Effect of Human Male Senescence on Mucosal Immune Responses During Bacterial Urinary Tract Infections

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(وَقُل رَبِ أَنزِلْني مُنزَلاً مُبارَكاً وأَنت خَيْرُ المُنزِلِين)

المؤمنين /٢٩

Dedication

To my dearest family..
To my respectable supervisor Prof. Dr. Ibrahim M. S. Shnawa..
& to whom I am concerned ...
With respect ..

Zainab K. Ahmed

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ABSTRACT:

The present study aims at evaluating the effect of senescence on urinary mucosal immunoglobulins (UMIGs) in urinary tract infection patients (UTIP). Such evaluation was made to fifty three urinary tract infected patients their ages were (٦٠-٩٥) and twenty five from adolescent patients their ages were(٢٢ – ٤٠) years.

UMIGs were separated by ٦٪ PEG (٦٠٠٠ MW).The concentration and titer was determined in elderly patients and adolescent as control groups . The significant differences were observed in cases of *Enterobacter spp, E. coli ,Pseudomonas auroginosa and Staphylococus epidermidis* . During the reaction of bacterins of the isolated organisms with UMIGs, ٢ mercaptoethanol sensitive ,and resistant components were noted. The sensitive component was guessed as of serum origin. The study proved that the titers of antibodies in adolescent patients were rather higher than elderly patients of ٢ -١١ folds. Thus , UMIGs could be used as an infection probe in elderly as well as in adolescent, while, it is worth mentioning that senescence may induce some inhibitory action on humoral mucosal responses as induced in those elderly UTI patients.

List of contents .

LIST OF ABBREVATIONS .

Abbreviations	Means .
DNA	Deoxyribonucleic acid .
RNA	Ribonucleic acid .
mRNA	messenger Ribonucleic acid ..
Rb	Retinoblastoma .
ROS	Reactive oxygen species .
TSH	Thyrotropin stimulating hormone.
mt DNA	Mitochondrial DNA.
NAD	Nicotinamide adinine dinucleotide phosphate .
NADH	Redused nicotinamide adinine dinucleotide phosphate .
ATP	Adenosin triphosphat .
Ab	Antibody
Ag	Antigen .
UTI	Urinary tract infection .
Sig A	Secretory immunoglobulin A .
M cells	Mucosal cells.
Iu	International unit
IL -٢	Interleukin -٢
IL -٤	Interleukin -٤
IL-٦	Interleukin -٦
AGEs	Advanced Glycosylation end-products .
MLSP	Maximum lifespan potential .
MUIg	Mucosal urinary immunoglobulin .

IgG	Immunoglobulin G .
IgE	Immunoglobulin E .
IgM	Immunoglobulin M .
Ia	Immune associated
CD	Clusters of designation or cluster of differentiation .
Sc	Secretory component .
IFN	Interferon .
TNF	Tumour necrosis factor .
٢-ME	٢- Mercaptoethanol .
OVA	Ovine albumin .
CFA	Complete Freund Adjuvant .
CT	Cholera toxin .
TT	Tetanus toxin .
TcR	T –cell receptor .
CAP	Community acquired pneumonia .
PGE -٢	Prostaglandin E-٢ .
CMI	Cell mediated immunity .
AMI	Antibody mediated immunity .
TH	T-helper cell .
TGF	Transforming growth factor .
MALT	Mucosa associated lymphoreticular tissue .
Pn	Pyelonephritis
MSSU	Mid stream specimens of urine .
Fsc	Free secretory component .
APC	Antigen presenting cell .
LPS	Lipopolysaccharide .
mAb	Mucosal Ab
PG	Peptidoglycan
B.K.C.	Benzal Konium Chloride
٢-ME	٢-Mercaptoethanol

LIST OF TABLES

List of Figures .

CHAPTER ONE

I- INTRODUCTION

I-١ OVERVIEW

At most ,human aging can be associated with lonely life, disability, stress and/or pruning to metabolic, neoplastic, as well as microbial infection (Lamberts *et al*, ١٩٩٧; Johnson *et al*., ١٩٩٩; David and Lipschitz, ١٩٩٩; Gems, ٢٠٠٣; Troen, ٢٠٠٣).Thus, the theme of aging is the subject of past ,present and future .

١-٢ BIOLOGY OF AGING

Aging changes appear to be very divers and subject to numerous environmental and genetic influences. Aging processes thus show a great deal of plasticity and potential for modification. The senescence in adult life leads to predictable complete loss of function during aging in all human populations. Although some individuals carry genes that predispose them to early onset of specific degenerative diseases, there is mach reason to anticipate that interventions will be possible. The reduced rates of death from ischemic heart disease in recent decades show the importance of lifestyle in the outcomes of aging. Many biologists and geriatricians are convinced that the potential for successful aging by maintaining health and independent at advanced ages is far greater than recognized by the general public (Goldman & Bennett ,٢٠٠٠) . Although the terms “aging” and “senescence” are often used interchangeably, senescence more often refers to the latter stages of this process, more

proximal to death, while aging can be considered to be the process that occurs throughout the adult life span (Cohen,١٩٩٩).

١-٣ Theories of Aging

Two major types of theories have been proposed: the cell damage/ error theories and the program theories. It is likely that components of each of the concepts actually contribute to determining the aging process.(Cristofalo *et al*.,١٩٩٩;Schaie,١٩٩٩ and Solomon,١٩٩٩).

١-٣-١ Cell Damage/Error Theories

Cell damage/error theories are generally stochastic in nature. That is to say, they assume that events occurring on a random basis gradually cause the accumulation of damage to vital areas of cellular organ function. This damage would then result in what we see as the phenotype of aging. The so-called "error catastrophe" theory was earliest of these, which proposed that random errors are occurred during the synthesis of new proteins such that the rapid accumulation of such error-containing molecules would eventually be incompatible with normal function. However, little experimental evidence has been produced to support such a theory. On the other hand, there has been considerable experimental support for changes occurring at a post-synthetic (i.e., post-translational) point. The two major sources of damage currently thought to contribute to this process are free radicals and glycosylation (Cristofalo *et al*.,١٩٩٩).

١-٣-١-١ Free radical theory

This theory proposes that highly reactive free radical species, which may be either externally generated, or internally generated as by products of oxidative metabolism, then react with key cellular components resulting in alterations in function leading to the changes consistent with

aging. There are a number of reasons for the attractiveness of this theory. First, molecules of many sorts, including lipids, proteins, and DNA that are critical to survival, may be affected by free radical attack(Sohal and Weindruch,١٩٩٦).

The body has evolved an extensive system of intrinsic cellular antioxidant defenses that have the potential to control such reactions, suggesting that they are of considerable importance. Thus, free radical generation in mammals inversely correlates with longevity and the levels of antioxidant enzymes have been noted to be higher in longer lived species. However, evidence of the role such processes has in truly determining longevity is incomplete, and it is of interest that over-expression of antioxidants in lower species does not necessarily increase survival. One particular focus for the potential effects of the free radical damage has been on the mitochondria, since this organelle is the site of much of the free radical production in cells. It is felt that free radical damage may be responsible for the decline in energy production that results as a cell ages perhaps as a result of mitochondrial DNA damage (Solomon,١٩٩٩).

١-٣-١-٢ Glycosylation

Non-enzymatic glycation occurs with increasing frequency during the aging process. This non-enzymatic attachment of glucose to many vital components, including DNA and proteins but especially to some of the longer lived proteins such as collagen, appears to be associated with damage and functional alterations. This type of attack results in damage including cross-linking and accumulation of cross-linked protein within cells and tissues that appears to have the potential to affect bodily

functions adversely, as well as to interfere with the biosynthetic and energy generating systems. In addition, the presence of advanced glycation end products (AGE) also appears to initiate inflammatory reactions. Such chronic inflammatory processes might create many of the phenotypes of aging, including a number of the degenerative processes occurring in this setting. (Baker & Martin,١٩٩٧ , Cohen, *et al*., ١٩٩٧and Solomon, ١٩٩٩) .

١-٣-٢ Program Theories

Program theories suggest that the processes of aging and senescence are a result of genetic programs some what analogous to the genetic programs controlling embryogenesis, growth, development and maturation. In this context aging is a result of certain genes being shut down (Gene exclusion) while others become overly expressed. The fact that there is such a dramatic difference in interspecies maximal lifespan suggests that there is some degree of genetic control, at least at the species level. To what extent such controlling processes explain aging differences within any given species is not known.(Fossel ,١٩٩٨).

While neuroendocrine and immunologic factors have been associated with the aging process and are noted to change during it, little evidence has been generated to support the role of either of these systems indirectly contributing to the control of the aging process. On the other hand, a large body of work has now accumulated to suggest that there are at least several genes involved in genetic control of maximal lifespan(Finch &Tanzi,١٩٩٧). Such genes have been noted in nematodes, yeast, and fruit flies, but to a much lesser degree in

mammalian systems. There has been compelling evidence for genetic control of cellular aging with a number of genes including several tumor suppressor genes such as *Rb* and *p٥٣*, implicated in replicative senescence at this level. How this translates to control of the aging process at the organism level is yet to be determined. Another potentially important indicator of genetic control of senescence has also been determined in *in vitro* systems. This relates to the role of the telomere in controlling cellular senescence. Telomeres are the terminal ends of the chromosomes and appear to have as their major roles the prevention of chromosomal degradation and/or fusion with other chromosomal ends. It has been demonstrated that the average length of telomeres decreases during both *in vitro* and *in-vivo* aging of fibroblasts as well as peripheral blood lymphocytes. Such telomere shortening does not occur in immortalized cells, perhaps related to the reactivation of the enzyme telomerase in such cells. Recently it has been shown that activation of telomerase in human cells *in vitro* can significantly delay the onset of senescence and extent the lifespan of such cells, as can experimental elongation of telomeric length(Fossel,١٩٩٨) .

I-٤ IMMUNO- PHYSIOLOGY OF AGING

A broad spectrum of physiologic changes occurs during the normal aging process and independent of disease.(Taffet,١٩٩٩). Before considering some of the individual organ changes in brief, it is useful to consider the overall impact of such changes. In general, most of the impact of these changes is noted in impaired responses to external stimuli. Thus, a decrease in physiological reserve generally leaves base line function of any given organ or indeed of a combination of organ

functions relatively unchanged. But it leaves a smaller amount of reserve capacity with which the individual can respond to external stimuli and maintain basic homeostasis. This decrease in the functional reserve capacity has become a hallmark of the approach to the geriatric patient since it creates a setting of heightened vulnerability, which is so commonly played out in clinical settings. Several areas of regulatory function are affected, including blood pressure regulation with significant alterations of beta adrenergic receptor mediated vasodilatation; thermoregulation with reduced heat production, impaired vasoconstrictor activity and altered temperature perceptions; and volume regulation with decreased thirst drive and age-related renal changes .(Taffet,١٩٩٩; Leipzig,١٩٩٩).

The aging changes include:

١-Cardiovascular system.

٢-Pulmonary system.

٣-Endocrine system.

٤-Gastrointestinal system.

٥-Nervous system.

٦-Organ systems relating to drug handling .

These involve predominantly the hepatic and renal system in addition to the already noted gastrointestinal changes. (Taffet,١٩٩٩; Leipzig,١٩٩٩).

٧- Immune system.

Age-related thyroid dysfunction is also common in the elderly (Mariotti,et al ,١٩٩٥). Lowered plasma thyroxine (T٤) and increased thyrotropin stimulating hormone (TSH) concentrations occur in ٥ to ١٠٪ of elderly. These abnormalities are mainly caused by autoimmunity and are therefore an expression of age-associated disease rather than a consequence of the aging process(Lamberts,*et al*.,١٩٩٧ and Cohen,١٩٩٩).

١-٤-١ *Mitochondrial* DNA

Genetic instability outside of the nuclear genome might also contribute to aging (Lee *etal.,* ١٩٩٧ and Wallace *et al*.,١٩٩٨). The mutation rate for mitochondrial DNA (mtDNA) is ١٠- to ٢٠-fold greater than for nuclear DNA, and it is believed that mtDNA mutations may compromise mitochondrial functions in different ways:

First, defects in electron transport and oxidative phosphorylation could lead to declines in ATP levels and the NAD:NADH ratio. Second, defective electron transport might increase free radical production by mitochondria —perhaps enabling a positive feedback loop to produce further mtDNA mutations. Third, and more speculatively, age-associated mitochondrial defects might induce cell death (Apoptosis), (Johnson, *et al.,* ١٩٩٩).

١-٤-٢ Cell Death

Is there a connection between cell death and aging? Cells die via mechanisms that range from necrosis, which is a relatively passive outcome of cell injury, to apoptosis, or programmed cell death, which is an active and ordered process. Apoptosis is triggered by a myriad of stimuli, such as steroid hormones, DNA damage, withdrawal of growth factors, or receptor-mediated apoptosis as in clonal deletion of immune cells. This pathway involves activation of a family of proteases, termed caspases, and nucleases, leading to the controlled degradation of cellular structures, followed by removal of the membrane- bound debris by phagocytic cells. There has been speculation that dysregulation of programmed cell death might contribute to aging (Warner *et al*., ١٩٩٧). Both apoptotic and necrotic forms of cell death can be mediated by mitochondria (Green and Reed, ١٩٩٨). Given the evidence for changes in mitochondrial function during aging , one wonders whether these changes contribute to cell death. Mitochondrial events that can mediate cell death include (١) release of mitochondrial stores of caspase activators including cytochrome c, (٢) disruption of the respiratory electron transport chain, and (٣) production of ROS. Age-dependent changes in mitochondria might trigger the above mechanisms leading to cell loss. There is as yet no direct evidence for increased release of caspase activators from mitochondria with age, but the activity of electron transport complexes appears to decline (Lee et al., ١٩٩٧) and the rate of ROS production increases with age in many mammals (Sohal *et al*., ١٩٩٤ , Johnson *et al*.,١٩٩٩).

١-٥ REASONING

Recurrent and / or persistent urinary tract infection are mostly noted among elderly rather than among adolescent . Meantime, it may be accompanied by prostatitis and /or urolithiasis which are being problematic to patient and their own family (Esposito, *et al*, ١٩٨٠; Mulholland, ١٩٩٠).

١-٦: AIMS OF THE STUDY:

The aim of the present work was to investigate the possible effect of aging on humoral- mucosal immunology of urinary tract during infection. To verify this, number of steps have been followed:

١-Selection of elderly (٦٠-٩٥ years), adolescent(٢٢-٤٠ years) urinary tract infected males patients .

٢-Collection of urine samples for isolation of causative micro organisms .

٣-Separation of Urinary Mucosal Immunoglobulin UMIg and its partial characterization.

٤-Estimate the uropathogen specific antibody titers in elderly and adolescent.

ABSTRACT:

The present study was aimed to evaluate the effect of senescence's on urinary mucosal immunoglobulins (UMIGs) in urinary tract infection patients (UTIP). Such evaluation was made using: (١) Single urine sample of seven ml s volume, (٢) PEG concentration of urinary globulin and (٣) bacterial agglutination test.

UMIGs were separated by ٦٪ PEG (٦٠٠٠ MW).The concentration and titer was determined in elderly patients and adolescent as control groups . During the reaction of bacterins of the infection organism with UMIGs, ٢ mercaptoethanol sensitive ,and resistant components were noted. The sensitive component was guessed as serum origin. The study proved that the titer of antibodies in adolescent patients were rather higher than elderly from ٢ -١٠ fold. Thus , UMIGs could be used as an infection probe in elderly as well as in adolescent, while, it is worth mentioning that senscen may induce some what inhibitory action on humoral mucosal responses as induced in those elderly UTI patients.

CHAPTER TWO

LITERATURE REVIEW

٢-١- OVERVIEW ON THE IMPORTANCE OF STUDYING THE SENESCENCE

Some individuals, due to the age have a compromised immune system. They are susceptible to all of the following problems: arthritis: reduced wound healing capacity; reduced bone marrow proliferation with resulting lowered white cell counts and anemia; increased incidence of cancers; and increased incidence of viral, fungal, and bacterial infection (Cohen,١٩٩٩). Infectious diseases account for one third of all deaths in people ٦٥ years and older. Early detection is more difficult in the elderly because the typical signs and symptoms, such as fever and leukocytosis, are frequently absent. A change in mental status or decline in function may be the only presenting problem in an older patient with an infection. An estimated ٩٠ percent of deaths resulting from pneumonia occur in people ٦٥ years and older Mortality resulting from influenza also occurs primarily in the elderly. Urinary tract infections are the most common cause of bacteremia in older adults. Asymptomatic bacteriuria occurs frequently in the elderly; however, antibiotic treatment does not appear to be efficacious. Despite advances in antibiotic therapy, infectious diseases continue to be a major cause of mortality in older adults. The diagnostic and therapeutic nuances of man aging infections in older adults create special challenges for physicians. Between ١٩٨٠ and ١٩٩٢, the infectious disease mortality rate in patients ٦٥ years and older actually rose ٢٥ percent (Pinner *et al.*, ١٩٩٦). That comparative mortality rate is nine times the rate in patients between ٢٥ and ٤٤ years of age (Mouton *et al.*,

٢٠٠١ and Marik & Kaplan, ٢٠٠٣). approximately ٢٠٪ of the United States population will be aged ٦٥ years or older(Muss, ٢٠٠١). Consequently, cancer care will become increasingly important. (Lewis *et al.*, ٢٠٠٣).

Many factors contribute to increase mortality in the elderly, including comorbid conditions, an increase in the number of invasive procedures performed and decreased physiologic reserves. Urinary tract infections (UTIs) are the most frequent bacterial infection and the most common source of bacteremia in older adults (Yoshikawa, ١٩٩١). Factors that predispose older adults to UTIs include the use of urethral or condom catheters, and neurogenic bladders with increased residual urine. Contributing factors specific to gender include prostate enlargement in men, an increase in vaginal pH, vaginal atrophy that is due to postmenopausal estrogen depletion, and incomplete emptying of the bladder in women. These factors provide the opportunity for bacterial colonization and are likely to contribute to the higher rates of asymptomatic bacteriuria and UTIs in the elderly (Zhanel *et al.*, ١٩٩٠).

٢-٢ Mucosal Immune System

The mucosal surface, which includes the oral, respiratory, synovial, gut, urinary and reproductive epithelium, is one of the first important interfaces between pathogens and the host, and as such is critical in prevention of infectious disease. M cells, specialized epithelial cells at the mucosal surface, serve as a portal of entry for proteins, peptides, and microbes. Further understanding of the regulation and role of these cells could lead to new approaches to prevent infection (Mangan and Gruber, ١٩٩٧).

Special immune cells called immunocytes produce secretory immunoglobin A (SIgA), an important antibody that attacks pathogens and foreign organisms that come in contact with the mucosal barrier. Our hormones direct the production of SIgA, which is a vital part of the healthy mucous that coats the cavities of the body for our first line immune defense. SIgA attacks invading, infectious organisms such as parasites, harmful bacteria like Anthrax, unfriendly yeast, fungi, and viruses, making it an essential part of the physical barrier of defense in the linings of the body. Mental and emotional stress stimulates our sympathetic nervous system, creating the fight or flight response. Chronic over stimulation of the sympathetic nervous system can lead to an overload on the body resulting in suppressed immunity and hormone exhaustion. During suppressed immunity caused by response to stress, output of S-IgA is reduced. Saliva is decreased, dry mouth occurs during stress, and all mucous secretions are diminished. Therefore your total immune defense suffers and cannot adequately protect the body. You become prey to pathogens and disease. Compromised immunity can expose us to many pathogens and disease. A weakened immunity also accelerates chronic degenerative disease and early aging (Hansen,*et al.*,٢٠٠١).

IgA is the major immunoglobulin found at the mucosal surface, but other immunoglobulins may play a role in protection against infection at mucosal surfaces. Recently, it has been suggested that IgA, in addition to its traditional role in the lumen, may be important in the intraepithelial neutralization of viruses. As IgA traverses the epithelial cell, it may encounter virus intracellularly, where it has the potential to neutralize the pathogen. This idea could lead to innovative approaches to prevent

infectious diseases, particularly those caused by intracellular pathogens (Mangan and Gruber, ١٩٩٧).

The eptithelial cells of mucous membranes play an important role in promoting the immune response by delivering small samples of foreign antigen from the lumina of the respiratory, digestive, and urogenital tracts to the underlying mucosal associated lymphoid tissue. This antigen transport is carried out by specialized cells, called M cells (Roitt and Rabson,٢٠٠٠). Mucosal humoral immunology of human during persistent pyuria have been investigated in this area (Shnawa and Mehdy, ٢٠٠٤).Comparative mucosal and systemic immune responses both at humoral and cellular levels in persistent pyuria patients have also been done in this area (Al-Amidi, ٢٠٠٣).

٢-٣-Immune concept of senescence in normal case.

