in the subacute and chronic phases. **2-** Thrombosis in the blood vessels in the three phases.

Exudation: 1-Intraepithelial lymphocytosis in both villi and crypts. **2-**Inflammatory exudates were infiltrating villi cores and lamina propria. **3-**Vasculitis

Proliferation: 1-Villi and crypts hyperplasia and goblet cell metaplasia of the lining epithelium in the subacute phase. **2-** Fibrocytic cells proliferation was infiltrating villi cores and lamina propria in the subacute and chronic phases. **3-** Germination of submucosal lymphoid follicles.

These inflammatory reactions lead to changes in the **shapes** of villi and crypts and decrease of villi **heights** and crypts **depths**.

In local food allergy, the **degenerative and necrobiotic** changes of the villi and crypts lining epithelium appeared in subacute phase in the three small intestinal segments. The changes in the jejunal crypts were postponed to the chronic phase. In systemic food allergy, the changes were observed in both **villi and crypts** lining epithelium in acute ileitis, subacute jejunitis and chronic duodenitis.

In local food allergy, **thrombosis** was due to local antigenic vasculitis and in systemic food allergy was due to systemic antigenic vasculitis. The **vasculitis** was due to local antigenic stimulus in local food allergy and was due to systemic antigenic stimulus in systemic food allergy.

In local food allergy, the increase **IELs** in both **villi** and **crypts** was more or less the same in the three intestinal segments. In systemic food allergy, the increase of **villi IELs** and **crypts** was higher than in local food allergy in the three small intestinal segments. That is probably because of previous sensitization. The increase of **IELs in crypts** started earlier in systemic allergic duodenitis and ileitis than in allergic jejunitis.

In local food allergy, the **exudation** was **serous** rich in eosinophils and macrophages in acute stage, **sero-catarrhal** exudates rich in lymphoid cells in subacute stage and **chronic catarrhal** exudates rich in dense lymphocytic reaction in the chronic stage. Differential for systemic food allergy was the **early appearance of mature lymphocytes** and **diffuse lymphoid cells** reaction observed in the acute stage due to previous sensitization.

Hyperplasia and metaplasia of the villi and crypts lining epithelium in the three small intestinal segments represented the phenomena of atypical regeneration in both local and systemic food allergy.

In systemic food allergy, **germination** of the **submucosal lymphoid follicles** was earlier in the three small intestinal segments due to previous sensitization.

The **villi heights and crypts depths** were decreased in the three small intestinal segments in both local and systemic food allergy. The **decrease** was lower in local food allergy than in systemic food allergy in the three small intestinal segments.

Omega-3 was better than dexamethasone in the correction of: **1-IELs** of the villi and crypts in local allergic duodenitis and jejunitis and in systemic allergic ileitis. **2-** The **villi heights** in the three small intestinal segments in both local and systemic food allergy. **3-** The **crypts depths** in the duodenum and ileum in local food allergy and in the three small intestinal segments in systemic food allergy. **4-** In normalizing the atypical regeneration in the three small intestinal segments in systemic food allergy. **5-** In transforming the submucosal lymphoid follicles to diffuse mature lymphocytes in the three small intestinal segments in both local and systemic food allergy, vise versa to dexamethasone which caused lymphoid exhaustion.

Dexamethasone was better in the correction of: 1-**Crypts depths** in local allergic jejunitis. **2- IELs** in both villi and crypts in systemic allergic duodenitis and jejunitis. **3- In** normalizing the **atypical regeneration** in the jejunum and ileum in local food allergy.

The **two drugs** had similar effects in the following: **1**- In preventing **vasculitis** and **thrombosis** in the three small intestinal segments in both local and systemic food allergy. **2**- In preventing the **IELs** in both ileal villi and crypts in local food allergy. **3**- In normalizing the **villi shape** in the three small intestinal segments in both local and systemic food allergy.

Finally, we suggest the use of daily course of **omega-3** treatment together with **dexamethasone** injection weekly for 45 days.

SUMMARY

Immunologically mediated **enteropathies** consist of a group of different disease that is characterized by varying degree of villous destruction in the small intestine. Examples of these diseases are celiac disease and food allergy (Marsh, 1996 and Westerholm -Ormio, 2004). **Food allergy** is treated in human and experimental animals by using either **omega-3** (Nagafuchi, et al., 2000; Nagura, et al., 2002; and Takano et al., 2004) or **dexamethasone** (Krishnaswamy, et al., 2001; Sampson, 2003 and Kamingawa and Nanno, 2004).