Immune dysfunction occurs with aging. There is a progressive decrease in thymic mass and production of thymic hormones resulting in a decrease in naive lymphocytes and a corresponding increase in memory cells. Lymphocyte proliferative responses decline, perhaps related to decreased IL٢ production. On the other hand, certain cytokines , IL٦, IL-١_, TGF_ increase with age. Specific antibody response to a challenge decreases, but nonspecific immunoglobulin levels may be elevated. Monoclonal immunoglobulin protein prevalence increases progressively with age, perhaps related to T-cell regulatory abnormalities and/or the influence of IL-٦.(Cohen, ١٩٩٩; Miller, ١٩٩٦).

The immunologic theory of aging is based upon two main observations: (a) the functional capacity of the immune system declines with age, as evidenced by a decreased response of T cells to mitogens and reduced resistance to infectious disease; and (b) autoimmune

phenomena increase with age, such as an increase in serum autoantibodies (Walford, ١٩٧٤; Caruso *et al.*, ٢٠٠١). There is a shift toward increasing proportions of memory T cells. Humoral(B-cell mediated) immunity also declines with age, as evidenced by decreased antibody production and a disproportionate loss in the ability to make high affinity IgG and IgA (immunoglobulin G and A) antibodies. In addition, differences in the Maximum lifespan potential (MLSP) of different strains of mice have been related to specific alleles in the major histocompatibility gene complex (Yunis and Salazar, ١٩٩٣).

The genes in this region also contribute to the regulation of mixed-function oxidases (P-٤٥٠ system), DNA repair, and free-radical-scavenging enzymes. Caruso *et al.*, ٢٠٠١ suggest that mouse and human histocompatibility genes may be associated with longevity via different mechanisms, in mice via susceptibility to lymphomas and in humans via infectious disease susceptibility , there is also evidence that cytokine gene polymorphisms may interact with histocompatibility genes to influence longevity (Caruso *et al.*, ٢٠٠١). Although the immune system obviously plays a central role in health maintenance and survival, similar criticism can be directed at the immunologic theory as has been directed at the neuroendocrine theory. Complex immune systems are not present in organisms that share aspects of aging with higher organisms. In addition, the inability to distinguish between fundamental changes occurring in many types of cells and tissues, not just those of the immune system, and the secondary effects mediated by the aging-altered immune system (Troen, ٢٠٠٣).

٢-٣-١:T- Lymphocytes..

In aging humans and experimental animals, one of the most obvious changes that occur, starting in adolescence, is involution of the

thymus with ensuing loss of thymic hormones, such as thymosin (Song *et al.*, ١٩٩٣; Lewis *et al.*, ١٩٧٨).

Subsequently, changes in T lymphocytes are seen, with declines in "virgin" or reactive T cells and increases in "memory" or primed T cells (Miller, ١٩٩١; Xu *et al.*, ١٩٩٣). The accumulation of memory cells occurs in $CD_{٤+}$ T-helper cells (Kudlacek *et al.*, ١٩٩٥) and $CD_{٨+}$ T-suppressor cells. (Jackola *et al.*, ١٩٩٤) While the number of naive T cells declines in old animals, those remaining produce greater amounts of interleukin (IL)-٢ than naive cells from young animals, (Dobber *et al.*, ١٩٩٥).

٢-٣-٢-B Lymphocytes

With advanced of age, changes in B cells have recently become more apparent than changes in T cells. The number of circulating B cells does not appear to change appreciably with age (Makinodan, ١٩٧٧). Studies on aged mice have shown structural changes in B-cell membranes(Callard *et al.*, ١٩٧٩) and a decrease in estimated numbers of bone marrow B-cell precursors (Zharhary, ١٩٨٨; Ben-Yehuda *et al.*, ١٩٩٤; Viale *et al.*, ١٩٩٤). Similar to what has been described for T cells, B cells from old individuals proliferate less efficiently to mitogen stimulation (Hara *et al.*, ١٩٨٧). The ability of B cells to generate antibody responses undergoes mostly depressive changed with age, (Delafuente, ١٩٨٥) although much of this is related to declining T-cell function. The decrease in T-dependent antibody responses is obvious in experimental animals, with ٨٠٪ fewer antibody-forming cells in older animals.(Miller, ١٩٩١) The B-cell undergoes repertoire changes with age, with altered ability to recognize antigen (Russo *et al.*, ١٩٩٣; Schwab *et al.*, ١٩٩٢). A recent study in mice showed that immunization with sheep red blood cells led to a significantly greater rise in the proportion of

immunoglobulin-M (IgM)-secreting cells that reacted with self-antigens in old animals, (Zhao *et al.*, ١٩٩٥) The accumulation of antibodies directed against other antibodies (anti-idiotypes) with increasing age may also interfere with the production of specific antibody (Arreaza *et al.*, ١٩٩٣ and Cinader and Thorbecke, ١٩٨٩).

The ability to respond to a novel (primary) or previously encountered (secondary) specific antigen challenge with specific antibody production is decreased in aging, (Delafuente, ١٩٨٥; Whittingham, ١٩٧٨).

B cells from old adults produce less specific antibody when stimulated in vitro with specific antigen, such as tetanus toxoid, regardless of the source and type of T-cell help provided in the cultures, (Kishimoto *et al.*, ١٩٨٢). Even recently immunized old adults display lower levels of antibody in vivo, fewer numbers of B cells producing antibody in vitro, and less antibody produced by each B cell. One reason for the decreased response appeared to be lack of precursor cells, (Burns *et al.*, ١٩٩٠). Reimmunizing subjects led to an increase in the number of specific antibody-producing B-cells in old and young, but the old adults still had significantly fewer B cells producing specific antibody (Burns *et al.*, ١٩٩٣). Booster immunizations did not alter the mean amount of antibody produced per B cell for either age group.

After immunization with influenza vaccine, the antibody isotypes produced that are important in the agglutination response (specifically IgG, IgG١) are decreased in elderly humans compared with young humans, (Remarque *et al.*, ١٩٩٣). Although most investigators agree that the changes in antibody production described above are the result of declines in T-lymphocyte function, there is also evidence for a decline in intrinsic B-cell function. Findings from our laboratory and others suggest

a diminished ability of purified B cells to respond to isolated T-helper cells or to T-cell-derived helper factors, (Ennist *et al.*, ١٩٨٦; Whisler *et al.*, ١٩٩١). Some murine studies have shown that certain subsets of B cells function at a significantly lower level than the same cells in young mice, while other subsets produce comparable levels of antibody. (Hu *et al.*, ١٩٩٣). Old mice produce amounts of antibody comparable to young after vaccination with phosphocholine, but with a molecular shift in the antibody repertoire, (Nicoletti *et al.*, ١٩٩٣; Nicoletti *et al.*, ١٩٩٥). In the old mice, the genes encoding the variable heavy portions of the antibody molecule are different from those in young animals.

The antibody produced by old mice has diminished affinity for its target and is less effective in preventing infection, (Nicoletti *et al.*, ١٩٩٥; Miller and Kelsoe, ١٩٩٥). Vaccination also seems to stimulate production of antibodies that cross-react to self antigens in old but not young mice, (Borghesi, ١٩٩٤).

٢-٣-٣- Macrophages

The function of macrophage in aging has been studied less than other leukocyte subpopulations. Early work suggested that they appear to produce similar levels of cytokines, (Delfrassy *et al.* ١٩٨٢; Delfraissy *et al.*, ١٩٨٠) and that differences in function may be modulated through changes in T- and B-cell responses to such substances. More recent studies of human monocytes have shown decreased IL-١ secretion with mitogen stimulation, (Mclachlan *et al.*, ١٩٩٥). Studies of cutaneous wound-healing in mice also suggest a decline in macrophage function with aging, with prolonged wound healing in aged animals, (Danon *et al.*, ١٩٨٩). Adding peritoneal macrophages from animals of different ages to wounds on old mice sped healing, but macrophages from young mice accelerated the healing process to the greatest degree, (Danon *et al.*,

١٩٨٩). Other murine studies of bone marrow in senescence-accelerated mice suggested that stem cells are defective in their ability to generate granulocyte-macrophage precursor cells, (Izumi-Hisha *et al.*, ١٩٩٠). Studies of both mouse and human macrophage function in aging suggest defects in macrophage T-cell interactions. Macrophages from old mice that are antigen- sensitized stimulate significantly lower levels of Tcell proliferation than young macrophages, (Kirshmann *et al.*, ١٩٩٢) Work from Szakal *et al.*, ١٩٩٢ has found serious age-related compromise in the ability of dendritic cells to stimulate the formation of germinal centers in lymph follicles where B-cell memory develops. T cells from old adults are able to function at the same level as T cells from young adults when macrophages are replaced with other sources for activation, suggesting a defect in macrophage T-cell communication, (Beckman *et al.*, ١٩٩٠) Compared with monocytes from young adults, monocytes from old adults display lower cytotoxicity against certain tumor cell lines, decreased production of reactive oxygen intermediates ($H_٢O_٢$ and $NO_٢$), and lower IL-١ secretion than monocytes from young adults, (Melachlan *et al.*, ١٩٩٥). These findings of decreased secretion were observed when monocytes were stimulated with nonspecific mitogens, (Melachlan *et al.*, ١٩٩٥).

٢-٣-٤ Interleukins

The response to IL-٢ has been extensively studied as one potential mechanism underlying the age-related defect in cellular immunity. Several laboratories have been demonstrated decreased production of IL-٢ after mitogen stimulation, decreased density of IL-٢ receptor expression, decreased expression of IL-٢ mRNA, and decreased proliferation of T cells in response to IL-٢, (McElhaney *et al.*, ١٩٩٠;

Negoro *et al.*, ١٩٨٦; Goonewardene *et al.*, ١٩٩٣). Additional experiments suggest that the picture might be more complex, with defects in production of or sensitivity to IL-٢ varying with the activation signal, (Nijhuis, ١٩٩٤; Ajitsu *et al.*, ١٩٩٠). Some investigators have found no difference in T-cell proliferation or IL-٢ production when memory T cells from old and young humans were stimulated with a variety of activating signals, (Nijhuis, ١٩٩٤) $CD_{٤+}$ T cells from old mice accumulate similar levels of IL-٢ transcripts, though secretion of IL-٢ is lower than in cells from, young mice, (Hobbs *et al.*, ١٩٩١) IL-١ and -٢ play a primary role in activation, recruitment, and proliferation of T lymphocytes. Activated T cells go on to produce a variety of cell growth and differentiation factors such as IL-٤, IL-٦, and IFN-γ . Evidence has been accumulating that there are age-related declines in lymphocyte production and response to other cytokines, such as IL-١ and tumor necrosis factor (TNF), (Miller, ١٩٩١; Wu *et al.*, ١٩٨٦). Monocytes from aged humans secrete less IL-١ when stimulated with lipopolysaccharide, although they appear to produce comparable amounts of IL-١ precursor, (Mclachlan *et al.*, ١٩٩٥). Under conditions of mixed lymphocyte culture, lymphocytes from old individuals produce higher levels of IL-١, IL-٢, and TNF- γ. than those from healthy young individuals, (Molteni *et al.*, ١٩٩٤& Burns & Leventhal, ٢٠٠٠).

٢-٤ The development of age-associated immunologic alterations

The central importance of the mucosal immune system has been well recognized as the first line of defense by which the host combats numerous pathogens that are encountered after ingestion or inhalation, and that subsequently colonize the gastrointestinal or upper respiratory tracts, if Ag-specific immune responses are to be induced at these

mucosal barriers, the common mucosal immune system, which consists of distinct mucosal IgA inductive and effector tissues (McGhee *et al.*, ١٩٩٣ and McGhee *et al.*, ١٩٩٨). must be brought into play. Mucosal immune responses have been effectively induced by both oral and nasal immunization, because IgA inductive tissues such as the gut- and nasopharyngeal-associated lymphoreticular tissues can be stimulated by protein Ag given with mucosal adjuvants (dysregulation occurs in the mucosal immune system as early as ١٢–١٤ month of age, while systemic immunity remains essentially normal. This unexpected result was revealed by our oral immunization regimen which effectively induces both serum and mucosal Ab responses through help provided by CD_4 Th٢-type cells. Ag-specific Ab responses in mucosal as well as parenteral tissues of aged mice (both ١- and ٢-year-old mice) at both the protein and cellular levels were lower than those seen in young adult mice. Furthermore, CD_4 T cell proliferative responses and cytokine synthesis were also abrogated at the protein and molecular levels in both groups of aged mice. It has been shown that aging is associated with several dysfunctional stages in lymphocyte activation, particularly with progression of lymphocytes to a state of immune unresponsiveness to antigens and to an increased incidence of autoimmune disease (Hodes, ١٩٩٧; LeMaoult *et al.*, ١٩٩٧).

Especially affected are T cell responses including IL-٢ production, IL-٢ receptor expression, signal transduction, and programmed cell death, all of which have been reported in the elderly (Knight, ١٩٩٥; Miller, ١٩٩٦; Zhou *et al.*, ١٩٩٥; Haynes *et al.*, ١٩٩٧). Age-associated immune dysregulation occurs in the mucosal system at both cellular and molecular levels much earlier than occurs in the lymphoid systemic. Study on mice was showed that CD_4. ligand-deficient mice immuniz ed

with ova albumin (OVA) and complete fruend adjuvant (CFA) revealed significantly elevated OVA-specific CD_4 T cell-proliferative but not antibody responses (Kweon *et al.*, ١٩٩٩). Also vaccine prevent influenza and *Streptococcus pneumoniae* pulmonary pneumonia are less effective in the elderly. Thus, one may postulate that induction of mucosal immunity in middle-aged as well as aged individuals would be difficult to achieve and may explain vaccine failures. In addition, innate immunity also plays important roles in host defense as well as maintaining immune homeostasis. Because adoptive immunity is impaired in aged mice.

CD_4 T cells from aged mice exhibited lower proliferative responses than those taken from young adult mice, it is possible that the age-associated reductions in antigen-specific antibody and T cell-proliferative responses could involve an alteration in responsiveness to T cell growth factors such as IL-٢. Indeed, a reduced frequency of IL-٢-producing CD٤ T cells and a low IL-٢ receptor expression by this T cell population (Nordin *et al.*, ١٩٨٣; Negoro and Collins, ١٩٨٦) are one result of aging. Mucosal IL-٢ treatment may allow us to overcome age-impaired mucosal immune responses by enhancing mucosal immunity or abrogating unresponsiveness in aged mice. Thus, it is possible that pretreatment of mice with mucosal IL-٢ could induce Ag-specific mucosal IgA and IgG responses in aged mice immunized orally with OVA and CT. With regard to IL-٤ synthesis, it has been reported that anti-CD_3 mAb-stimulated CD٤ T cells elicited higher levels of IL-٤ synthesis in senescent than in young adult mice. CD_4 memory T cells, the major T cell population occurring in senescence, to produce IL-٤. In contrast, antigen-induced IL-٤ synthesis may require the generation of effector memory cells from naïve CD_4 T cells, a pathway which appears to be defective in aged mice (Haynes *et al.*, ١٩٩٩). Thus, low levels of Ag-specific IgA and IgG

antibody responses in aged mice immunized orally with OVA and CT may be explained by a lack of these Th٢-type cytokine-producing cells. To support this contention, it was shown that impaired mucosal IgA antibody responses were detected in IL-٤-deficient mice immunized with protein Ag and CT as mucosal adjuvant (Okahashi *et al.*, ١٩٩٦; Vajdy *et al.*, ١٩٩٥). Further, it has been shown that both IL-٤ and IL-٥ are important B cell stimulating and growth factors (Vitetta *et al.*, ١٩٨٥; Beagley *et al.* ١٩٨٨).The prescence of a high frequency of γδ T-cell in epithelium of the intestine is one of the unique characteristics of the unique characteristic of the mucosal Immune system (Goodrnan and Lefrancois, ١٩٨٨; Bonneville *et al.*, ١٩٨٨). It was shown that a reduced frequency of intraepithelial γδ T cells occurs in the small intestine of senescent mice (Takeuchi *et al.*, ١٩٩٣). that these γδ T cells play an important role in the induction and regulation of mucosal IgA responses (Fujihashi *et al.*, ١٩٩٦). For example, TCR deficient mice, which lack gd T cells, exhibit impaired levels of both total and Ag-specific IgA Ab responses when immunized orally with TT and CT (Fujihashi *et al.*, ١٩٩٦). Thus, a low frequency of gd T cells in the epithelium of aged mice may partially explain why impaired mucosal IgA Ab responses are seen. In summary, the study has shown impaired mucosal B and T cell immunity for Ag-specific Ab and CD٤ T cell responses at the protein, cellular, and molecular levels. The results are especially important in that they show that age-associated alterations possibly arise first in the mucosal immune system (Kago *et al.*, ٢٠٠٠).

In study of Schmucker and his colleagues,٢٠٠١, in intestinal mucosa of elderly animals and humans was showed that the third event is the maturation of immunoglobulin A (IgA) immunoblasts and their migration from the Peyer's patches to the intestinal mucosa. Quantitative

immunohistochemical analyses suggest that the migration of these putative plasma cells to the intestinal effector site is compromised in old animals. Local antibody production by mature IgA plasma cells in the intestinal mucosa constitutes the fourth step. It was demonstrated *in vitro* an IgA antibody secretion by intestinal lamina propria lymphocytes from young and senescent rats is equivalent. The last event is the transport of IgA antibodies across the epithelial cells via receptor-mediated vesicular translocation onto the mucosal surface of the intestine. Receptor-binding assays did not detect age-associated declines in receptor number or binding affinity in either rodent or primate enterocytes as a function of donor age. Efforts to identify the mechanism(s) responsible for the age-related decline in intestinal mucosal immune responsiveness may benefit by focusing on the homing of IgA immunoblasts to the effector site (Schmucker *et al.*, ٢٠٠١).

٢-٥: IMMUNE CONCEPT OF SENESCENCE IN ILLNESS CASE .

Aging is not synonymous with illness. However, getting older does increase the risk for many diseases and disorders. Overall, elderly people have an increased rate of chronic disorders, arteriosclerosis, infections, autoimmune disorders, and cancer. significant part of this increased risk is probably related to aging changes in the immune system. The immune system protects against diseases. It seeks out and destroys viruses, bacteria, fungi, and cancerous cells before they can damage the body. It learns to tell the difference between "self" tissue and "non-self" particles (Lamberts *et al*, ١٩٩٧ and Johnson *et al*., ١٩٩٩).There is not much direct causal evidence linking age-specific changes in immunity to clinical

illnesses or mortality. The question of whether decreased immune responses contribute to morbidity and mortality in elderly persons has been addressed for the most part by studies looking for associations between abnormalities in a particular immune response and general health status. (Goodwin, ١٩٩٥) Elderly subjects who display declines in absolute lymphocyte counts, (Bender *et al.*, ١٩٨٦) have two or more suppressed immune parameters, (Ferguson *et al.*, ١٩٩٥) display decreased proliferative lymphocyte responses, (Murasko and.Weiner, ١٩٨٨; Goodwin, ١٩٩٥) or are anergic (Roberts *et al.*, ١٩٧٤; Goodwin *et al.*, ١٩٨٢; Wayne *et al.*, ١٩٩٠) have higher mortality rates anywhere from ٢ to ٧ years after measuring the immune parameter (Burns, and Leventhal, ٢٠٠٠).

In elderly type ١ diabetes is an autoimmune disease in which the insulin-secreting ß-cells of the pancreas are destroyed. Circulating islet autoantibodies and autoreactive T-cells are hallmarks of this islet cell specific autoimmune response (Padoa *et al.*, ٢٠٠٣). In elderly Many forms of glomerulonephritis involve immune complex localization in the kidney. Fc gamma receptors (FcgammaR) expressed on the surface of leukocytes bind the Fc (constant) portion of IgG. They link immune complex deposition to innate immune responses, including phagocytosis, cytokine release, formation of reactive oxygen species, and antibody-dependent cytotoxicity, also Inhibitor FcgammaR also have a specific role in the maintenance of B cell tolerance (Tarzi and Cook, ٢٠٠٣).

Community-acquired pneumonia (CAP) is a major cause of morbidity and mortality in the elderly, and the leading cause of death (Paul *et al.*, ٢٠٠٣).This due to. In aging humans and experimental animals, the involution of the thymus with ensuing loss of thymic hormones, such as thymosin. (Song *et al.*, ١٩٩٣; Lewis *et al.*, ١٩٧٨)

Subsequently, changes in T lymphocytes are seen, with declines in "virgin" or reactive T cells and increases in "memory" or primed T cells (Miller, ١٩٩١ and Burns, and Leventhal, ٢٠٠٠) .

The immune response to thymus-dependent Ags critically depends on the interaction between $CD_{٤٠}$ ligand ($CD٤٠L$), a molecule which is transiently expressed on the surface of activated $CD٤^{+}$ T lymphocytes, and $CD_{٤٠}$ expressed on the surface of B lymphocytes (interaction activates the resting B lymphocyte to produce Abs to thymus-dependent Ags and is important for germinal center creation, memory B lymphocyte formation, and Ig class switching. The declines in active T cell lead to IgG Ab response was very weak and the infection occur in elderly patients. (Jeurissen *et al.*, ٢٠٠٢). Later in life, the immune system also seems to become less tolerant of the body's own cells. Sometimes an autoimmune disorder develops -- normal tissue is mistaken for non-self tissue, and immune cells attack certain organs or tissues.

The immune system becomes less able to detect malignant cells, and cancer risk also increases with age as a result. The immune system also becomes less able to detect foreign particles, and infection risk is greater (Lamberts *et al*, ١٩٩٧ and Johnson *et al*., ١٩٩٩).

٢-٦ Urinary Tract Infection and the body immunity among elderly

A urinary tract infection (UTI) is a condition where one or more structures in the urinary tract become infected after bacteria overcome its strong natural defenses. In spite of these defenses, UTIs are the most common of all infections and can occur at any time in the life of an individual. Almost ٩٥٪ of cases of UTIs are caused by bacteria that typically multiply at the opening of the urethra and travel up to the

bladder (known as the ascending route). Much less often, bacteria spread to the kidney from the bloodstream (Simon *et al.*, ٢٠٠١).

٢-٦-١ Cause

A urinary tract infection is the result of an interaction between the bacterium and the host (patient). Virulent (aggressive) bacteria are able to overcome normal host defense mechanisms. Less virulent bacteria can lead to significant infections in patients with abnormal urinary tracts or compromised immunity.

Most bacteria reach the urinary tract via the ascending route, traversing the urethra, bladder and sometimes the ureters up to the kidneys. The main source of these bacteria is the large intestine of patient's. The female urethra is short and situated close to the fecal reservoir, therefore high incidence of urinary tract infections in females more than males.

The majority of infections can be attributed to facultative anaerobes, the most common of which is *Escherichia coli,* which is responsible for ٨٥٪ of infections in ambulatory patients and ٥٠٪ of nosocomial infections. *Proteus mirabilis, Klebsiella pneumonia*, and *Enterococcus fecalis,* are the next most frequent isolates (Ofek and Beachey ,١٩٨٠).

In diabetics and immuno-compromised patients, fungi such as candida and viruses (adenovirus, cytomegalovirus) account for a significant percentage of urinary tract infections. Certain special organisms reach the kidneys via the bloodstream rather than the ascending route. These include Mycobacterium tuberculosis, which causes TB, and *Staphylococcus aureus*, which can cause a renal abscess (*Roux*, ٢٠٠٤).

The usual route of inoculation in males is with gram-negative aerobic bacilli from the gut, with *Escherichia coli* being the most common offending organism. In males aged ٣ months to ٥٠ years, incidence of UTI is low; therefore, the possibility of anatomical abnormalities must be entertained in this age group The frequency of male UTI is related to age.In elderly patients, UTI is a significant cause of morbidity and death, with the expected death rate as high as ٣٪ in those who develop pyelonephritis. The high mortality rate is largely due to delayed presentation and the development of bacteremia/sepsis. enlargement of the prostate, prostatitis, and subsequent instrumentation of the urinary tract are the primary causes of UTI.. In elderly patients, pyelonephritis carries a ٣٪ mortality rate. (Howes, ٢٠٠٢). UTIs are typically caused by introduction of bacteria during instrumentation of the urinary tract, such as catheterization. The precipitous increase in the incidence of UTIs in older men appears to be largely a consequence of prostatic hypertrophy, which this patient had. Bladder outlet obstruction by the enlarged prostate and subsequent pooling of postvoiding residual urine has been proposed as a predisposing factor for infection in these cases. However, there are scant data to support this proposal; indeed, one study on the relationship of postvoiding residual urine and UTIs found no statistically significant relationship between the two. all UTIs in men are complicated. The rationale is that because UTIs do not normally occur in men, they must be related to an underlying genitourinary abnormality (Lipsky *et al.*, ٢٠٠٠).

٢-٦-٢ Agents of UTI

Most UTIs are bacterial in nature. It is proposed that the host's defense mechanisms must be transiently or persistently abnormal for bacterial colonization to occur as continual instillation of bacteria into

intact urinary tracts for ٢ weeks to ٣ months failed to establish an infection (Pullman, ٢٠٠٣).

٢-٦-٣ Bacterial profile

The bacteria which responsible for infecting of UTI are:

١-Gram- negative bacteria

Escherichia coli,*Proteus mirabilis Klebsiella pneumoniae,Pseudomona aeruginosa ,Enterobacter spp* ,other *Proteus Serratia,Citrobacter,Salmonella.*

٢-Gram- positive bacteria

Staphylococcus epidermidis, Enterococci, Lactobacilli, group B streptococci.

٣-Mycobacteria

Mycobacterium tuberculosis ,atypical mycobacteria .

٤-*Mycoplasma*s

Ureaplasma .

٥-Fungi

Candida ,Aspergillus ,Cryptococcus .

٦-Viruses

Cytomegalovirus ,Adenovirus .(Cattell,١٩٩٦).

٢-٦-٤ PATHOGENESIS

Bacteria must first attach (adhere) to the epithelial surface of the urinary tract before they can proliferate (colonization). The epithelium of the urinary tract produces a mucoprotein which coats the surface of the urinary tract and reduces the adherence of bacteria. Macrophages in the

bladder wall and local IgA production assist in elimination of bacteria. Anything which cause damages the epithelial lining of the urinary tract can predispose to the infection including: urinary catheterization, calculi, neoplasia, or cytoxic drugs in urine (cyclophosphamide). Impaired immunocompetence from immunosuppressive drugs or cortisol can affect cellular or humoral immunity and predispose to infection(Pullman, ٢٠٠٣).

Urine itself has antimicrobial properties which are enhanced when the urine is concentrated. Dilute urine is more likely to support bacterial growth.(Cattell,١٩٩٦).

The renal cortex is more resistant to infection than the renal medulla because there is less blood flow to medulla which leads to less antibody, less complement, and fewer leukocytes. High osmolality inhibits migration and phagocytosis by leukocytes. High ammonia concentration inhibits complement. The medulla is called an "immunologic desert". Renal infections develop in the medulla (Pullman, ٢٠٠٣).

Catheterization can cause UTI by causing physical damage to the mucosa or by allowing bacterial migration through, around or introduced by the catheter. In one study of ٧٠ normal dogs, catheterization induced a positive urine culture in ٠/٣٥ males and ٧/٣٥ (٣٠٪) of females. Use the smallest and most flexible catheter possible and atraumatic/aseptic technique to avoid damage (Pullman, ٢٠٠٣).

All older adults are at risk who are immobilized, catheterized, or dehydrated. Nursing home patients, particularly those who are incontinent and demented, are at very high risk for UTIs. Up to ٤٠٪ of elderly patients who live in nursing homes will contract a urinary tract infection. In most cases, the infections are asymptomatic and no more harmful than similar infections in the general population. Nursing home

patients, however, are at higher risk for developing symptoms (Simon *et al.*, ٢٠٠١).

٢-٦-٥-Specific Risk Factors for Complicated UTIs .

Catheters and Hospitalizations. About ٤٠٪ of all infections that develop in hospitalized patients are in the urinary tract, and ٨٠٪ of those are due to catheters. Nearly all patients who need urinary catheters develop high levels of bacteria in their urine, and the longer the catheter is in place, the higher the risk for infection. Catheterized patients who develop diarrhea are nine times more likely to develop UTIs than are patients without diarrhea. In most cases of catheter-induced UTIs (٩٠٪ in one study) the infection produces no symptoms. Because of the risk for wider infection, however, anyone requiring a catheter should be screened for infection. Catheters should be used only when necessary and should be removed as soon as possible (Getliffe *et al* ,٢٠٠٠).

Kidney Stones. Kidney stones, in some cases, can cause obstruction and cause infection, particularly pyelonephritis. Symptoms of severe urinary tract infection in people with a history of kidney stones may indicate obstruction of the urinary tract(Cattell,١٩٩٦) .

Diabetes. Diabetes puts women (but not men) at significantly higher risk for asymptomatic bacteriuria. The longer a woman has diabetes, the higher the risk. (Control of blood sugar has no effect on this condition.) The risk for symptomatic complicated UTIs may also be higher in people with diabetes. In fact, certain UTI-related abscesses are reported only in patients with diabetes. These patients are also at higher risk for fungal-related UTIs (Cattell,١٩٩٦).

Prostate Conditions in Men, prostatic hyperplasia can produce obstruction in the urinary tract and increase the risk for infection. In men,

recurrent urinary tract infections are associated with prostatitis, an infection of the prostate gland that can also be caused by *E. coli* (Lipsky,١٩٩٨) .

Sickle-Cell Anemia. Patients with sickle-cell anemia are particularly susceptible to kidney damage from their disease, and UTIs put them at even greater risk (Cattell,١٩٩٦) .

Anatomical Abnormalities. Some people have structural abnormalities of the urinary tract that cause urine to stagnate or flow backward into the upper urinary tract. Such conditions include the following:

- A prolapsed bladder (cystocele) can result in incomplete urination so that urine collects, creating a breeding ground for bacteria.

- Crevasses called diverticula sometimes develop inside the urethral wall and can become tiny pockets for urine and debris, further increasing the risk for infection.(Simon *et al.*, ٢٠٠١).

Kidney Problems. Nearly any kidney disorders increased with the risk of complicated UTIs (Simon *et al.*, ٢٠٠١).

٢-٦-٦-Host defense mechanisms.

Host defense mechanisms operating in the lower urethra include the flow of urine. The most important defense mechanisms operating in the bladder are bladder emptying and the antimicrobial properties of the bladder mucosa, elderly conditions in the bladder correspond to a static chamber and the frequency of voiding and residual volume are crucial factor in the development of bladder infection (Robert,١٩٩٦). A residual volume of more than ١ ml is associated with bacteriuria. Uretric defense mechanisms include urinary flow and the vesicoureteric valves which prevent reflux of urine during bladder emptying. In elderly ureteric or

intra-renal obstruction and vesicoureteric reflux are associated with a high risk of renal infection. The peristaltic action of the ureter causes turbulent flow of urine which contributes to the elimination of ascending bacteria, diminished ureteric peristalsis during aging may contrbute to the increased incidence of pyelonephritis.urine production and concentration at different times of day and the composition of urine has significant effects on phagocytic function and complement activation (Cattel, ١٩٩٦). Concentrations of IgA and IgG in the plasma increase with age, this may reflect decreased plasma volume (Akimoto *et al.*, ٢٠٠٣). Age-related changes in immunity primarily involve alterations in T cell function.... Altered B cell function also occurs with aging....” immune function that decay with age. Immuno-suppressive Prostaglandin E-٢ (PGE٢) levels increase with age, even in healthy aged adults, antibody responses of aged individuals are characterized by lower, slower, and shorter responses than those observed in young subjects.” (Lesourd, ١٩٩٧) “Normal aging in human beings is associated with increased basal interleukin-٦ (IL-٦) production by lymphocytes. Dysregulation of this cytokine with increased basal secretion has been proposed to contribute to age-associated diseases, Immune senescence [aging] is characterized by specific cytokine changes that favor Th٢ T-helper responses (antibody production, including auto [self] antibody production) while suppressing Th١ responses (cytotoxic T cell and macrophage activation, i.e. cell-mediated immunity.” (High, ١٩٩٩) TH١, cell-mediated immunity (CMI) is more effective (and youthful) immunity; TH٢ antibody-dominated immunity is less effective and more troublesome, due to autoimmune disease (and typical of aged immunity). Unfortunately, the main stimulator of TH١ CMI is thymic hormones (Stein, ١٩٨٦), yet thymic hormones decrease radically with ageing (Boukaiba, ١٩٩٣ ;Mocchegiani, ١٩٩٥; Hadden, ١٩٩٥ and Lesourd, ١٩٩٧).

Another key determinant of immune power is the T٤:T٨ cell ratio (Kouttab, ١٩٨٩). Too many T٨ cells tends to suppress CMI; not enough T٨ cells allows CMI to run rampant, with possible damage to the body itself. The ideal T٤:T٨ ratio is about ٢:١; less than ١:١ represents serious immune weakness ,thymic hormones tend to normalize T٤:T٨ ratios in a broad range of conditions, including bacterial infection (Kouttab, ١٩٨٩).

The predominant antibody class in the serum were of the IgG and IgM class whereas in the urine, the predominant antibodies were of the IgG and IgA class. Antibodies against this domain would block adherence of type ١-fimbriated *E. coli* to the bladder mucosa in situ and in vivo in an established mouse model of cystitis (Thankavel, ١٩٩٧). Host immune mechanism operating in the urinary tract include local and systimic antibody production, complement mediated killing, neutrophil phagocytosis, and cell mediated immunity. Secretory IgA and IgG are normally found in urine. Secretory IgA and IgG inhibit bacterial adhesion and the intraction between antigen and antibody activates complement. A range of antibody are detected in the serum following pyelonephritis. These antibodies are directed against various bacterial components including fimbriae, O antigen, and capsular polysaccharide. Lower urinary tract infection are not usually associated with a significant serum antibody response, and humoral immunity is therefore thought to play relatively minor role in the elimination of bacteria from the bladder. The classical complement pathway is activated by the presence of specific antibody and the alternative pathway may be activated by bacterial surface antigen. The result of complement activation is bacterial killing. However, some serotypes are relatively resistant to complement lysis and these organisms appear to predominate in cases of pyelonephritis. Phagocytosis of bacteria by neutrophils and macrophages occurs if

organisms invade the bladder or kidney but is probably of little importance in most lower urinary tract infection as the composition of urine inhibit phagocyte function (Cattel, ١٩٩٦). Bacterial toxins induces both mucosal and systemic immune responses via a Th٢ cell-dependent pathway in cells from rats orally fed bovine serum albumin (Thomas and Parrott, ١٩٧٤). Later, a large number of studies showed that oral immunization with protein antigen induced $CD_{٤+}$ Th cells in mucosaassociated tissues that supported IgA responses, whereas suppressor T cells were induced in systemic compartments such as spleen that downregulated antigen-specific IgM, IgG, and IgE Ab responses (Ngan and Kind, ١٩٧٨; Mattingly and Waksman, ١٩٧٨; Kagnoff, ١٩٨٠; Kiyono *et al.*, ١٩٨٠; Richrman *et al.*, ١٩٨١; Kiyono *et al.*, ١٩٨٢; Mowat *et al.*, ١٩٨٨).

Furthermore, the helper T cells for IgA responses tended to remain in Peyer patches, whereas the suppressor T cells were found to migrate into the systemic compartment (for example, the spleen). These observations were considered to be logical explanations for cellular mechanisms of oral tolerance in which Peyer patch-derived $CD_{٤+}$ Th cells supported IgA responses, whereas splenic T suppressor cells induced systemic unresponsiveness. It is now generally agreed that a functional suppressor mechanism exists for the downregulation of systemic immune responses; however, the nature and properties of these suppressor T cells are disputed (Mowat *et al.* ,١٩٨٨).

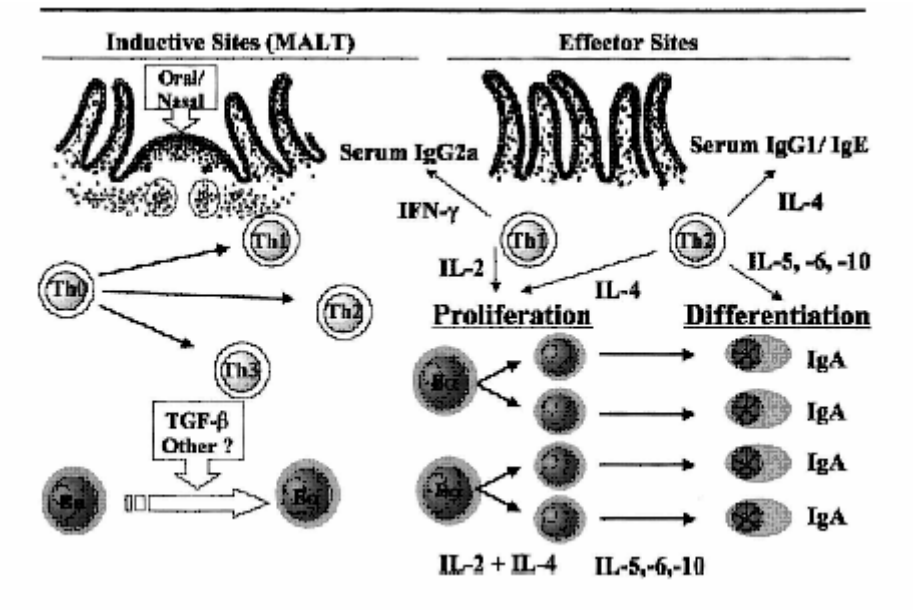

Fig- ١: Regulation of Mucosal And Systemic Immune Responses .. (Fujihashi *et al.*, ٢٠٠١).

Systemic immune responses were also diminished in aged mice given oral OVA , CT as well as the common mucosal immune system, mucosal inductive sites must play a central role in the induction of antigen-specific immune responses in both mucosal and systemic tissues. Thus, the decreased IgG responses in ١-year-old mice immunized with oral OVA plus toxin may simply be due to the impaired mucosal immune system in these mice. To support this, systemic immunization resulted in intact OVA-specific T-cell responses and toxin-B-specific Ab responses in ١-year-old mice. These results indicate that age-associated alterations arise in the mucosal immune system earlier than in the parenteral immune compartment (Fujihashi *et al.*, ٢٠٠١).

Approaches to retarding, preventing or reversing thymic atrophy as well as systemic studies of the consequences of maintaining vigorous thymic function throughout life age-related changes in the morphological integrity of mucosal (regional) lymphoid tissues and in the functional

competence of the cells that participate in immune responses at mucosal sites effects of senescence on B cell receptor and T cell receptor signaling cascades with attention to receptor phosphorylation, protein kinases and costimulatory pathways such as the CD٢٨/B٧ and CD٤٠/CD٤٠L pathways. (Oaks *et al.*, ١٩٩٦) .

٢-٧- MUCOSAL IMMUNITY IN ELDERLY MEN DURING URINARY TRACT INFECTION.

There is some waning of immune responses in the elderly. Most infection of the urinary tract occure by organisms ascending the urethra from the perineum. Age –related changes in the urethra result in loss of the physical barrier normally presented by the closed urethra. This predisposes the elderly individual to urinary incontinence and infection. The aging changes include loss of urethral smooth muscle and replaced by connective tissue as well as thinning of the urinary epithelium, and mucosal atrophy. Flushing of the lower urinary tract also prevents ascend of contaminating organisms. Many elderly patients, especially those with urinary incontinence, those who live in institutions, and those who are acutely ill from other causes, have a reduced fluid intake and hence reduced urinary output (Cattell, ١٩٩٦).In elderly thinning in the epithelial layer cause change in susceptibility to urinary tract infection (UTI). Epithelial cells of urinary tract have interleukin-٨ receptor that responsible on the neutrophils migrate to infected mucosal sites that they protect against invading pathogens and induce T cell activation and differentiation (Frendeus *et al.*, ٢٠٠٠)**.** Rantes is produced by lymphoid and epithelial cells of the mucosa in response to various external stimuli and is chemotactic for lymphocytes. also increased Ag-specific Ab titers

in mucosal secretions and these Ab responses were associated with increased numbers of Ab-forming cells, derived from mucosal and systemic compartments. Rantes also enhance mucosal and systemic humoral Ab responses throug help provided by Th١- and select Th٢-type cytokines as well as through the induction of costimulatory molecule and cytokine receptor expression on T lymphocytes. These effects could serve as a link between the initial innate signals of the host and the adaptive immune system (Lillard *et al.*, ٢٠٠١).

Neutrophils migrate to infected mucosal sites that they protect against invading pathogens. Their interaction with the epithelial barrier is controlled by the chemokines and by their receptors. In experimental study of Frendéus on mice was shown in control groups (have intact epithelial layer with interleukin-٨ receptor) stimulated an epithelial chemokine response and increased chemokine receptor expression. neutrophils migrated through the tissues to the epithelial barrier that they crossed into the lumen, and the mice developed pyuria, while in aged mice the chemokine response was intact, but the epithelial cells failed to express IL-٨R, and neutrophils accumulated in the tissues. The aged mice were unable to clear bacteria from kidneys and bladders and developed bacteremia and symptoms of systemic disease, but control mice were fully resistant to infection, suggesting that chemokine receptor expression may also influence the susceptibility to UTIs in humans. The results provide a first molecular clue to disease susceptibility of patients prone to acute pyelonephritis (Frendéus *et al.*, ٢٠٠٠).

Previous studies showed that epithelial cells of bladder were capable of presenting antigen to T lymphocytes. All epithelial cell lines were observed to function as APC. and observed to activate IFNy production by $CD٤^{+}$ Th ١ clone (Lattime *et al.*, ١٩٩٢) .