The aim of this work is to induce **OVA food allergy** and to study their pathogenesis, gross and microscopic changes and try to treat the induced condition by using **omega-3** fatty acids and **dexamethasone**.

1-Experimental design

(A)- Local anaphylaxis protocol

The animals were divided into **4 groups**. **All rats** except the control group were exposed to chicken egg albumin by daily gavages dosing for 44 days without the use of an adjuvant. The **dexamethasone** treated group received single intra-peritoneal injection of 1 mg of dexamethasone per week and the **omega-3** treated group received daily gavage dosing with 0.1 ml of code liver oil (that provide 6.8mg eicosapentaenoic acid **(EPA)** and 4.9mg docosa-hexaenoic acid **(DHA).**

(B) -Systemic anaphylaxis protocol

The animals were divided into **4 groups**. These animals except the control group received the sensitization dose which consisted of intra-peritoneal injection of 10 µg of chicken egg albumin protein and 10 mg of aluminum hydroxide [Al (OH) 3] as adjuvant in 0.9 % saline. **After 15 day sensitization**, the rats exposed to 1 mg chicken egg albumin protein / ml tap water, 1 ml per animal by daily gavages dosing for 44 days. The **dexamethasone** treated group received single

intra-peritoneal injection of 1 mg of dexamethasone per week and the **omega-3** treated group received daily gavage dosing with 0.1 ml of code liver oil.

2-Histopathological analysis

Tissue samples were taken from duodenum, jejunum and ileum and were prepared for morphometric analysis, IELs and morpho-pathological examination. The statistical analysis was performed by using **Students t-test** using GraphPad Prism version 5.01 Program by Graph Pad software Inc. The results were considered significant if $P < 0.05$.

In both local and systemic food allergic experiments, administration of **ovalbumin (OVA)** induced **allergic enteritis** in the duodenum, jejunum and ileum. This inflammation could be classified into: A-Acute serous enteritis. B-Subacute sero-catarrhal enteritis-Chronic catarrhal enteritis. The components of inflammation were: Degenerative and necrobiotic changes in the lining epithelium of villi and crypts, non significant in the acute phase and prominent in the subacute and chronic phases. Thrombosis in the blood vessels in the three phases. Intraepithelial lymphocytosis in both villi and crypts. Inflammatory exudates were infiltrating villi cores and lamina propria. Vasculitis. Villi and crypts hyperplasia and goblet cell metaplasia of the lining epithelium in the subacute phase. Fibrocytic cells proliferation was infiltrating villi cores and lamina propria in the subacute and chronic phases. Germination of submucosal lymphoid follicles. These inflammatory reactions lead to changes in the **shapes** of villi and crypts and decrease of villi **heights** and crypts **depths**.

Omega-3 was better than dexamethasone in the correction of: **1-IELs** of the villi and crypts in local allergic duodenitis and jejunitis and in systemic allergic ileitis. **2-**The **villi heights** in the three small intestinal segments in both local and systemic food allergy. **3-**The **crypts depths** in the duodenum and ileum in local food allergy and in the three small intestinal segments in systemic food allergy. **4-** In normalizing the atypical regeneration in the three small intestinal segments in

systemic food allergy.**5-**In transforming the submucosal lymphoid follicles to diffuse mature lymphocytes in the three small intestinal segments in both local and systemic food allergy, vise versa to dexamethasone which caused lymphoid exhaustion.

Dexamethasone was better in the correction of: **1-Crypts depths** in local allergic jejunitis. **2- IELs** in both villi and crypts in systemic allergic duodenitis and jejunitis. **3-** In normalizing the **atypical regeneration** in the jejunum and ileum in local food allergy.

The two drugs had similar effects in the following: **1**- In preventing **vasculitis** and **thrombosis** in the three small intestinal segments in both local and systemic food allergy. **2**- In preventing the **IELs** in both ileal villi and crypts in local food allergy. **3**- In normalizing the **villi shape** in the three small intestinal segments in both local and systemic food allergy.

Finally, we suggest the use of daily course of **omega-3** treatment together with **dexamethasone** injection weekly for 45 days.