Age-related changes in the morphological integrity of mucosal (regional) lymphoid tissues and in the functional competence of the cells that participate in immune responses at mucosal sites, Age-associated changes in the origins, lineages, phenotypic and functional features of B and T lymphocytes, with emphasis on studies that define changes in the commitment of hematopoietic progenitor cells to the lymphocyte and B and T cell pathways of differentiation. Physiological and intrinsic lifetime, circulation, re-circulation, homing patterns and proliferative potential of T cells and subsets of T cells of the elderly, including analyses of receptor and adhesion molecules, their biosynthesis, cell-surface topography and functions. Cellular and molecular mechanisms that account for the failure of de novo germinal center formation in lymphoid follicles of elderly subjects, the possible senescence of follicular dendritic cells and associated aberrations in antigen presentation, and the reasons for the compromised antibody isotype switching and affinity maturation in germinal center in the elderly (Oaks *et al.*, ١٩٩٦).

٢-٨- Antigenic competition .

In general large proteins are better antigens than small ones, because they have more potential determinants,. Furthermore, the more foreign an antigen (that is the less similar to self –configuration), is more effective in provoking of an immune response. Certain areas of the antigen are more immunogenic than other and are called the immunodominant regions of the antigen. These sites of high density are called epitope and often those parts are composed of peptide chains which protrude significantly from the globular surface of antigen (Roitt, ٢٠٠٠).

The present study showed (in case of dimicrobic infection) one organism induce significant antibody responses, this depend on antigenic competition, this depend on the nature of the signal for which t-cells are competing. Previous experiments have suggested that T-cell competition is antigen (Ag)-specific. CD ٨-T cell competition was studied *in vivo* by reconstituting lethally irradiated mice with mixtures of precursor bone marrow cells from normal non transgenic and T-cell receptor (TcR)-transgenic mice (Freitas, ١٩٩٦).It was shown that the proliferative capacity of the TcR-transgenic cell was diminished in the presence of other T-cells, indicating that competition between T cells occurred, non transgenic cells appeared to have a selective advantage over TcR-transgenic cells in seeding the peripheral lymphoid tissue, suggesting that cells were competing for Ag.Most of the competition can be attributed to competition for antigenic sites on Antigen presenting cells (APCs), (Borghans *et al.*, ١٩٩٩). Bacteria that induced high titer have Ag pocess immunodominant epitope, this known as intermolecular antigenic competition. Dasgupta (١٩٩٢) refered to the prescense of the antigenic competition between Ag s by description as a factor determined materials antigenicity. The term antigenic competition refer to inhibition process to immune responses for significant Ag or antigenic determinant due to exposure to another antigenic determinant.

There are two type of antigenic competition, they are:

١- Intrmolecular competition or T-cell competition :in this type the Ag determinants found on antigenic region that found on different immunogenic molecules.

٢- Intramolecular competition :This type occurred when found different antigens on the same immunogenic molecule . This type known as B-cell

competition, in this type B-cell that poses different receptors (different specificities) for different antigenic determinants (Taussig, ١٩٧٥).

Some bacteria can liberate antigenic surface components in a soluble form into the tissue fluids. These soluble antigens are able to combine with and "neutralize" antibodies before they reach the bacterial cells. For example, small amounts of endotoxin (LPS) may be released into surrounding fluids by Gram-negative bacteria (Todar, ٢٠٠٢).

Due to the fact, that the activation and later suppression of each immune response are antigen-specific, several immune responses can produced at one time and be at different stages. A response to one antigen may be in the suppression phase, while a response to another antigen is just beginning.

The strength of the response to an antigen is shown by the maximum height of the activity curve (Fig-٢). The strength of the response may be different to different antigens. Response strength depends on the number of cells in that lymphocyte clone; clones with more cells produce bigger responses. For example in the Figure below, clone ١ produced in response to antigen ١ contains more cells than clone ٢ produced in response to antigen ٢; consequently, the strength of the immune response is greater to antigen ١ than to antigen ٢.

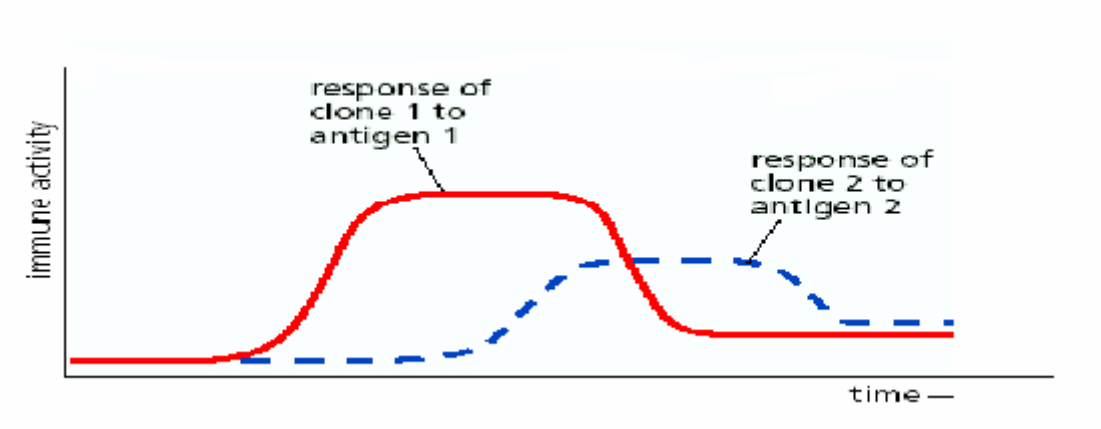

Fig-٢: Activation and suppression to two antigens occurs independently but at the same time (Anonymous, ٢٠٠٤) .

A large group of proteins can be produced by LPS-activated macrophages, including cytokines, such as tumor necrosis factor-α (TNF-α), IL-١, IL-٦, IL-٨, IL-١٢; metalloproteases, such as elastase and cathepsin; lipid mediators such as prostaglandins; as well as reactive oxygen and nitrogen species. However, up to a ١٠٠٠-fold higher concentration of PG may be required to induce secretion of many of those compounds compared with LPS. It is not known, however, whether sufficient levels of Peptidoglycan (PG) are reached *in vivo* after severe bacterial infection to induce those macrophage functions *in vitro*. Thus, differential production of autocoids by probiotic bacteria (Erickson and Hubbard, ٢٠٠٠).

The FimH subunit of type ١-fimbriated *Escherichia coli* has been implicated as an important determinant of bacterial adherence and colonization of the urinary tract.Fim- H of *E.coli* composed from ١ – ٢٦٤ amino acids, only that functionally important domains s-FimH$_{١-٢٥}$ failed to exhibit any binding activity despite its capacity to evoke an antiadhesive antibody. Perhaps, s-FimH$_{١-٢٥}$ contains only a portion of the receptor binding region or this peptide is located sufficiently close to the

binding domain such that its corresponding antibody sterically blocks FimH-mediated adherence.

FimH-specific IgA antibodies were detected in the serum as well as in the urine of the mice. Because the amounts of IgA relative to IgG levels in the urines appeared to be higher than that found in the serum, the IgA antibodies detected in the urine were likely to be locally generated (Thankavel *et al.*, ١٩٩٧).

٢-٩- IMMUNOGLOBULIN DIFICIENCY

٢-٩-١ -Humoral immune responses .

Humoral immune responses at the mucosal level are mainly of the immunoglobulin (Ig)A isotype. Although IgG-, IgM- and IgE-secreting cells are also present, their levels of activity and number are much lower. In contrast to IgA in the serum, secretory IgA (sIgA) is present as a dimeric form in the gut. After synthesis, IgA binds to the membrane receptor on the abluminal surface of the epithelial cells. The polymeric IgA is transported to the mucosal surface while still bound to the membrane of the transport vesicle. After fusion with the cell membrane at the mucosal surface, IgA with the secretory component is released. Secretory IgA is resistant to proteolysis; it does not participate in an inflammatory response. Thus, a major function of sIgA is to mediate immune exclusion of foreign antigens by preventing binding to the epithelial cells and penetration of microorganisms (Erickson and Hubbard, ٢٠٠٠).

Immune deficiency diseases are a group of disorders in which normal host defenses against disease are impaired. defects in non-specific host defenses (e.g., complement deficiency; functional white blood cell disorders), and defects in specific host defenses (e.g.,

immunosuppression caused by pathogenic bacteria, viruses and parasites; combined immune deficiency; IgA deficiency; growth hormone deficiency (Dodds, ٢٠٠٤).

٢-٩-٢ Etiology of immunoglobulin deficiency in elderly

Age-associated changes in cellular and molecular mechanisms that account for the failure of de novo germinal center formation in lymphoid follicles of elderly subjects, the possible senescence of follicular dendritic cells and associated aberrations in antigen presentation, and the reasons for the compromised antibody isotype switching and affinity maturation in the elderly (Oaks *et al.*, ١٩٩٦).

Tolerance is a property of the host in which there is an immunologically-specific reduction in the immune response to a given Ag. Tolerance to a bacterial antigen does not involve a general failure in the immune response but a particular deficiency in relation to the specific antigen(s) of a given bacterium. If there is a depressed immune response to relevant antigens of a parasite, the process of infection is facilitated. Tolerance can involve either AMI or CMI or both arms Immune tolerance : The MALT usually responds in two opposite fashions, i.e., in a positive manner for immunity to pathogenic organisms and in a negative manner to a large number of antigens of food as well as bacteria in the mucosal environment. This tolerance prevents the immune system from over responding extensively to potential antigens. This unresponsiveness may be both T- and B-cell mediated. One potential mechanism is the induction of antigen-specific suppressor T cells found in Peyer's patches. Although the mechanism is unknown, antigen-nonspecific regulatory cells can also play an important role in down-regulating responses to specific antigens. Another possible mechanism would be a direct effect of antigen on mucosal lymphocytes resulting in

the induction of clonal inhibition (Toy and Mayer ١٩٩٦) . Tolerance to a bacterium or one of its products might arise when large amounts of bacterial antigens are circulating in the blood (Erickson and Hubbard, ٢٠٠٠) .

Some pathogens (mainly viruses and protozoa, rarely bacteria) cause immunosuppression in the infected host. This means that the host shows depressed immune responses to antigens in general, including those of the infecting pathogen. Suppressed immune responses are occasionally observed also during chronic bacterial infections such as leprosy and tuberculosis. In mild cases of leprosy there is frequently an associated immunological suppression that is specific for *M. leprae* antigens. This is separate from tolerance, since unique antigens (proteins) of *M. leprae* have been associated as the cause of this immunosuppression. The most likely explanations for this are due to (١) lack of costimulatory signals (interference with cytokine secretion); (٢) activation of suppressor T cells; (٣) disturbances in TH١/TH٢ cell activities. At present, little is known of the mechanisms by which pathogens inhibit immune responses. It seems probable that it is due to interference with the immune functions of B cells, T cells or macrophages. Since many intracellular bacteria infect macrophages, it might be expected that they compromise the role of these cells in an immunological response (Todar, ٢٠٠٢) .

CHAPTER THREE

MATERIALS & METHODS

٣-١-SOLUTIONS

٣-١-١-FORMAL SALINE

This solution was prepared at concentration ٠,٥٪ by adding ٠. ٠٥ ml of formaldehyde(BDH) to ٩٩,٥ml(v/v)of ٠,٨٥٪ normal saline . It was used as dissolvent to urinary immunoglobulins (Pearse, ١٩٨٥) and to prepare the antigen of Gram negative bacteria(Lehmann ***et al.,*** ١٩٦٨).

٣-١-٢- TRIS BUFFER

It was prepared by dissolving ١٢ gm of tris base (TAAB)company (m.wt=١٢١,١٤)in ١٠ ml of distilled water in volumetric flask and complete the final volume to ١ liter. The pH of tris buffer was adjusted to ٧ by adding acid HCL(٠,٠١N).This solution was used to prepare poly ethylene glycol solution (Johnstone&Thorpe,١٩٨٢)

٣-١-٣ -POLY ETHYLEN GLYCOL SOLUTION

The concentration of this solution was ٦٪ . It was prepared by dissolving ٦ gm from poly ethylene glycol material (BDH) company

(m.wt= ٦٠٠٠) in ١٠ ml of tris buffer solution and complete the final volume to١٠٠ ml.

٣-١-٤- ٢-MARCAPTO ETHANOL

The concentration of this solution was ٠,٠٥ molary. It was prepared by adding ٣,٩ ml from stock of ١٢,٨ molary of Collbiochem company to ١٠ ml of normal saline and complete the final volume to ١ liter. The solution was used to detect the effect of this material on secretory immunoglobuline as reducing factor (Cruishshank *et al*. , ١٩٧٥ and Farell, ١٩٩٦.)

٣-١-٥ BIURET SOLUTION

This solution was prepared by dissolving ٣ gm from cupper sulfate (CUSO٤,٥H٢O) –BDH company (m.wt=١٦٦)in half liter distilled water with adding ٩ gm from sodium potassium tartarat ($NaKC_{\varepsilon}H_{\varepsilon}C_{٦},٤H_{٢}O$)-BDH company (m.wt=١٦٦) after dissolving of those three components, ١٠٠ ml from sodium hydroxide (NaOH) ٠,٦ N was added, the final volume was completed to ١ liter by adding distilled water. This solution was used in Biuret method to measure the concentration of immunoglobulins (Ross, ١٩٨٥).

٣-١-٦ STANDARD ALBUMIN SOLUTION.

This solution was prepared by dissolving (٦٠)gm from dry-egg albumin-BDH company(m.wt=٦٥٤٠٠) in small amount of sodium hydroxide (٠,٦N) and the final volume was completed to one liter by using (NaOH). The final concentration of albumin was (٦٠)gm/liter. Standard dilution from this solution was prepared

(١:١,١:٢,١:٤,١:٨,١:١٦,١:٣٢,١:٦٤,١:١٢٨,١:٢٥٦ and ١:٥١٢) that represented the following concentrations

(٦٠,٣٠,١٥,٧,٥,٣,٧٥,١,٨٧٥,٠,٩٣٧٥,٠,٤٦٨٧٥,٠,٢٣٤٣٧٥ and ٠,١١٧)gm/liter respectively.The diluant was sodium hydroxid solution(٠,١N) and the researcher used this solution to prepared standard curve to detect the concentration of immunoglobulins(Ross,١٩٨٥) .

٣-٢ REAGENTS.

٣-٢-١-KOVACS REAGENT.

This reagent was prepared by dissolving ١gm from dimethyl amino benzyldehyde in ١٥٠ ml from amyl-alcohol mixture, then ٥٠ ml HCL(B.D.H) was added gradually . The principle of this test is to determine the ability of an organism to form indol from tryptophane (Macfaddin,٢٠٠٠)

٣-٢-٢-METHYL RED REAGENT.

This reagent was prepared by dissolving ٠,١ gm from methyl red (Fluka) in ٣٠٠ ml from ٩٥٪ethyl alcohol, then ٢٠٠ ml distilled water was added to the alcohol-indicator mixture, the total volume is ٥٠٠ ml (Macfaddin,٢٠٠٠).Methyl red result is considered as valuable characteristics for the identification of bacterial species that produce strong acid from glucose.

٣-٢-٣- CATALASE REAGENT.

Catalase test was performed in the standard manner with (٣٪)$H_٢O_٢$ by adding (٣)ml from hydrogen peroxide ($H_٢O_٢$) to ٩٧ml from distilled water. This reagent was used for detecting catalase enzyme .

٣-٢-٤- OXIDASE REAGENT.

This reagent was prepared immediately during uses by dissolving ١ gm (tetra methyl-para phenylene-di amin mono hydrochloride)in ١٠٠ ml distilled water and allow to stand ١٥ min before using it. Finally it is stored in dark glass – stoppered bottle with avoiding undue exposure to light. This reagent is used to determine the presence of oxidase enzyme. (Macffadin,٢٠٠٠).

٣-٣ CULTURE MEDIA.

All cultures media were prepared following the recommendation of producing company. Those media were sterilized by using the autoclave in ١٢١c°,١٥ Ib,١٥ min while other's heat labile solutions were sterilized by filtration by using membranes filter ٠,٤٥ micrometer (Sartorious membrane filter Gm Bh W.Germany). Media for biochemical tests that were followed for identification of isolates were made as in Baron and his colleagues ,١٩٩٤;Cattell ,١٩٩٦ and Macfaddin,٢٠٠٠ .

٣-٤ API ٢٠ E.

An api ٢٠ E is miniaturized and confirmative identification system for *Enterobacteriaceae* and other non fastidious Gram negative rods which uses (٢١) biochemical test and a data base the complete list of those organism that it is possible to identify with this system is given in the identification table at the end of this system is given in the identification table at the end of this package insert. The api ٢٠ E strip consists of ٢٠ micro tubes containing de hydrated substrates. These tests are inoculated with a bacterial suspensions that reconstitutes the media during incubation, metabolism produces color changes that are either spontaneous or revealed by the addition of reagents. The reactions are read according to the reading table and the identification is obtained by referring to the analytical profile index or using the identification soft ware.

٣-٥-CASE HISTORY

This study was performed in Al- Hilla Educational Hospital Babylon governorate via information chart.

٣-٦-DISPOSABLE TOOLS.

٣- ٦-١- DISPOSABLE TUBE TYPE (AFMA)

These tubes were used to collect mid stream urine sample and other biochemical tests.

٣-٦-٢- DISPOSABLE PLATES.

Those were used to cultivate the causal organism.

٣-٧- PATIENTS.

Fifty three elderly men were included in this study ,Their age ranges between ٦٠ -٩٥ years .

٣-٨- CONTROL GROUPS.

Twenty five adolescent patients, their age ranges between ٢٢-٤٠ years were included in the control croups

٣-٩- SAMPLING.

٣-٩-١- COLLECTION OF SPECIMENS.

A clean catch mid stream specimens of urine (MSSU) were collected in sterile disposable container or directly in to a sterile

specimen bottle and so far possible done sample collection was made early in the morning before the washout effect of drinking fluid. (Cattel, ١٩٩٦).

٣-٩-٢- TRANSPORT OF SPECIMENS.

Urine was examined within one hour of collection, since delay may result in proliferation of contaminant bacteria, the death of fastidious microorganisms and the deterioration of cellular constitutes. In practical sense if delay was expected. Samples were left in refrigerated as soon as possible by ice box, (Cattel, ١٩٩٦).

٣-١٠-ISOLATION OF ASSOCIATED BACTERIAL CAUSALS.

٣-١٠-١- METHOD FOR ISOLATION OF ASSOCIATED BACTERIAL CAUSALS.

Two methods were made to isolate the causals organism :

٣-١٠-١-١ DIRECT METHOD (D) .

From clean catch mid stream specimens of urine(MSSU), loopful inoculum was cultured on MacConkey agar and blood agar by quadrate streaking method, then inoculated Petridish was incubated at ٣٧c° at ٢٤ hour in aerobic condition (Collee *et al*. ,١٩٩٦).

٣-١٠-١-٢ INDIRECT METHOD (ID) .

One ml from urine sample (MSSU) was mixed with (١)ml from nutrient broth, this mixture was incubated on ٢٤ hour at ٣٧c°, after that loopfull inoculum was subcultured into the blood agar and MacConkey agar petridishs and were incubated on ٣٧c° at ٢٤ hour in aerobic condition (Al- Nasiri,٢٠٠٢) .

٣-١١-PREPARATION OF SURFACE ANTIGEN

٣-١١-١-BENZAL KONIUM CHLORIDE

The concentration of this solution was ١:١٠٠٠ (V\V). It was prepared by adding ٠,٢ml from[Alkyl benzyl dimethyl ammonium chloride(٥٠٪conc.)] to ١٠ ml of normal saline and complete the final volume to ١٠٠ ml. This solution was used to prepare surface antigen of the gram positive bacteria .(Banber,١٩٨٠) .

٣-١١-٢- PREPARATION OF SURFACE ANTIGEN OF THE GRAM POSITIVE BACTERIA.

This was prepared depending on (McCoy &Kenndy,١٩٦٠,Garvy etal.,(١٩٧٧) and Banker (١٩٨٠) by using the following method :

١- Pure culture was prepared on nutrient agar.

٢- Six mls from normal saline was added to the surface of growth then swept by sterile loop.

٣- The suspension was collected by using sterile Pasture pipette and was tubed in sterile glass tube.

٤- Five mls from this suspension was centrifuged in ٤٠٠٠ rpm at ٥ min.

٥- The deposit was washed by adding ٥ ml normal saline.

٦- Benzyl-conium chloride was added to the deposit and mixed with it.

٧- One ml from this suspension was took and was tubed in opacimeter with adding benzyl chonium chloride solution (١:١٠٠٠ concentration)to the opacimeter until the turbidity become equal to the standard tube. The final concentration of antigen is equal to the (١٠)international unit.

٨- Five international units were prepared by taking ٥ ml from final suspension and mixed with ٥ml from benzyl chonium chlorid solution.after that the solution was mixed well and was incubated in ٣٧ c° in half hour.

٩- Sterility test was made by taking loop full from this suspension and streaking it on nutrient agar, then culture was incubated in ٣٧c° at ٢٤ hour. The culture must be sterile.

٣-١١–٣- PREPARATION OF SURFACE ANTIGEN OF THE GRAM NEGATIVE BACTERIA.

It was prepared according to (Smith,١٩٧٥ &Svanborg et al.,١٩٨٥) with some modification.

١- Twenty four hours pure culture was prepared by transporting an inoculum the growth from MacConkey agar to the nutrient agar and was incubated for٢٤ hour.

٢- Six mls formal saline were added to the surface of nutrient agar and the surface growth was swept by using sterile loop.

٣- The suspension was collected by using sterile Pasture pipette.

٤- This suspension was centrifuged in ٥ ml at ٤٠٠٠rpm for ٥ min.

٥- Washing by adding ٥ ml of formal saline to the deposit then centrifuged at ٣٥٠٠ rpm for ٥ min.

٦- Suspension was removed and the deposit was suspended by adding ٥ ml from the formal saline and mixed well.

٧- One ml from this suspension was tubed in opacimeter tube by adding the formal saline to the opacimeter tube until the turbidity become equal to the standard tube. Then the final concentration of antigen is equal to ١٠ international unit.

٨- Five international unit was prepared by taking ٥ ml from final suspension and mixed with ٥ ml from formal saline.

٩- The antigen suspension was heat killed in water bath at ٦٠c°for ١,٥ hour .

١٠- Sterility test was made.

٣-١٢- URINE FILTERATION.

Before separation of immunoglobulins, part of the urine sample was filtered to separate cellular organic components and salt from urine (Bienenstock & Tomasi,١٩٦٨;Burdon,١٩٧٠ &Kaufman et al. ,١٩٧٠).This was established using filter paper (Whatman no. ١).

This paper was moistured by using sterile distilled water. This method was considered the best method to filtrate urine (Shnawa & Mahdi,٢٠٠٤).

٣-١٣- SEPRATION OF IMMUNOGLOBULIN FROM URINE.

Poly ethylene glycol was used in separation of immunogloulin from urine (Burdan,١٩٧٠).

١-Twelve mls from urine sample (MSSU) was centrifuged at ٣٠٠٠ rpm for (٥)min with removing the precipitate and collecting the supernatant.

٢- Ten mls from supernatant was filtered by using moisture filter paper (Whatman no.١).

٣- Five mls from poly ethylene glycol was added to ٥ ml from filtered urine and was kept in refrigerator for ١ hour.

٤- The mixture was centrifuged in ٥٠٠٠ rpm in ٢٠ min after that the suspension was removed and the precipitate was dissolved in ٠,٥ ml of formal saline. and it was transferred to the appendrof tube.

٣-١٤- MEASURMENT OF URINARY IMMUNOGLOBULINS CONCENTRATION.

Biuret method was used in measuring of immunoglobulin in urine (Bienenstock & Tomasi, ١٩٦٨ and Uehling & Steihm, ١٩٧١).

١- Five ml of Biuret solution was tubed in spectronic-٢٠ tube.

٢- ٠,٢ ml of immunoglobulin solution was added to the Biuret solution. this tube was represented as tube of test run.

٣- ٠,٢ ml of distilled water was added to ٥ ml from Biuret solution, this tube represented as control tube.

٤- The tubes were mixed and left aside for ٣٠ min in room temperature for ١٥-٣٠ min.

٥- The optical density was measured on wavelength ٥٤٠ nanometer.

The immunoglobulin concentration was measured depending to the standard curve that has been prepared from dilutes of egg albumin solution.

٣-١٥- SEROLOGY TEST.

٣-١٥ -١ TUBE AGGLUTINATION TEST.

Serial two fold tube dilution technique of urinary mucosal immunoglobulin was attempted against the ٥ IU density suspension of the causal organism. Likewise, a tube dilution technique using , ٢ME-

saline as a substitutant to saline as in the case of simple standard tube agglutination (Cruickshank *et al.*, ١٩٧٥; Alousi, ١٩٧٩ and Shnawa & Mehdi, ٢٠٠٤).

٣-١٦- STUDY MENU.

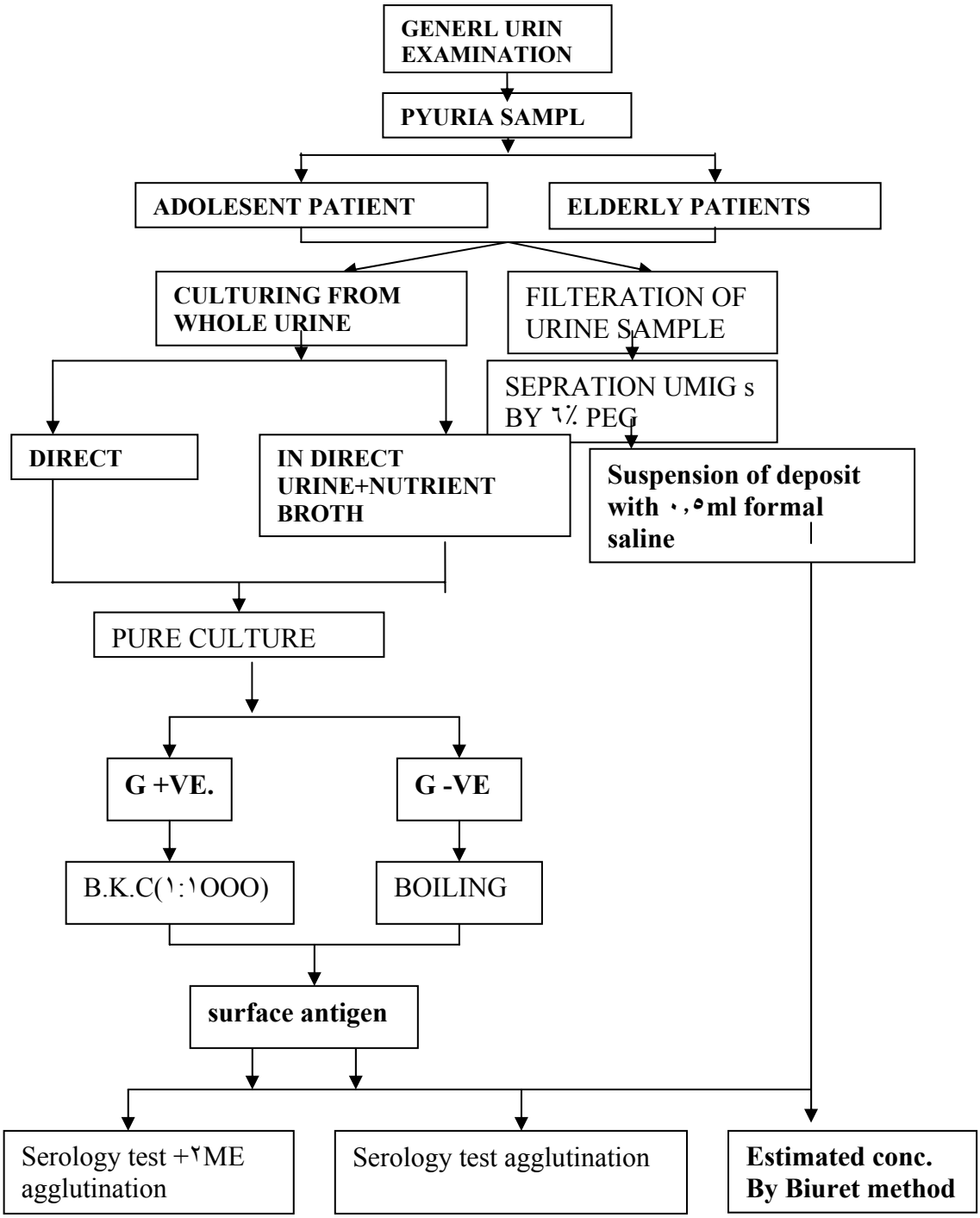

Fig-٣- Schematic diagram for checking of urine sample during the study of local immunity in urinary tract infection patients .

٣-١٧-STATISTICAL ANALYSIS

Two statistical tests were followed these are :

٣-١٧-١-CORRELATION FACTOR (r)

To study the correlation between immunoglobulin concentration and the titer of specific immunoglobulin (Dawed and Al-Yas, ١٩٩٠).

$$r = \frac{\sum XY - \left(\sum X \cdot \sum Y / N\right)}{\sum X^2 \left[\left(\sum X\right)^2 / N\right] \sum Y^2 - \left[\left(\sum Y\right)^2 / N\right]}$$

r= titer

y`=mean of titer

x= concentration

x`=mean of concentration

The Y^ was calculeated depend on the equation of simple linear regression

$Y\hat{} = a + bx$

Y^ represented the value of titer depend on study of standard curve that was referred to the correlation between immunoglobulin concentration and antibody titer.

a= intercept of curve with y

b= slop

a= ý- b x`

$$b = \frac{sxy}{sxx}$$

٣-١٧-٢- t-test

Paired observation t – statistic was made to determine the significant differences of the specific urinary immunoglobulin titer between adolescent and elderly patients (Dawed and Al-Yas, ١٩٩٠).

$$t = \frac{X_1' - X_2'}{\sqrt{\frac{s_1^2}{n_1} + \frac{s_2^2}{n_2}}}$$

x_1`=mean of titer in adolescent patients.

X_2`=mean of titer in elderly patients.

s_1^2: variant on titer in adolescent patients.

S_2^2: variant on titer in elderly patients.

n_1, n_2:number of case in adolescent and elderly patient respectively.

CHAPTER FOUR

RESULTS

٤-١- AGE DISTRIBUTION OF ELDERLY PATIENTS .

The age of elderly patients were distributed in four groups (table-١).The first group was ranged between ٦٠-٧٠ years while the second group was ranged between ٧١-٨٠ years. The third group was ranged between ٨١-٩٠ years and the fourth group was ranged between ٩١-١٠٠ years .Forty one male patients (٧٧,٣٥٪) were with in age group (٦٠-٧٠)years. Other age groups were ranged from ٢-٧ patients .

٤-٢- ELDERLY UTI, UNDERLYING DISEASES AND UMIG CONCENTRATION.

The concentration of urinary mucosal immunoglobulin in elderly with out underling disease was ٠,٥٤ gm\ liter. While those elderly with diabetes mellitus + prostate disease was ١٢. ٠٩٤ gm \liter and with urolithiasis was ١٧. ٠٩٧٨ gm \liter (table -٢).

٤-٣-UROPATHOGENS.

It was evident that there was no elderly specific uropathogen, but there was a difference in each of the specific uropathogen incidence

among elderly and adolescent. *Klebsiella* species and *Proteus* species were higher among elderly than in adolescent patients (table- ٣).

TABLE-١- AGE DISTRIBUTION OF ELDERLY UTI.

age (years)		No. of patients.
١	٦٠ -٧٠	٤١
٢	٧١ -٨٠	٧
٣	٨١-٩٠	٣
٤	٩١ -١٠٠	٢

TABLE-٢- Elderly UTI patients with underling disease.

no.	underling disease	no. of cases	Mean of UMIG conc.
١-	prostate	٣٢	٠,٦٤٤٤
٢-	prostate +renal failure.	٢	٩. ٠٧١٠٥
٣-	urolithosis	٤	١٧. ٠٩٣٨
٤-	bladder infection.	٣	٣. ٣١١٥٦
٥-	diabetes mellitus.	٣	٢. ٧٨٧٩
٦-	pylonephritis +renal failure.	٢	٢. ٨٥٥٥
٧-	prostate +diabetes mellitus.	٢	١٢. ٠٩٤٣٦
٨-	with out underling disease.	٥	٠,٥٤١٢٦

٤-٤- NATURE OF THE ASSOCIATED UROPATHOGEN.

The most common causative organisms were *Pseudomonas aeroginosa* (٢٢,٦٤%, ٢٤%) in elderly and adolescent patients respectivly, while *Klebsiella spp*. were the second among elderly patients. Meantime

the *Staphylococcus spp*. and *Enterobacter spp* were in the second order among adolescent patients. Other organisms such as *E. coli*,. were more common in younger than in elderly individuals. The incidence of *Proteus spp*. in both elderly and younger individuals are resemble ٥,٦% and ٤ % respectively. The infection by dull causal organisms was less rate in both elderly and younger patients (٣,٦٣٪, ٤,١٦٪) respectively (table-٣).

TABLE- ٣- INCIDANCE OF UROPATHOGEN AMONG ELDERLY AND ADOLESCENT.

no.	Elderly	percentage (%)	adolescent	the percentage(%)
١-	*P.aeroginosa*	٢١,٨١	*P.aeroginosa*	٢٥
٢-	*Klebsiella spp.*	٢٠,٧	*Klebsiella spp*.	٤
٣-	*Enterobacter spp.*	١٣,٢٠	*Enterobacter spp.*	١٦
٤-	*E.coli*	١٠,٩	*E.coli*	١٢,٥
٥-	*Staphylococcus spp.*	١٥,٠٩	*Staphylococcus spp.*	١٦
٦-	*Proteus spp.*	٥,٦	*Proteus spp.*	٤
٧-	٢- causal organisms	٣,٧	٢- causal organisms	٤

٤-٥- *P. aeroginosa* specific urinary mucosal humoral response in elderly and adolescent patients.

Twelve cases of *Psedomonas aeroginosa* urinary tract affection were noted among elderly male patients. The age range of those patients were (٦٠-٨٤) years. The mean ,median and range of their urinary mucosal immunoglobulin concentration were ٠,٨٢٥٢٨١٦ gm/l , ٤,٣١٥٩٦٢ gm/L and ٠,٠٠٠٥٦- ٨,٦٣١٣٥ gm/L respectively, while the mucosal specific antibody titer mean, median and range were ٢٤, ٦٦, ٤-١٢٨ accordingly(table-٤). Statistics for linear regression analysis showed that r is non significant (r= -٠,١٧١٦٧). Comparatively there were six cases of *P. aeroginosa* in adolescent male patients. The age range was (١٨-٣٨) years, The titer mean, median and range were ٥٨،٦٦ and ٤-١٢٨ accordingly. Statistic for linear regression analysis showed that r is significant (r=٠,٧١٤). However paired observation analysis using t statistics showed that calculated t value was higher than the table t value which on df ١٦ was ١,٣٠١ at p = ٠,١٥ . Such finding means that it was statistically significant .

Table ٤

٤-٦- *Escherishia coli* SPECIFIC URINAR MUCOSAL HUMORAL IMMUNE RESPONSES IN ELDERLY AND ADOLESCENT PATIENTS.

Six cases of *Escherishia coli* urinary tract infection were noted among elderly male patients. The age range of those patients were (٦٠-٧٣) years. The mean, median and range of their urinary mucosal immunoglobulin concentration were ٣,٣٦٤٧٥٨ gm/l, ٦,٨٩٩٤ gm/l and ٠,٠١٦-١٣,٧٨٢٨ gm/l respectively. While the *E. coli* mucosal specific antibody titer mean, median and range were ٢١,٢, ٣٣ and ٢-٦٤ accordingly. Statistics for linear regression analysis showed that r is significant, r = ٠,٩٨٦٦٢٢ while ٣ cases of young adult patients with *E. coli* the age range of those patients were ٢٤-٤٠, the mean, median and range of urinary mucosal immunoglobulin concentration were ٣,٢٤١٤٠٨٣, ٤,٢٨٩١٢ and ٠,٢٧٠٨٠-٨,٣٠٧٤٤ g/l respectively, while the urinary mucosal specific antibody titer, mean, median and range were ٤٤, ٣٤, ٤-٦٤ accordingly. Statistics for linear regression analysis showed that r = ٠,٤١ while the paired observation t statistic showed that calculated t value was higher than the table t value that t at df ٧ was ١,٠١ at p= ٠,٢, such finding means that it was statistically significant (table-٥) .

Table 0

٤-٧- URINARY MUCOSAL HUMORAL IMMUNE RESPONSE OF *Klebsiella pneumoniae* IN ELDERLY PATIENTS.

Eight cases ·f *K. pneumoniae* urinary tract infection were noted among elderly male patients. The age range of those patients were (٦٠-٨٥) years. The mean, median and rang of urinary mucosal immunoglobulin concentration were ٠,٥٩٦٥٣٥٧, ١,٣٦٨٦٥ and ٠,٠٨٥٠١-٢,٦٥٢٢٩ respectively. While the mucosal specific antibody titer, mean, median and range were ١٥،٤٣ and ٤-٦٤ g/l accordingly (table -٦). Statistic for linear regression analysis is shown that r is non significant (-٠,١٩٠٤).

TABLE-٦- *Klebsiella pneumoniae* SPECIFIC URINARY MUCOSAL HUMORAL IMMUME RESPONSES AMONG ELDERLY WITH UTI .

no.	age	culture .		UMIg.conc.(g/l)	UMIg titer with out ٢ME.	UMIg titer with ٢ME.
		direct	indirect			
١-	٦٠	*K.pneumoniae*	ND	٠,٢٧٠٨	٦٤	٦٤
٢-	٨٥	*K.pneumoniae*	ND	٢,٦٥٢٢٩	٨	٨
٣-	٦٥	*K.pneumoniae*	ND	٠,٦٥٩٢٧	٤	٤
٤-	٦٥	*K.pneumoniae*	ND	٠,٣٠٤٥٨	٨	٨
٥-	٦٠	*K.pneumoniae*	ND	NT	٤	٤
٦-	٦٠	*K.pneumoniae*	ND	٠,٠٨٥٠١	١٦	١٦
٧-	٦٧	NG	*K.pneumoniae*	٠,٠٨٥٠١	٨	٨
٨-	٧٠	*K.pneumoniae*		٠,١١٨٧٩	٨	٨
mean				٠,٥٩٦٥٣٥٧	١٥	
median				١,٣٦٨٦٥	٤٣	
range				٠,٠٨٥٠١- ٢,٦٥٢٢٩	٤-٦٤	
a	١٩,١٧٥٧٧					
b	- ٤,٣٦٥٨					
r	- ٠,١٩١٠٤					
equation- y=١٩,١٧٥٧٧ – ٤,٣٦٥٨ x						

٤-٨- URINARY MUCOSAL HUMORAL IMMUNE RESPONSE OF *Klebsiella oxytoca* AMONG ELDERLY MALE PATIENTS .

Three cases of *Klebsiella oxytoca* urinary tract affection were noted among elderly male patients. The age range of those patients was (٦٥-٨٥) years old. The mean, median and range of their urinary mucosal immunoglobulin concentration were ١,٥٩٦٦٦ g/l, ١,٥٩٦٦٦ g/l and ٠,٣٠٤٥٨- ٢,٨٨٨٧٥ g/l respectivly,while the mucosal specific antibody titer mean, median and range were ١٠،١٠ and ٤-١٦ accordingly (table -٧). Statistical linear regression analysis showed that r was significant (r=١).

TABLE-٧-*Klebsiella oxytoca* SPECIFIC URINARY MUCOSAL HUMORAL IMMUME RESPONSES AMONG ELDERLY WITH UTI .

no.	age	culture		**UMIg** conc. (g/l)	**UMIg** titer with out ٢ME.	**UMIg** titer with ٢ME.
		direct	**indirect**			
١-	٦٥	*K.oxytoca*	ND	NT	/	/
٢-	٧٥	*K.oxytoca*	ND	٢,٨٨٨٧٥	١٦	١٦
٣-	٧٢	*K.oxytoca*	ND	٠,٣٠٤٥٨	٤	٤
mean				١,٥٩٦٦٦	١٠	
median				١,٥٩٦٦٦	١٠	
range				٠,٣٠٤٥٨- ٢,٨٨٨٧٥	٤ -١٠	
a	٢,٥٨٥٦٣٥					
b	٤,٦٤٣٦٥٧					

r	١				
equation	Y=٢,٥٨٥٦٣٥+٤,٦٤٣٦٥٧X				

NT: non tested .

٤-٩- URINARY MUCOSAL HUMORAL IMMUNE RESPONSE OF *Enterobacter spp.* IN ELDERLY AND ADOLESCENT MALE PATIENTS.

Seven cases of *Enterobacter spp.* urinary tract infection were noted among elderly male patients. The age range of those patients was ٦٠ -٧٣ years. The mean, median and range of their urinary mucosal immunoglobulin concentration were ٠,٧٠ g/l, ٠,٢٨٢٥٩٥g/l and ٠,٠٠٧٢٦-٠,٥٥٧٩٣ g/l respectively. While the mucosal specific antibody titer mean, median and range were ١٤،١٨ and ٤-٣٢ accordingly (table-٨). Statistics for linear regression analysis showed that r=- ٠,٦١٥١٩. While four cases of *Enterobacter spp*. in adolescent male patients their ages range were (٢٥-٣٨)years. The mean, median and range of urinary mucosal immunoglobulin concentration were ٠,١٠٥٤٨٦٦٩ g/l ,٢,٠٨٦٤٢٥ g/l ,and ٠,٠٣٢-٤,١٤٠٨٥ g/l respectively while the mucosal specific antibody titer mean, median and range were ٨٠,٥ ,٦٥ and ٢-١٢٨ accordingly (table-٨). Statistics for linear regression analysis showed that r=٠,٥,however paired observation analysis t statistic showed calculated t=٢. ١٩٤٨ was higher

than the table t value(t table =١. ٨٩٥) on df=٧ and ٠,٠٥ significant, such finding means that it was statistically significant .