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الملخص العربي للرسالة

تتكون الالتهابات المعوية المناعية من مجموعة من الامراض المختلفة التي تتميز بدرجات متفاوتة من الدمار الزغابي في الامعاء الدقيقة. من امثلة هذه الامراض مرض الاضطرابات الهضمية والحساسية الغذائية.

تعالج حساسية الغذاء في الانسان وحيوانات التجارب باستخدام عقار الاحماض الدهنية أوميجا-٣ او عقار الديكساميثازون.

الهدف من هذا العمل هو احداث حساسية غذاء باستخدام زلال البيض ودراسة التغيرات المرضية الظاهرية و المجهرية مع علاج هذه الحالة بعقار الاحماض الدهنية اوميجا-٣ وبعقار الديكساميثازون.

١- التصميم التجريبي

أ- حساسية الغذاء الموضعية

تم تقسيم الفئران الي ٤ مجموعات تلقت جميع الحيوانات عدا المجموعة الضابطة زلال البيض وذلك بتجريعها واحد ملجم زلال بيض لكل ١ مل ماء يوميا لمدة ٤٤ يوم بدون استخدام مادة مساعدة. تلقت المجموعة المعالجة بعقار الديكساميثازون جرعة ١ ملجم من عقار الديكساميثازون اسبوعيا بالحقن البريتوني لمدة ٤٤ يوم. كما جرعت المجموعة المعالجة بالاحماض الدهنية اوميجا-٣ بجرعة ١و مل زيت كبد الحوت يوميا لمدة ٤٤ يوم (والذي يوفر٦,٨ ملجم من الحمض DHA و ٤,٩ ملجم من الحمض الدهني EPA.

ب- حساسية الغذاء الجهازية :

تم تقسيم الفئران الي ٤ مجموعات. تلقت جميع الفئران عدا المجموعة الضابطة جرعة تحسيسية من الحقن البريتوني لخليط من ١٠ ميكرو جرام زلال بيض و ١٠ ملجم هيدروكسيد الألومنيوم كمادة مساعدة مذابة في محلول فسيولوجي ٠,٩% .بعد مرور ١٥ يوم من الجرعة التحسيسية تم تجريع هذه الحيوانات١ملجم من زلال البيض يوميا لمدة ٤٤ يوم .تلقت المجموعة المعالجة بعقار الديكساميثازون ١ ملجم من الديكساميثازون اسبوعيا بالحقن البريتوني لمدة ٤٤ يوم .كماجرعت المجموعة المعالجة بالاحماض الدهنية اوميجا-٣ بجرعة ١و مل زيت كبد الحوت يوميا لمدة ٤٤ يوم.

٢- التحليل الباثولوجى

أخذت العينات من القطع المعوية الثلاثة العفج ، الصائم ،اللفائفي تم تثبيتها في محلول الفورمالين ١٠ % واعداد القطاعات وصباغتها بصبغة الهيماتوكسلين والايوسين وذلك لفحصها كالاتي :

١- قياس ارتفاع الزغابات المعوية .

٢- قياس اعماق الغدد المعوية .

٣- عدد الليمفاويات بين الخلايا الظهارية المبطنة للزغابات والغدد المعوية.

٤- فحص القطاعات مجهريا لتحديد اي تغيرات مرضية في الغلالات المختلفة المكونة للجدار المعوي .

٣- التحليل الاحصائي

تم اجراء التحليل الاحصائي لهذه القياسات باستخدام **اختبار t.**

أحدث تجريع زلال البيض التهاب معوي تحسسي في العفج والصائم واللفائفي في كل من حساسية الغذاء الموضعية والجهازية. يمكن تصنيف هذه الألتهابات الى ثلاثة انواع هي :

١- التهاب معوي حاد مصلي.

٢- التهاب معوي تحت الحاد مصلي نزلي .

٣- التهاب معوي مزمن نزلي

وكانت عناصر الالتهاب هي :

١- تغيرات تهدمية وموت للخلايا الظهارية المبطنة للزغابات والغدد المعوية ولغدة برونرز، وهذه التغيرات كانت بارزة في الالتهاب المعوي تحت الحاد والمزمن .

٢- تجلط الدم في الاوعية الدموية ، كانت بارزة في الالتهاب المعوي الحاد وتحت الحاد والمزمن .