Table ٨:

٤-١٠- URINARY MUCOSAL HUMORAL IMMUNE RESPONSE OF *P. morganii* and *P. mirabilis* IN ELDERLY AND ADOLESCENT MALE PATIENTS.

One case of *P. morganii* showed that mucosal immunoglobulin titer was of ٨. and two cases of *P. mirabilis* in elderly with titers of ٢. ٢ME treatment was not reducing mucosal immunoglobulin titers . While in young patients only one case of *P. mirabilis* and was showed that the mucosal immunoglobulin concentration was ٠,٠٨٥٠١ g/l and the mucosal immunoglobulin titer was ١٢٨ (table-٩ and table-١٠).

Table-٩-*Proteus morgani* urinary mucosal humoral immune responses among elderly with UTI .

case no.	age	culture		UMIg conc.(g/l)	UMIg titer with out ٢ME.	UMIg titer with ٢ME.
		Direct.	Indirect.			
١-	٦٠	*P. morganii*	ND	٠,٠٦٨١٢	٨	٨

Table-١٠-*P. mirabilis* specific urinary mucosal humural immune response among elderly and adolescent with UTI.

no. A/Elderly	age	culture		UMIg conc.(g/l)	UMIg titer with out ٢ME.	UMIg titer with ٢ME.
		Direct.	Indirect.			
١-	٦٠	NG	*P.*mirabilis	auto agglutination		
٢-	٦٠	*P.mirabilis*	ND	٠,٠٥١٢٨	٢	٢
B/Adolescent						
١-	٣٥	*P.mirabilis*	ND	٠,٠٨٥٠١	١٢٨	١٢٨

٤-١١- *S. aureus* specific urinary mucosal humoral immune responses among elderly .

Four cases of *S. aureus* urinary tract affection were noted among elderly male patients. The age range of those patients was (٦٣-٩٥) years. The mean, median and range of their urinary mucosal immunoglobulin concentration were ٤,٩٣٨٠٧ g/l, ٥,٩٦٢٧٣ g/l and ٠,١٦٩٤٦-١١,٧٥٦ g/l respectively(table-١١). While their mucosal specific antibody titer mean,

median and range were ٢٦,٦٦ , ٢٤ and ١٦-٣٢ accordingly. Statistics for linear regression analysis showed that r was non significant (r=٠,٢٩٢). While in young patients only one case of *S.aureus* and was showed that the mucosal immunoglobulin concentration was ٠,٨٢٨١٧ g/l and the mucosal immunoglobulin titer was ١٢٨.

Table-١١- *S. aureus* specific urinary mucosal humoral immune responses among elderly and adolescent patients with UTI .

no. A/Elderly	age	culture		UMIg conc.(g/l)	UMIg titer with out ٢ME.	UMIg titer with ٢ME.
		Direct.	Indirect.			
١-	٦٣	NG	*S.aureus*	no Ig	/	/
٢-	٦٣	*S.aureus*	ND	٢,٨٨٨٧٥	١٦	١٦
٣-	٩٣	*S.aureus*	ND	٠,١٦٩٤٦	٣٢	٣٢
٤-	٩٥	NG	*S.aureus*	١١,٧٥٦	٣٢	٣٢
mean				٤,٩٣٨٠٧	٢٦,٦٦	
median				٥,٩٦٢٧٣	٢٤	
range				٠,١٦٩٤٦-١١,٧٥٦	١٦-٣٢	
a-	٢٤,٤٦١٤٥					
b-	٠,٤٤٦٥٧٥					
r-	٠,٢٩٢٩١٢					
Equation	y=٢٤,٤٦١٤٥ +٠,٤٤٦٥٧٥x					
B/ Adolescent						
١-	٢٢	*S.aureus*	ND	٠,٨٢٨١٧	١٢٨	١٢٨

٤-١٢- URINARY MUCOSAL HUMORAL IMMUNE RESPONSES OF *S.epidermidis* AMONG ELDERLY AND ADOLESCENT PATIENTS .

Four cases of *S. epidermidis* urinary tract infection were noted among elderly male patients, the age of those patients were ٦٠ years. The mean, median and range of their urinary mucosal immunoglobulin concentration were ٣,٠٣٦٣١٢٥ g/l, ٥,٨١٨٧١٥ g/l and ٠,٠٥١٢٣-١١,٥٨٦٢ g/l respectively. While their mucosal specific. antibody titer mean, median and range were ٦،٦ and ٤-٨ accordingly (table ١٢). Statistics for linear regression analysis showed that r=٠,٥٦ while ٣ cases of *S. epidermidis* in adolescent male patients, their age range were(٢٤ -٤٠) years. The mean, median and range of urinary mucosal immunoglobulins concentration were ١٣,٢٤٣٠٦٦ g/l, ١٠,٢٢٨٥٧٥ g/l and ١,١٨٥١-١٩,٢٧٢٠٥ g/l, while the mucosal specific antibody titer mean, median and range were ٦٦. ٦٦٦, ٦٨ and ٨-١٢٨ accordingly (table ١٢), statistical for linear regression analysis showed that r=٠,٨٤٦١٥٤. t- statistic showed that calculated t value(١,٧٤٩٠١١٤) was higher than the table t value(١,٤٧٦) at df =٥ , at ٠,١ significantly, such finding means that it was statistically significant .

Table ١٢

٤-١٣- URINARY MUCOSAL HUMORAL IMMUNE RESPONSES IN DIMICROBIC INFECTION .

Two cases of bacterial infections by *S. epidermides, E. coli* and *Pseudomonas aeroginosa, E. coli* were noted among elderly male patients, their age range was (٦٠ -٦٢)years. The mean, median and range of urinary mucosal immunoglobulin concentration were ٠,١٨٦٢٣٥ g/l, ٠,١٨٦٢٣٥ g/l and ٠,٠٨٥٠١- ٠,٣٢١٤٧ g/l respectively ,while the mucosal specific antibody titer mean, median and range were ٧،٩ and ٢-١٦ accordingly, while only one case in adolescent patient was infected by *S.epidermidis* and *K.pneumoniae* was recorded with out UMIg, (table-١٣).

median				٠,١٨٦٢٣٥	٩		
Range				٠,٠٨٥٠١- ٠,٣٢١٤٧	٢-١٦		
B/ Adolescent no.	age	culture		UMIg	UMIg titer with out ٢ME.		UMIg titer with ٢ME.
A/Elderly ١-	٢٣	١-*S.epidermidis* ٢-*K.pneumoniae*	Direct. ND Indirect.	No UMIg conc.(g/l)			
١-	٦٠	١-*S.epidermidis*	٢-*E.coli*	٠,٠٨٥٠١	١-	٢	٢
					٢-	٢	٢
٢-	٦٢	١-*P.aeroginosa* ٢-*E. coli*	ND	٠,٣٢١٤٧	١-	١٦	١٦
					٢-	٨	٨
mean				٠,١٨٦٢٣٥	٧		

Table-١٣-Urinary mucosal humoral immune responses in dimicrobic infection.

٤-١٤-NIL URINARY MUCOSAL HUMORAL IMMUNE RESPONSES .

Three elderly patients with *S. aureus, E. coli* and *Enterobacter*, their age range was (٦١-٧٣) years, urine positive culture but they had nil urinary mucosal humoral immune responses. No mucosal urinary immunoglobulin can be obtained (table-١٤) .

Table-١٤- Nil urinary mucosal humoral immune responses.

case no.	age	culture D.	
		direct	indirect
١-	٦٣	*S. aureus*	ND
٢-	٦١	NG	*Enterobacter*
٣-	٧٣	*E. coli*	ND

٤-١٥ - CULTURE NEGATIVE UTI:

Three cases of sterile pyuria were noted among elderly male patients. The age range of those patients was (٧٠-٧٥) years. The mean, median and range of urinary mucosal immunoglobulin concentration were ١. ١١٥٣ g/l, ١. ٤٥٣١ g/l and ٠,١٦٩٤٦ -٢. ٧٣٦٧٤ g/l respectively(table-١٥).

Table-١٥- Culture negative UTI.

case no.	age	UMIg conc.(g/l)
١-	٧٥	٠,٤٣٩٧
٢-	٧٠	٠,١٦٩٤٦
٣-	٧٢	٢. ٧٣٦٧٤
mean		١. ١١٥٣
median		١. ٤٥٣١
range		٠,١٦٩٤٦- ٢,٧٣٦٧٤

٤-١٦- COMPARATIVE URINARY MUCOSAL HUMORAL IMMUNE RESPONSES FOR ELDERLY AND ADOLESCENT DURING UTI .

There were differences between specific antibody titers for uropathogen among elderly and adolescent for the same uropathogens. Paired observation t-statistics were showing significant t value in case of *S. epidermides* ١,٧٤٩٠ at p= ٠,١ and for *Enterobacter spp* ٢,١٩٤٨ at p=٠,٠٥. (table ١٦).

Table -١٦- Comparative urinary mucosal humoral immune responses for elderly and adolescent during UTI.

eq.	causal organisms	geriatric titer	adolescent titer	t-statistic		significance
				calculate	table	
١-	*P. aeroginosa*	٢٤	٤٢	١. ٣٠١	١. ٠٧١	٠,١٥
٢-	*E. coli*	٢١. ٢	٤٤	١. ٠١	٠,٨٩٦	٠,٢
٣-	*S. epidermides*	٦	٦٦. ٦٦٦	١. ٧٤٩٠	١. ٤٧٦	٠,١
٤-	*Enterobacter spp.*	١٤	٨٠,٥	٢. ١٩٤٨	١. ٨٩٥	٠,٠٥

CHAPTER FOUR

RESULTS.

٤-١ PATIENTS:

Elderly male patients suffering from UTI with age range of (٦٠ - ٩٥) years old were elected from the patients attending urology consultation unit / Hilla- Surgical Hospital during the period of December ٢٠٠٣ till April ٢٠٠٤.

٤-٢ Test battery:

Elderly UTI test group of ٥٥ and ٢٥ adolescent UTI patients as control. Urine samples were processed by direct and indirect enrichment then quadrate plating, mucosal immunoglobulin separation and specific local mucosal antibody titer determination.

٤-٣ SCORE.

Moderate to heavy growth of one colony morphotype indicate single, while the growth of equivalent colony population indicate dimicrobic infection. Mucosal urinary immunoglobulin was characterized by the ٢-ME resistance. Positive biuret and immune specifity to the uropathogen.

٤-٤- RESULT PRESENTATION.

Results will be presented in comparative manner for elderly and adolescent. Results will be evaluated by regression analysis and paired observation t- test statistics.

٤-٥ AGE DISTRIBUTION OF ELDERLY PATIENTS ..

Twenty nine patients (٥٣%) were noted with in age group (٦٠-٦٢)years. Other age groups, however, were ranged from (١-٧)patients (table- ١).

٤-٦ ELDERLY UTI, UNDERLYING DISEASES AND UMIG CONCENTRATION.

The concentration of urinary mucosal immunoglobulin in elderly with out underling disease was (٠,٥٤) gm\ liter. While those elderly with diabetes mellitus was (١٢. ٠٩٤)gm \liter and with urolithiasis was (١٧. o٩٧٨)gm \liter (table -٢).

٤-٧-UROPATHOGENS:

It was evident that there was no elderly specific uropathogen, but there was a difference in each of the specific uropathogen incidence among elderly and adolescent. *Klebsilla* species and *Proteus* species were higher among elderly than in adolescent patients (table- ٣).

TABLE-١: AGE DISTRIBUTION OF ELDERLY UTI.

elderly UTI patients, age distribution.		No. of patients.
١	٦٠ -٦٢	٢٩
٢	٦٣ -٦٥	٧
٣	٦٦ -٦٨	١
٤	٦٩ -٧١	٦
٥	٧٢ -٧٤	٥
٦	٧٥ -٧٧	٢
٧	٧٨ -٨٠	/
٨	٨١ -٨٣	١
٩	٨٤ -٨٦	٢
١٠	٩٣ -٩٥	٢

TABLE-٢- Elderly UTI patients with underling disease.

seq.	underling disease	case no.	mean MIC
١-	prostate	٣٢	٠,٦٤٤٤
٢-	prostate +renal failure.	٢	٩. ٠٧١٠٥
٣-	urolithosis	٤	١٧. ٠٩٣٨
٤-	bladder infection.	٣	٣. ٣١١٥٦
٥-	diabetes mellitus.	٣	٢. ٧٨٧٩
٦-	pylonephritis +renal failure.	٢	٢. ٨٥٥٥
٧-	prostate +diabetes mellitus.	٢	١٢. ٠٩٤٣٦
٨-	with out underling disease.	٦	٠,٥٤١٢٦

٤-٨- NATURE OF THE ASSOCIATED UROPATHOGEN.

The most common causative organisms were *Psedomonas aeroginosa* (٢١,١٨٪, ٢٥٪) in elderly and adolescent patients respectivly, while Klebsiella sp. were the second among elderly patients. Meantime the *Staph sp*. and *Enterobacter sp.* in the second order in adolescent

patients. Other organisms such as *E. coli*,. were more common in younger than in elderly individuals. The incidence of *Proteus sp*. in both elderly and younger individuals are resemble ٥,٤٪ and ٤,١٦٪ respectively. The infection by dull causal organisms was less rate in both elderly and younger patients (٣,٦٣٪, ٤,١٦٪) respectively (table-٣).

TABLE- ٣ INCIDANCE OF UROPATHOGEN AMONG ELDERLY AND ADOLESCENT.

seq.	Elderly	the percent	adolescent	the percent
١-	*Pseudomonas aeroginosa*	٢١,٨١٪	*Pseudomonas aeroginosa*	٢٥ %
٢-	*Klebsiella sp.*	٢٠ %	*Klebsilla sp*.	٤,١٦ %
٣-	*Enterobacter sp.*	١٢,٧٢ %	*Enterobacter sp.*	١٦,٦٦٪
٤-	*E.coli*	١٠,٩ %	*E.coli*	١٢,٥ %
٥-	*Staphylococcus sp.*	١٤,٥٤ %	*Staphylococcus sp.*	١٦,٦٦ %
٦-	Proteus sp.	٥,٤٥٤ %	Proteus sp.	٤,١٦ %
٧-	٢- causal organisms	٣,٦٣ %	٢- causal organisms	٤,١٦ %

٤-٩ *Pseudomonas aeroginosa* specific urinary mucosal humoral response in elderly and adolescent patients.

Twelve cases of *Psedomonas aeroginosa* urinary tract affection were noted among elderly male patients. The age range of those patients of urinary mucosal immunoglobulin concentration were ٠,٨٢٥٢٨١٦ to ٤,٣١٥٩٦٢ and ٠,٠٠٠٥٦- ٨,٦٣١٣٥ respectively, while the mucosal specific antibody titer mean, median and range were ٢٤, ٦٦, ٤-١٢٨ accordingly(table-٤). Statistics for linear regression analysis showed that r is non significant (r= -٠,٢١٣٩٩). Comparatively there were six cases of *P. aeroginosa* in adolescent male patients. The age range was (١٨-٣٨) years, The titer mean, median and range were ٥٨،٦٦ and ٤-١٢٨ accordingly. Statistic for linear regression analysis showed that r is non significant (r=٠,٢١٩٨٤٧). However paired observation analysis using t statistics showed that calculated t value was higher than the table t value which on df ١٦ was ١,٣٠١ at p = ٠,١٥ . Such finding means that it was statistically significant .

Table ٤

٤-١٠ *Escherishia coli* SPECIFIC URINAR MUCOSAL HUMORAL IMMUNE RESPONSES IN ELDERLY AND ADOLESCENT PATIENTS.

Six cases of *Escherishia coli* urinary tract affection were noted among elderly male patients. The age range of those patients were (٦٠-٧٣) years. The mean, median and range of their urinary mucosal immunoglobulin concentration were ٣,٣٦٤٧٥٨, ٦,٨٩٩٤ and ٠,٠١٦-١٣٠٧٨٢٨ respectively. While the *E. coli* mucosal specific antibody titer mean, median and range were ٢١,٢, ٣٣ and ٢-٦٤ accordingly. Statistics for linear regression analysis showed that r is significant, r = ٠,٩٨٦٦٢٢ while ٣ cases of young adult patients with *E. coli* the age range of those patients were ٢٤-٥٠, the mean, median and range of urinary mucosal immunoglobulin concentration were ٣,٢٤١٤٠٨٣, ٤,٢٨٩١٢ and ٠,٢٧٠٨٠-٨٠٣٠٧٤٤ g/l respectively, while the urinary mucosal specific antibody titer, mean, median and range were ٤٤, ٣٤, ٤-٦٤ accordingly. Statistics for linear regression analysis showed that r = -١ while the paired observation t statistic showed that t at df ٧ was ١,٠١ at p= ٠,٢.

Table ٥

٤-١١ URINARY MUCOSAL HUMORAL IMMUNE RESPONSE OF *Klebsiella pneumoniae* IN ELDERLY PATIENTS.

Eight cases ·f *K. pneumoniae* urinary tract affection were noted among elderly male patients. The age range of those patients were (٦٠-٨٥) years. The mean, median and rang of urinary mucosal immunoglobulin concentration were ٠,٥٩٦٥٣٥٧, ١,٣٦٨٦٥ and ٠,٠٨٥٠١-٢٠٦٥٢٢٩ respectively. While the mucosal specific antibody titer, mean, median and range were ١٥،٤٣ and ٤-٦٤ g/l accordingly (table ٦). Statistic for linear regression analysis is shown that r is non significant (-٠,١٩٠٤).

TABLE-٦ *Klebsiella pneumoniae* SPECIFIC URINARY MUCOSAL HUMORAL IMMUME RESPONSES AMONG ELDERLY WITH UTI .

seq.	age	culture D.	culture ID.	conc.	titer with out ٢ME.	titer with ٢ME.
١-	٦٠	*K.pneumoniae*		٠,٢٧٠٨	٦٤	٦٤
٢-	٨٥	*K.pneumoniae*		٢,٦٥٢٢٩	٨	٨
٣-	٦٥	*K.pneumoniae*		٠,٦٥٩٢٧	٤	٤
٤-	٦٥	*K.pneumoniae*		٠,٣٠٤٥٨	٨	٨
٥-	٦٠	*K.pneumoniae*		NT	٤	٤
٦-	٦٠	*K.pneumoniae*		٠,٠٨٥٠١	١٦	١٦
٧-	٦٧		*K.pneumoniae*	٠,٠٨٥٠١	٨	٨
٨-	٧٠	*K.pneumoniae*		٠,١١٨٧٩	٨	٨
mean				٠,٥٩٦٥٣٥٧	١٥	
median				١,٣٦٨٦٥	٤٣	
range				٠,٠٨٥٠١- ٢,٦٥٢٢٩	٤-٦٤	
a	١٩,١٧٥٧٧					
b	- ٤,٣٦٥٨					
r	- ٠,١٩١٠٤					
equation- y=١٩,١٧٥٧٧ – ٤,٣٦٥٨ x						

٤-١٢ URINARY MUCOSAL HUMORAL IMMUNE RESPONSE OF *Klebsiella oxytoca* AMONG ELDERLY MALE PATIENTS ..

Three cases of *Klebsiella oxytoca* urinary tract affection were noted among elderly male patients. The age range of those patients was (٦٥-٨٥) years old. The mean, median and range of their urinary mucosal immunoglobulin concentration were ١,٥٩٦٦٦ g/l, ١,٥٩٦٦٦ g/l and ٠,٣٠٤٥٨- ٢,٨٨٨٧٥ g/l respectivly,while the mucosal specific antibody titer mean, median and range were ١٠،١٠ and ٤-١٦ accordingly (table -٧). Statistical for linear regression analysis showed that r was significant (r=١).

TABLE-٧ *Klebsiella oxytoca* SPECIFIC URINARY MUCOSAL HUMORAL IMMUME RESPONSES AMONG ELDERLY WITH UTI .

seq.	age	culture D.	culture ID.	conc.Of MIg	titer with out ٢ME.	titer with ٢ME.
١-	٦٥	*K.oxytoca*		NT	/	/
٢-	٧٥	*K.oxytoca*		٢,٨٨٨٧٥	١٦	١٦
٣-	٧٢	*K.oxytoca*		٠,٣٠٤٥٨	٤	٤
mean				١,٥٩٦٦٦	١٠	
median				١,٥٩٦٦٦	١٠	
range				٠,٣٠٤٥٨- ٢,٨٨٨٧٥	٤ -١٠	
a	٢,٥٨٥٦٣٥					
b	٤,٦٤٣٦٥٧					

r	١				
equation	Y=٢,٥٨٥٦٣٥+٤,٦٤٣٦٥٧X				

٤-١٣ URINARY MUCOSAL HUMORAL IMMUNE RESPONSE OF *Enterobacter sp.* IN ELDERLY AND ADOLESCENT MALE PATIENTS.

Seven cases of *Enterobacter sp.* urinary tract affection were noted among elderly male patients. The age range of those patients was ٦٠ -٧٣ years. The mean, median and range of their urinary mucosal immunoglobulin concentration were ٠,٧٠, ٠,٢٨٢٥٩٥ and ٠,٠٠٧٢٦-٠,٥٥٧٩٣ respectively. While the mucosal specific antibody titer mean, median and range were ١٤،١٨ and ٤-٣٢ accordingly (table-٨). Statistics for linear regression analysis showed that r=- ٠,٦١٥١٩. While four cases of *Enterobacter sp*. in adolescent male patients their ages were (٢٥-٣٨)years. The mean, median and range of urinary mucosal immunoglobulin concentration were ٠,١٠٥٤٨٦٦٩ ,٢,٠٨٦٤٢٥ ,and ٠,٠٣٢-٤,١٤٠٨٥ respectively while the mucosal specific antibody titer mean, median and range were ٨٠,٥ ,٦٥ and ٢-١٢٨ accordingly (table-٨). Statistics for linear regression analysis showed that r=- ٠,٦٠٦٨٣ ,however

paired observation analysis t statistic showed calculate t=٢. ١٩٤٨, t table =١. ٨٩٥ on df=٧ and ٠,٠٥ significant.

٤-١٤ URINARY MUCOSAL HUMORAL IMMUNE RESPONSE OF *Proteus morganii* and *P. mirabilis* IN ELDERLY MALE PATIENTS.

One case of *p. morganii* showed that mucosal immunoglobulin titer was of ٨. and two cases of P. mirabilis with titers of ٢. ٢ME treatment was not reducing mucosal immunoglobulin titers (table-٩ and table-١٠).

Table-٩-*Proteus morgani* urinary mucosal humoral immune responses among elderly with UTI ..

case no.	age	culture		conc.	titer with out ٢ME.	titer with ٢ME.
		D.	ID.			
١-	٦٠	*P. morganii*		٠,٠٦٨١٢	٨	٨

Table-١٠-*P. mirabilis* specific urinary mucosal humural immune response among elderly with UTI.

case no.	age	culture		conc.	titer with out ٢ME.	titer with ٢ME.
		D.	ID.			
١-	٦٠		*P.* mirabilis	auto agglutination		

٢-	٦٠	*P.* mirabilis		٠,٠٥١٢ ٨	٢	٢

٤-١٥- *Staphylococcus aureus* specific urinary mucosal humoral immune responses among elderly .

Four cases of *S. . aureus* urinary tract affection were noted among elderly male patients. The age range of those patients was (٦٣-٩٥) years. The mean, median and range of their urinary mucosal immunoglobulin concentration were ٤,٩٣٨٠٧, ٥,٩٦٢٧٣ and ٠,١٦٩٤٦-١١. ٧٥٦ respectively. While their mucosal specific antibody titer mean, median and range were ٢٦,٦٦, ٢٤ and ١٦-٣٢ accordingly. Statistics for linear regression analysis showed that r was non significant (r=٠,٢٩٢). While in young patients one case of *S.aureus* showed that the mucosal immunoglobulin concentration was ٠,٨٢٨١٧ and the mucosal immunoglobulin titer was ١٢٨.

Table-١١ *Staphylococcus aureus* specific urinary mucosal humoral immune responses among elderly with UTI ..

seq.	age	culture D.	culture ID.	conc. of MIG.	titer with out ٢ME.	titer with ٢ME.
١-	٦٣		*S.aureus*	no Ig	/	/
٢-	٦٣	*S.aureus*		٢,٨٨٨٧٥	١٦	١٦
٣-	٩٣	*S.aureus*		٠,١٦٩٤٦	٣٢	٣٢
٤-	٩٥		*S.aureus*	١١,٧٥٦	٣٢	٣٢
mean				٤,٩٣٨٠٧	٢٦,٦٦	
median				٥,٩٦٢٧٣	٢٤	
range				٠,١٦٩٤٦-١١,٧٥٦	١٦-٣٢	
a-	٢٤,٤٦١٤٥					
b-	٠,٤٤٦٥٧٥					
r-	٠,٢٩٢٩١٢					
equation	y=٢٤,٤٦١٤٥ +٠,٤٤٦٥٧٥x					

٤-١٦ URINARY MUCOSAL HUMORAL IMMUNE RESPONSES OF *Staphylococcus epidermidis* AMONG ELDERLY AND ADOLESCENT PATIENTS .

Four cases of *S. epidermidis* urinary tract affection were noted among elderly male patients, the age range of those patients were ٦٠ years. The mean, median and range of their urinary mucosal immunoglobulin concentration were ٣,٠٣٦٣١٢٥, ٥,٨١٨٧١٥ and ٠,٠٥١٢٣-١١,٥٨٦٢ respectively. While their mucosal specific. Antibody titer mean, median and range were ٦،٦ and ٤-٨ accordingly (table ١٣). Statistics for linear regression analysis showed that r=٠,٩٩٩ while ٣ cases of *S. epidermidis* in adolescent male patients, their age range were(٢٥ -٤٠) years. The mean, median and range of urinary mucosal immunoglobulins concentration were ١٣,٢٤٣٠٦٦, ١٠,٢٢٨٥٧٥ and ١,١٨٥١-١٩,٢٧٢٠٥ while the mucosal specific antibody titer mean, median and range were ٦٦. ٦٦٦, ٦٨ and ٨-١٢٨ accordingly (table ١٣), statistical for linear regression analysis showed that r=٠,٨٤٦١٥٤. t- statistic showed that calculated t at df =٥ was ١,٧٤٩٠١١٤ at ٠,١ significantly.

Table-١٢ *Staphylococcus aureus* specific urinary mucosal humoral immune response among adolescent patients with UTI.

seq.	age	culture D.	culture ID.	conc.	titer with out ٢ME.	titer with ٢ME.
١	٢٢	*S. aureus*		٠٨٢٨١٧	١٢٨	١٢٨

Table ١٣

٤-١٧ URINARY MUCOSAL HUMORAL IMMUNE RESPONSES IN DIMICROBIC AFFECTION. .

Two cases of bacterial affections by *S. epidermides, E. coli* and *Pseudomonas aeroginosa, E. coli,* their age range was (٦٠ -٦٢)years. The mean, median and range of urinary mucosal immunoglobulin concentration were ٠,١٨٦٢٣٥, ٠,١٨٦٢٣٥ and ٠,٠٨٥٠١- ٠,٣٢١٤٧ respectivly,while the mucosal specific antibody titer mean, median and range were ٧،٩ and ٢-١٦ accordingly (table-١٤).

Table-١٤-Urinary mucosal humoral immune responses in dimicrobic affection.

case no.	age	culture D.	culture ID.	conc.	titer with out ٢ME.		titer with ٢ME.
١-	٦٠	١-*S. epidermidis*	٢-*E. coli*	٠,٠٨٥٠١	١-	٢	٢
					٢-	٢	٢
٢-	٦٢	١-P. aeroginosa ٢-E. coli		٠,٣٢١٤٧	١-	١٦	١٦
					٢-	٨	٨
mean				٠,١٨٦٢٣٥	٧		
median				٠,١٨٦٢٣٥	٩		
range				٠,٠٨٥٠١- ٠,٣٢١٤٧	٢-١٦		

٤-١٨-NIL URINARY MUCOSAL HUMORAL IMMUNE RESPONSES. .

Three elderly patients with *S. aureus, E. coli* and *Enterobacter*, their age range was (٦١-٧٣) years, urine positive culture but they had nil urinary mucosal humoral immune responses. No mucosal urinary immunoglobulin can be obtained.

Table-١٥- Nil urinary mucosal humoral immune responses.

case no.	age	culture D.	culture ID.
١-	٦٣	*S. aureus*	
٢-	٦١		*Enterobacter*
٣-	٧٣	*E. coli*	

٤-١٩. . CULTURE NEGATIVE UTI:

Three cases of sterile pyuria were noted among elderly male patients. The age range of those patients was (٧٠-٧٥) years. The mean, median and range of urinary mucosal immunoglobulin concentration were ١. ١١٥٣, ١. ٤٥٣١ and ٠,١٦٩٤٦ -٢. ٧٣٦٧٤ respectively.

Table-١٦- Culture negative UTI.

case no.	age	conc.
١-	٧٥	١. ١١٥٣ ٠,٤٣٩٧
٢-	٧٠	١. ٤٥٣١ ٠,١٦٩٤٦
٣-	٧٢	٢. ٧٣٦٧٤
mean		
median		

range		٠,١٦٩٤٦- ٢,٧٣٦٧٤

٤-٢٠- COMPARATIVE URINARY MUCOSAL HUMORAL IMMUNE RESPONSES FOR ELDERLY AND ADOLESCENT DURING UTI. .

There were differenses between specific antibody titers for uropathogen among elderly and adolescent for the same uropathogens. Paired observation t-statistics were showing significant t value in case of *S. epidermides* at p= ٠,١ and for *Enterobacter* at p=٠,٠٥. (table ١٧).

Table -١٧- Comparative urinary mucosal humoral immune responses for elderly and adolescent during UTI.

eq.	causal organisms	geriatric titer	adolescent titer	t-statistic		significnt
				calculate	table	
١-	*P. aeroginosa*	٢٤	٤٢	١. ٣٠١	١. ٠٧١	٠,١٥
٢-	*E. coli*	٢١. ٢	٤٤	١. ٠١	٠,٨٩٦	٠,٢
٣-	*S. epidermides*	٦	٦٦. ٦٦٦	١. ٧٤٩٠	١. ٤٧٦	٠,١
٤-	*Enterobacter sp.*	١٤	٨٠,٥	٢. ١٩٤٨	١. ٨٩٥	٠,٠٥

CHAPTER FIVE

DISCUSSION

٥-١- Age distribution

Among elderly patients UTI s were found of dominance at the age range of ٦٠ -٧٠ (٧٧,٣٥ %) followed by ٧١-٨٠ (١٣,٢٠ %), then the age range of ٨١-٩٠(٥,٦٦ %) and the age range ٩١- ١٠٠ (٣,٧ %) (table-٢).Simon *et al.*, (٢٠٠١) have found that ٥-١٥ % of men over the age of ٦٥ will have a symptomatic bacteriuria. Cattell (١٩٩٦) found that in those elderly patients of ٦٥ years of age , the prevalence of bacteriuria is greater in women than in men. In Finland , it was found that UTI was ٢٪ in men and ١٧٪ in women at the age range between ٦٥-٦٩ years (Cattle, ١٩٩٦).Thus generally speaking the study results are of parallel results to that of Cattle, (١٩٩٦) and Simon *et al.*, (٢٠٠١).

٥-٢:UNDERLYING DISEASE TO UTI IN ELDERLY.

Six male patients without underling disease conditions, prostatic disease, urolithiasis and diabetes melites were the common underling diseases to UTI in elderly (Table-٣).Prostatic disease were leading to ٥٨,١٨٪ of UTI infection in elderly due to obstruction of urinary tract (Lipsky,١٩٨٩ and Simon *et al.*, ٢٠٠١).Urolithiasis, obstructive renal calculi are among the predisposing factors of UTI in elderly patients(Cannistra and Etkin, ٢٠٠٠). The hormonal unbalance of patients

with diabetes melietis made them more prone to UTI than non diabetic elderly or adolescent ((Lamberts,*et al*.,١٩٩٧ and Cohen,١٩٩٩).

٥-٣- INCIDENCE OF UROPATHOGEN AMONG ELDERLY AND ADOLESCENT

Highest ratio (١٢ case) were noted for *P. aeroginosa*(٢٢,٦٤%) among elderly and highest in adolescent (٢٤%).The result in elderly patients were consistent with Kawahara and Ohi,(١٩٩٤) and Cattell (١٩٩٦), he was found that bacterial infection of the genito-urinary tract in the compromised host with underling disease in compromised uro-patients was recurrent *P. aeroginosa* urinary tract infection (UTI) and chronic bacterial prosttitis were evaluated, respectively. While this results in adolescent was disagrees with that of Ofek &Beachey(١٩٨٠) &Walsh *et al.* ,(١٩٩٧),because they proved that the most common organism was *Esherichia coli* which is responsible for ٨٥٪ of infection in ambulatory patients and ٥٠٪ of nosocomial infection . Other groups were with percents of bacteria are as that of Pullman, (٢٠٠٣), and these results in agreement with Meyrier, *et al*., (١٩٩٩) and Cattell (١٩٩٦), they were shown that *E.coli* and *Enterobacter* are the predominant uropathogen in adolescent men while in elderly men *Psedomonas, Klebsiella* , *Enterobacter* and Proteus were increasingly prevalent.

٥-٤ *P.aeroginosa* SPECIFIC MUCOSAL HUMORAL IMMUNE RESPONSE AMONG ELDERLY AND ADOLESCENT WITH UTI.

P. aeroginosa almost never causes infection in the absence of; ١- A damage to the normal host defense mechanisms. ٢- Deficiency or

alteration in the defense mechanism. ٣-Bypass of normal defense mechanism (insertion of an indwelling urinary catheter, those neutropenia from disease (Goldman, Bennett, ٢٠٠٠), all these conditions were found in senescence patients. On aging three types of cellular changes in immune system which may lead to decline in immunological function, these are ١-An absolute decrease in the number of cells, ٢-relate to increase in regulatory cells with suppressive activity, ٣- decrease in function efficiency of immune cells, (Burns and Leventhal, ٢٠٠٠), also *P. aeroginosa* can help protect itself from defense mechanisms by producing glycocalyx, a carbohydrate produced by many bacteria, which by surrounding the cell and anchoring it to epithelial cell or invasive devices such as intravascular or urinary catheter, protect the bacteria from antibody, complement, and polymorphonuclear leukocytes or macrophages. After colonization, *P.aeroginosa* can invade in the appropriate setting through the effect of extracellular enzymes (toxins), these include elastase, alkaline protease, cytotoxin and hemolysins. Elastease and protease have been demonstrated to cause necrotizing lesions. *P.aeroginosa* bacteremia occur in patients with immunoglobulin or hypocomplementemia states, (Goldman and Bennet, ٢٠٠٠). *P.aeroginosa* elastease enzyme that inactivate component of complement (Todar, ٢٠٠٢). The results showed that this bacteria was in highest percent amongst others both in elderly and adolescent patients (table-٤), this may be because of: ١-Infection is more common in patients with lower urinary tract obstruction, ٢- Possibly due to decreased bacterial washout and increased bacterial adherence to the mucosa of the bladder, ٣- In the presence of obstruction, eradicating the infection is difficult since in non-Instrumented patients, the finding of unusual organisms such as (*Pseudomonas*, *Proteus)* in urine culture should suggest the presence of underlying obstruction (Goldman and Bennett, ٢٠٠٠).

This study proved that the relation between titer and immunoglobulin concentration was reversible in elderly patients, while in adolescents they were found to be of simple linear positive correlation between titer and Ig concentration with r=٠,٧this result was according with Mahdi, (٢٠٠٠) and Al-Amedi,(٢٠٠٣).

٥-٥ *E. coli* specific urinary mucosal humoral immune response in elderly and adolescent patients.

Six cases of *E. coli* urinary tract infection were represented ١١,٣٢ % among elderly while three cases of *E.coli* were they represented ١٢ % in adolescents. In elderly patients strong positive relationship was found between Ig concentration and titer with r=٠,٩, which indicates that *E.coli* antigens induced Secretory immune responses by production of SIg (Shnawa & Mahdi, ٢٠٠٤), P fimbria,was an important virulence factor that involved local immune response by mucosa derived antibody secreting cells and for urinary antibodies . the response to p- fimbriated *E.coli* was stronger among patients with p + PN (pyelonephritis) than among patients with PN caused by non-P-fimbriated *E. coli* (P-) (P< ٠٠١). Antibody response to pili of the infecting E. coli strain (have٣٦٦٠ - ٣٠٤٨ pili) was found in serum and urine, each anti-pili antibody totally blocked attachment of the homologous strain.. (Kantele, *et al*, ٢٠٠٣ and Svanborg, *et al*., ١٩٨٢). Lower bacteria specific mucosal Ab titer was noted among elderly than those reported for adolescent , as well as, the concentration of UMIg. This may due to decrease in B-lymphocyte producing antibody, or due to decrease synthesis and \ or increase in regulatory suppressor activity of T- cell finally it could be a net result of the ageing effects (Burns and Leventhal, ٢٠٠٠).

Distinct differences in the immune responses exist in the urinary bladder and kidney tissues . Kidney tissues which may be an important sites for the development of infections because the epithelial cells of some tubules were induced to express immune associated (IaS) antigens. A slight increase of what were most probably T-helper cells. In the pyelonephritic lesions there were large amounts of T-cells, mainly T-helper cells, Ia-expressing cells both rounded and irregular and also IgA and IgM-producing cells. IgA – producing cells demonstrated in the infected bladder. In the urinary bladder T-helper cells soon disappeared and there was instead on increase in irregular W٣/٢٥ – reactive cell that may be identical to the observed Ia – positive cell, (Hjelm, ١٩٨٤).

٥-٦ URINARY MUCOSAL HUMORAL IMMUNE RESPONSE OF *Klebsiella pneumoniae* IN ELDERLY MALE PATIENTS.

Eight cases of *Klebsiella pneumoniae* urinary tract infection representing ١٥,٠٩% percent while absent in adolescent patients. The result of UMIg concentration and UMIg titer were the lowest when compared with other infections, this result consistent with Anonymus, (٢٠٠٤), who found that the capsules of this organism have high component of sialic acid which prevent activation of complement and is poorly immunogenic, and the host response against capsulated or sheathed bacteria to acute pyelonephrites involve the production of serum antibody commonly to O antigen and occasionally to K antigen and type ١- fimbria .These antibody have been shown in animals to be protective against haematogenous or ascending infection while local production of immunoglobulins ,IgG and secretory dimeric IgA, occur at an increased level in response to infection such as acute pylonephrites but their

importance is not fully understood. The result of our study shows that the negative relationship between UMIg concentration and UMIg titer this results was in accordance with Anonymus,(٢٠٠٣), they proved that UMIg activity(agglutination or neutralization)was decreased in immunocompromised patients which including, ١-advanced age, ٢-diabetes, ٣-pregnancy.

٥-٧ URINARY MUCOSAL RESPONSE OF *K. oxytoca* IN ELDERLY MALE PATIENTS.

Three cases of *Klebsiella oxytoca* were represented ٥,٦ % of urinary tract infection were noted among elderly male patient while absent in adolescent patients. The result was shown that strong positive linear relationship between MUIg concentration and MUIg titer (r=١), this result was in agreement with Mahdi, ٢٠٠٠ and Al-Amedi,٢٠٠٣.

٥-٨ URINARY MUCOSAL HUMORAL IMMUNE RESPONSE OF *Enterobacter* IN ELDERLY AND ADOLESCENT MALE PATIENTS.

Seven cases of *Enterobacter spp*. urinary tract infection which comprises ١٣,٢% of all elderly cases while four cases represented ١٦ % in adolescent patients. This indicate that the infection with this bacteria is common in adolescents than in elderly patients , a finding which contradict other workers (Anonymous, ٢٠٠٣; Simon, *et al*, ٢٠٠٣). In elderly patients the relation between UMIg concentration and UMIg titer was negative with r=-٠,٦, this result according with (Walters, *et al*, ٢٠٠٣), he found that the change in the humoral immune response with age is a qualitative rather than a quantitative one, i.e. it is the affinity and specificity of the antibody that changes, rather than the quantity of

antibody produced, this may occur due to immune suppression and due to interference with the immune function of B-cell, T-cell or macrophage (Todar, ٢٠٠٢).Suppressed immune responses are occasionally observed during chronic bacterial infection. Since unique antigens (proteins) are the cause of this immunosuppression, the most likely explanation for this is due to : ١- Lack of co stimulatory signals (interference with cytokine secretion); ٢- Activation of suppressor T-cells; ٣-Disturbances in TH_1/TH_2 activities this lead to the production of MUIgA with low avidity ,or directed against unimportant antigenic determinants , they may have only week antibacterial action . Such ineffective (non-neutralizing) Abs might even aid a pathogen by combining with a surface Ag and /or blocking the attachment of any functional Abs that might be present . (Todar, ٢٠٠٢). While in adolescents the result was shown that positive linear relationship between MUIg concentration and MUIg titer (r=٥),this result was in agreement with Mahdi, (٢٠٠٠) and Al-Amedi,(٢٠٠٣).