٣- زيادة معنوية لعدد الليمفاويات بين الخلايا الظهارية المبطنة للزغابات والغدد المعوية .

٤- افرازات ألتهابية متخللة الزغابات المعوية والصفيحة المخصوصة والغلالة تحت المخاطية .

٥- التهاب الاوعية الدموية .

٦- زيادة في اعداد الخلايا الظهارية ، وتحول الخلايا الكاسية المبطنة الزغابات والغدد المعوية .

٧- انتشار الخلايا الليفية في صميم الزغابات المعوية والصفيحة المخصوصة وهذه التغيرات ظهرت بوضوح في الالتهاب المعوي تحت الحاد والمزمن.

٨- انبات الحويصلات الليمفاوية الموجودة في الغلالة المخاطية .

وهذه التفاعلات الالتهابية ادت الي :

أ- تغيير اشكال الزغابات والغدد المعوية .

ب- نقص ارتفاع الزغابات المعوية .

ج- نقص اعماق الغدد المعوية .

التاثير العلاجي:

التاثير العلاجي للاحماض الدهنية اوميجا-٣ افضل من عقار الديكساميثازون في تصحيح كل من :

١- اعداد الليمفاويات بين الخلايا الظهارية في الزغابات والغدد المعوية وذلك في الالتهاب التحسسي الموضعي للعفج والصائم و التهاب اللفائفي التحسسي الجهازي.

٢- ارتفاع الزغابات المعوية في القطع المعوية الثلاثة في كل من حساسية الغذاء الموضعية والجهازية .

٣- اعماق الغدد المعوية في العفج واللفائفي في حساسية الغذاء الموضعية واعماق الغدد المعوية في القطع المعوية الثلاثة في حساسية الغذاء الجهازية .

٤- في ارجاع الوضع الطبيعي للتجديد الغير نمطي في القطع المعوية الثلاثة في حساسة الغذاء الجهازية .

٥- في تحول الحويصلات الليمفاوية في الغلالة تحت المخاطية الي خلايا ليمفاوية ناضجة منتشرة في الغلالة تحت المخاطية وذلك في القطع المعوية الثلاثة في كل من حساسية

الغذاء الموضعية والجهازية وهذا عكس ما احدثه الديكساميثازون من ارهاق في الحويصلة الليمفاوية .

- وكان عقار الديكساميثازون افضل في تصحيح كل من :

١- اعماق الغدد المعوية في التهاب الصائم التحسسي الموضعي.

٢- تصحيح اعداد الليمفاويات بين الخلايا الظهارية في الزغابات والغدد المعوية في العفج والصائم في حساسية الغذاء الجهازية.

٣- في ارجاع الوضع الطبيعي للتجديد الغير نمطي في التهاب الصائم واللفائفي التحسسي الموضعي .

و كان للعقارين اثار مماثلة فيما يلي :

١- منع التهابات الاوعية الدموية وتجلط الدم عن القطع المعوية الثلاثة في كل من حساسية الغذاء الموضعية والجهازية .

٢- منع ظهور الليمفاويات بين الخلايا الظهارية المبطنة للزغابات والغدد المعوية في التهاب اللفائفي التحسسي الموضعي .

٣- اعادة الشكل الطبيعي للزغابات المعوية في القطع المعوية الثلاثة في حساسية الغذاء الموضعية الجهازية .

أخيرا نقترح استخدام جرعة يومية من عقار الاحماض الدهنية اوميجا-٣ بجانب الحقن الاسبوعي لعقار الديكساميثازون لمدة ٤٥ يوم .

جامعة أسيوط

كلية الطب البيطرى

الإحداث التجريبي لحساسية الغذاء الموضعية والجهازية " باستعمال زلال البيض في الفئران: الباثولوجيا والعلاج بواسطة الهرمونات القشرانية السكرية والأحماض الدهنية "أوميجا-٣

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بكالوريوس العلوم الطبيه البيطريه ١٩٩٢

ماجستير العلوم الطبية البيطرية تخصص باثولوجيا الحيوان ٢٠٠١

كلية الطب البيطرى – جامعة أسيوط

للحصول على درجة دكتوراه الفلسفة في العلوم الطبية البيطرية
(باثولوجيا الحيوان)

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١٤٣٢هـ - ٢٠١١م