٥-٩ URINARY MUCOSAL HUMORAL IMMUNE RESPONSE OF *Proteus spp*. AMONG ELDERLY AND ADOLESCENT.

One case of *P. morganii* was observed and ٢ –cases of *Proteus mirabilis* representing ٥,٦ % ,with low MUIg concentration and titer These results were in accordance with Mehdi, (٢٠٠٠). Only one case of *Proteus mirabilis* (٤%) was represented was recorded in adolescent patients with high UMIg titer (١٢٨), these results were in accordance with Al-Amedi ٢٠٠٣ (table-٩, table -١٠) .

Urinary tract infection due to *Proteus mirabilis* is not common and mostly reported in individuals with structural abnormalities of the urinary tract and is frequently isolated from the urine of elderly patients undergoing long term catheterization. Bacteria are attached to the penetrate tissue, resist host defenses and induce change to host tissue. *Proteus mirabilis* produces several virulence factors e.g., pore- forming hemolysins (Fraser, *et al*, ٢٠٠٢), proticine, leukocidin, endotoxin, IgA and IgG proteases (Walker, *et al*, ١٩٩٩), urease (Jones and Mobley, ١٩٨٨), deaminase, adhesions (Svanborg and Manp, ١٩٨٧), polysaccharide capsules (Gygi, *et al*, ١٩٩٥), pili /fimbiae (Bahrani *et al.*, ١٩٩٣ a, ١٩٩٤ b, Lix, *et al*, ٢٩٩٩).The ability to form biofilm (Rather, *et al*, ١٩٩٩; Sturgill *et al.*, ٢٠٠٢), and swarming ability. The above mentioned virulence factors enable the pathogens to overcome the various defense mechanisms of the host. During infection tones are formed due to the action of urease .The result was low titer, this because of; ١- *P. spp*. produce IgA proteases that inactivate secretory IgA by cleaving the molecule at the hinge region, detaching the Fc region on the immunoglobulin. ٢- *Proteus spp.* can avoid forces of the host antibody response by changing from one type of fimbriae to another or by switching fimbrial types. This makes the original AMI response obsolete by using new fimbriae that do not bind the previous antibodies. Pathogenic bacteria can vary (change) other surface proteins, especially outer membrane proteins, that are the target of antibodies. Antigenic variation usually results from site-specific inversion or gene conversion or gene rearrangements in the DNA of the microorganisms, (Todar, ٢٠٠٢;Pellegrino, *et al*, ٢٠٠٣). ٣-*Proteus mirabilis* caused coating of the bacterial surface with IgA and this processes effect on immune responses (Riedasch,*et al*, ١٩٨٤).

The result was shown that one case with auto agglutination . This Proteus auto agglutination can be attributed to an impairment in their LPS fine structure (Krajewska, ١٩٩٩).

٥-١٠ *S. aureus* SPECIFIC URINARY MUCOSAL HUMORAL IMMUNE RESPONSES AMONG ELDERLY AND ADOLESCENT MALE PATIENTS.

Four cases of *S.aureus* urinary tract infection presenting ٧,٥٤% in elderly patients and only one case ٤% was represented was recorded in adolescent patients. The only important *S.aureus* infection of the genitourinary tract are those that result from hematogenous dissemination. These include micro abscesses, renal carbuncles, and perinephric abscesses. The presence of *S.aureus* in the urine should never be assumed to be secondary to an ascending urinary tract infection. This organism possesses resistant factors that may promote local infection by thwarting host defense, they include coagulase that prevent neutrophile access to infection site , microcapsule(inhibit phagocytosis), protein A ((inhibits IgG –mediated opsonization) (binds Fc fragment) and exert its antibacterial activity)) , clumping factor(fibrinogen receptor) inhibit opsonization (fibrin coating) ,catalase(interferes with intracellular killing),proteases, nuclease, lipase and cytolysins (α,β,δ) (liquefaction necrosis and phagocyte dysfunction) , Leucocidin and gamma toxin (neutrophil cytolysis) , Fatty acid-metabolizing enzyme(activates bactericidal lipids) (Goldman and Bennett, ٢٠٠٠) .

Also *S. aureus* exist in nature as multiple antigenic type or serotypes meaning that they are variant strains of the same pathogenic species. If the immune response is the main defense against pathogen, they will, be able to shed their old antigens and present new ones to the immune system. Antigenic variation is an important mechanism used by pathogenic microorganisms for escaping the neutralizing activities of antibodies (Todar,٢٠٠٢) .

The result was shown that found low titer in elderly people with high concentration of Ig this may be due to the changes in secretory IgA, because of protein A, produced by *S. aureus* may remain bound to the staphylococcal cell surface or it may be released in a soluble form. Protein A will bind to the Fc region of Ig On the cell surface, protein A binds Ig in the wrong orientation to exert its antibacterial activity, and soluble protein A agglutinates and partially inactivates Ig . thus coating the bacteria with antibodies and canceling their opsonizing ability(Todar ,٢٠٠٢). Also the observed variation was with advance age patients, (James *et al*., ١٩٩٧). While in adolescent found high titer (١٢٨) with low conc. Of UMIg these results according with Mehdi, (٢٠٠٠) and Al-Amidi, (٢٠٠٣).

٥-١١ *S.epidermidis* SPECIFIC MUCOSAL HUMURAL IMMUNE RESPONSE AMONG ELDERLY AND ADOLESCENT DURING UTI .

Four cases of *S. epidermidis* urinary tract infection (٧,٥٤ %), while three cases of *S. epidermidis* (١٢ %) were recorded in elderly and adolescent patients respectively. Our results of elderly patients were in accordance witm Mehdi ,(٢٠٠٠). In both elderly and adolescent patients positive linear correlation appeared between UMIg concentration and UMIg titer in r=٠,٥and ٠,٨ respectively. These results also in agreement with Mehdi, (٢٠٠٠) and Al-Amedi, (٢٠٠٣), but the titer in adolescents was ١١time more than it was in elderly patients. This due to :١- Age related changes in the immune system. ٢- Mechanism of decline in the

immune function & ٣- Mechanism of disease associated with declining immune function, (Shnawa *et al*., ١٩٩٩).

٥-١٢ URINARY MUCOSAL HUMORAL IMMUNE RESPONSES IN DIMICROBIC INFECTION .

Two cases in elderly (٣,٧%) were found to have been infected with two microorganisms, one with *E.coli* and *Staphylococcus epidermidis* and the other with *E.coli* and *Pseudomonas aeroginosa* . In the first case the MUIg titer was equal in both microbes, this is consistent with Mehdi, (٢٠٠٠), probably because of non antigenic competition between both microbes and have equal immunodominant epitop. While in second case it was shown that *P. aeroginosa* cause mucosal immune responses higher than that of *E. coli*, these depend on antigenic competition or inter molecular antigenic competition,which indicate that *P. aeroginosa* have immunodominant epitope (Dasgupta, ١٩٩٢), while only one adolescent patient was infected by *S.epidermidis* and *K.pneumoniae* and represented ٤٪ was recorded with out UMIg, this due to high persistent doses of circulating Ag induce tolerance, tolerance to a bacterium or one of its products might arise when large amounts of bacterial antigens are circulating in the blood (Todar,٢٠٠٢).

Staphylococcus aureus produces cell – bound coagulase and clumping factor that cause fibrin to clot and to deposit on the cell surface. It is possible that this disguises the bacteria immunologically so that they are not readily identified as antigens and targets for an immune response. (Todar, ٢٠٠٢).

Some pathogen, persistent in the luminal surface of the GI –tract, oral cavity and the urinary tract or the lumen of the salivary gland,

mammary gland or the kidney tubule. If there is no host cell destruction, the pathogen may avoid inducing an inflammatory response, and there is no way in which sensitized lymphocytes or circulating antibodies can reach the site to eliminate the infection (Todar, ٢٠٠٢).

٥-١٣ NIL SECRETORY IMMUNE RESPONSE IN ELDERLY MAY BE EXPLAINED ON THE BASES OF ONE OR MORE OF THE FOLLOWING .

١- Decreased mucosal immunoglobulin synthesis so at the applied methodology rather unsuccessful for detection of separable detectable concentration (Kago *et al.*, ٢٠٠٠).

٢- Urinary mucosal immunoglobulin may be synthesized, released and catabolized by immunoglobulin splitting enzymes (Walker *et al.*, ١٩٩٩).

٣-Mucosal lymphocyte traffic to other effector sites of the mucosal immune system (Areazg, *et al.*, ١٩٩٣; Cinader & Thorbecke, ١٩٩٠ and Borghesi and Nicoletti, ١٩٩٤).

٤- Regulatory immune suppression via T- suppressive subsets, that suppress B-lymphocytes from synthesis and secretion of antibodies (Miller, ١٩٩١).

٥- Immunophysiological regulatory compensatory effect to depletion elsewhere in the body (Goodwin, ١٩٩٥).

٦-Possibley due to technical errors.

٥-١٤ CULTURE NEGATIVE UTI .

Three cases of sterile pyuria were noted among elderly male patients and represented ٥,٦٦ %, these cases may be due to :

١- Infection by *Mycoplasma hominis*, this case was dominant in elderly patients and causes acute pyelonephritis with peritoneal signs, (Yuen, ١٩٩٥).

٢- Urethral syndrome due to infection by *Ureaplasma urealyticum, Trichomonas*, *Chlamydia* or viruses (Collee *et al*., ١٩٩٦ and Simon *et al.*, ٢٠٠١).

٣- Antibody coated bacteria (Al-Nasri, ٢٠٠٣).

٤- Urinary tract tumor.

٥- Cell wall defective bacteria .

٦- Trauma, including recent instrumentation.

٧- Viral infection.

٨- *Mycobacterial* infection (tuberculosis), (Nolte & Metchock, ١٩٩٥).

٥-١٥ COMPARATIVE URINARY MUCOSAL HUMORAL IMMUNE RESPONSES FOR ELDERLY AND ADOLESCENT .

T-statistics for paired observations showed that the differences between the mucosal specific antibody titer in adolescent and elderly during urinary tract infections were significant in cases of *Enterobacter sp*.,*E .coli* , *P. aeroginosa* and *S.epidermidis* (table ٤-١٨). This mean that such mucosal humoral immunosuppressive effect may be due to aging effect (Hara, *et al*, ١٩٨٧).Aging may induce lower mucosal antibody synthesis by mucosal B-cell system (Delafuente, ١٩٨٥), or may antogonize the T-cell helper effect for the B- cell system (Ennist, Jones, Pierre, *et al*, ١٩٨٦; Whisler *et al*, ١٩٩١). Finally there may be a possibility for the presence of antagonizing peptide antigen that cause T-

helper antagonists (Ennist, Jones, Pierre *et al*., ١٩٨٦; Whisler *et al*., ١٩٩١).

CONCLUSION .

١. No specific bacteria can be detected only in elderly males, the profile was similar to adolescent except in incidence rate.

٢. Single and mixed infection were noted but the mixed type was of lower percentages.

٣. The concentration of mucosal urinary immunoglobulin is some what unrelated to specificity. Since it was noted that the low concentration with high titers, and in other, were high concentration with low titers.

٤. Mostly ,senescence was showed lowered bacterial specific antibody titers than adolescents.

٥. Cases producing mucosal Ig with out an apparent associated bacteria. Meantime, other cases are associated with infectious agent but with out detectable UMIg.

RECOMMENDATIONS .

Based on the results obtained in this study, one may recommend the investigation of mucosal cellular immune responses following same approach.

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Table ٤: *Pseudomonas aeroginosa* specific mucosal humoral immune response among elderly and adolescent during UTI

Sequences	Mucosal immune responses / humoral											
	Elderly						Sequences	Adolescent					
	Age	Culture		UMIg conc.(g/l)	UMIg titer with out ٢ME	UMIg titer with ٢ME		Age	Culture		UMIg conc.(g/l)	UMIg titer without ٢ME	UMIg titer with ٢ME
		Direct	Indirect						Direct	Indirect			
١	٧٠	*P. aeroginosa*	ND	٠,٠٦٨١٢	٤	٤	١-	٣٠	*P. aeroginosa*	ND	٠,٥٥٧٩٣	٦٤	٦٤
٢	٧٠	*P. aeroginosa*	ND	٠,٠٦٨١٢	٤	٤	٢-	٣٠	*P. aeroginosa*	ND	٠,٤٣٩٧	٨	٨
٣	٦٠	*P. aeroginosa*	ND	٠,٠٨٥	١٦	١٦	٣-	٣٥	*P. aeroginosa*	ND	٠,٧٧٧٥	١٢٨	٣٢
٤	٦٠	*P. aeroginosa*	ND	٠,٠٠٠٥٦	٤	٤	٤-	٢٠	*P. aeroginosa*	ND	٠,٤٩٠٣٧	١٢٨	١٢٨
٥	٦٢	*P. aeroginosa*	ND	٨,٦٣١٣٥	٤	٤	٥-	٢٥	*P. aeroginosa*	ND	٠,١٣٥٦٨	١٦	١٦
٦	٦٥	*P. aeroginosa*	ND	٠,٢٥٣٩١	٤	٤	٦-	١٨	NG	*P. aeroginosa*	٢,٧٠٢٩٦	٤	٤
٧	٦٥	*P. aeroginosa*	ND	٠,٣٠٤٥٨	١٦	٨							
٨	٨٤	*P. aeroginosa*	ND	٠,١١٨٥	٨	٨							
٩	٧٤	NG	*P. aeroginosa*	٠,٠٣٤٣٤	١٢٨	١٢٨							
١٠	٦٠	*P. aeroginosa*	ND	٠,٠٦٨١٢	٦٤	٦٤							
١١	٦٠	*P. aeroginosa*	ND	٠,٠١٦٦	٤	٤							
١٢	٦٠	*P. aeroginosa*	ND	٠,١٣٥٦٨	٣٢	٣٢							
Mean				٠,٨٢٥٢٨١٦	٢٤		Mean				٠,٨٥٠٦٩	٥٨	
Median				٤,٣١٥٩٥٥	٦٦		Median				١,٤١٩٠٧	٦٦	
Range				٠,٠٠٠٥٦- ٨,٦٣١٣٥	٤-١٢٨		Range				٠,١٣٥٦٨- ٢,٧٠٢٤٦	٤-١٢٨	
a-	٢٥,٤٦٣٢٨						a-	-١٧,٢٠٩٢					
b-	-٢,٦١٢١٣						b-	١٧٩,٠٩٧٧					
r-	-٠,١٧١٦٧						r-	٠,٧١٤					
t							t						

Equation	Y=٢٥,٤٦٣٢٨-٢,٦١٢١٣xi	Equation	Y=-١٧,٢٠٩٢+١٧٩,٠٩٧٧xi

D= Direct cultivation .
ID= In direct cultivation .
ND=Not done because they gave growth by direct cultivation method..
NG=No growth .
(This abbreviation will be noted in all coming tables in the same sense).

Table ٥: *E. coli* specific mucosal humoral immune response among elderly and adolescent during UTI

Sequences	Mucosal immune responses / humoral											
	Elderly						Sequences	Adolescent					
	Age	Culture		UMIg conc.(g/l)	UMIg titer without ٢ME	UMIg titer with ٢ME		Age	Culture		UMIg conc.(g/l)	UMIg titer without ٢ME	UMIg titer with ٢ME
		Direct	Indirect						Direct	Indirect			
١	٦٠	*E. coli*	ND	٢,٤٦٦٥	٦٤	٦٤	١	٤٠	*E. coli*	ND	٠,٢٧٠٨	٦٤	٦٤
٢	٦٠	*E. coli*	ND	٠,٤٠٥٩٢	١٦	١٦	٢	٣٦	*E. coli*	ND	٨,٣٠٧٤٤	٦٤	٦٤
٣	٦٠	*E. coli*	ND	٠,١٥٢٥٧	١٦	١٦	٣	٢٤	*E. coli*	ND	١,١٤٥٣٨٥	٤	٤
٤	٦٠	*E. coli*	ND	٠,٠١٦	٢	٢							
٥	٦٠	*E. coli*	ND	١٣,٧٨٢٨	٨	٨							
٦	٧٣	*E. coli*	ND										
Mean				٣,٣٦٤٧٥٨	٢١,٢		Mean				٣,٢٤١٤٠٨٣	٤٤	

Median		**٦,٨٩٩٤**	**٣٣**		**Median**		**٤,٢٨٩١٢**	**٣٤**	
Range		**٠,٠١٦-١٣,٧٨٢٨**	**٢.-٦٤**		**Range**		**٠,٢٧٠٨-٨,٣٠٧٤٤**	**٤-٦٤**	
a-	**٦,٧٧٦٤٢٨**				**a-**	٣٣,٥١٧٦٥			
b-	**٢٣,٣١٢٩**				**b-**	٣,٢٣٤٠٨٧			
r-	**٠,٩٨٦٢٢**				**r-**	٠,٤١١٦٤٥			
t					**t**				
Equation	**Y=٦,٧٧٦٤٢٨+٢٣,٣١٢٩x**				**Equation**	Y=٣٣,٥١٧٦٥+٣,٢٣٤٠٨٧x			

Table٨: ***Enterobacter spp.*** **specific mucosal humoral immune response among elderly and adolescent during UTI**

Sequences	Mucosal immune responses / humoral												
	Elderly						Sequences	Adolescent					
	Age	Culture		UMIg conc.(g/l)	UMIg titer without ٢ME	UMIg titer with ٢ME		Age	Culture		UMIg conc.(g/l)	UMIg titer without ٢ME	UMIg titer with ٢ME
		Direct	Indirect						Direct	Indirect			
١	٧٠	*Enterobacter*	ND	٠,٠٥٧٩٣	٤	٤	١	٣٠	NG	*Enterobacter*	٠,١٦٩٤٦	٦٤	٦٤
٢	٦٠	*Enterobacter*	ND	NT	٣٢	٣٢	٢	٣٨	*Enterobacter*	ND	٤,١٤٠٨٥	١٢٨	٦٤
٣	٦٠	*Enterobacter*	ND	٠,٠٦٨١٢	١٦	١٦	٣	٢٥	*Enterobacter*	ND	٠,٠٣٢	١٢٨	١٢٨
٤	٦٠	*Enterobacter*	ND	٠,٠٣٤	٨	٨	٤	٢٥	NG	*Enterobacter*	٠,١١٥	٢	٢
٥	٦١	NG	*Enterobacter*	NO Ig									
٦	٧٣	*Enterobacter*		٠,٠٣٤٣٤	١٦	١٦							
٧	٦٥			٠,٠٠٧٢٦	٨	٨							
Mean				٠,٧٠	١٤		Mean				٠,١٠٥٤٨٦٦٩	٨٠,٥	
Median				٠,٢٨٢٥٩٥	١٨		Median				٢,٠٨٦٤٢٥	٦٥	
Range				٠,٠٠٧٢٦- ٠,٠٥٧٩٣	٤-٣٢		Range				٠,٠٣٢- ٤,١٤٠٨٥	٢-١٢٨	
a-	١٢,٣٧٦١٦						a-	٦٣,٠٧٣٦٣٥					

b-	-١٤,٠٨٢٢	b-	١٥,٢٤٩٢٣٠١
r-	-٠,٦١٥١٩	r-	٠,٥٠٩٥٤٦٦٦
t	٢,١٩٤٨	t	
Equation	Y=١٢,٣٧٦١٦-١٤,٠٨٢٢x	Equation	Y=٦٣,٥٠٧٣٦٣٥+١٥,٢٤٩٢٣٠١xi

Table ١٢: ***Staphylococcus epidermidis*** **specific mucosal humoral immune response among elderly and adolescent during UTI**

Sequences	Mucosal immune responses / humoral												
	Elderly						Sequences	Adolescent					
	Age	Culture		UMIg conc.(g/l)	UMIg titer without ٢ME	UMIg titer with ٢ME		Age	Culture		UMIg conc.(g/l)	UMIg titer without ٢ME	UMIg titer with ٢ME
		Direct	Indirect						Direct	Indirect			
١	٦٠	*S. epidermidis*	ND	٠,٣٨٩٠٣	٤	٤	١	٤٠	*S. epidermidis*	ND	١٩,٢٧٢٠٥	١٢٨	١٢٨
٢	٦٠	*S.epidermidis*	ND	١١,٥٨٦٢	٨	٨	٢	٣٦	NG	*S. epidermidis*	١٩,٢٧٢٠٥	٦٤	٣٢
٣	٦٠	*S.epidermidis*	ND	٠,١١٨٧٩	٤	٤	٣	٢٤	NG	*S. epidermidis*	١,١٨٥١	٨	٨
٤	٦٠	*S.epidermidis*	ND	٠,٠٥١٢٣	٨	٨							
Mean				٣,٠٣٦١٢٥	٦		Mean				١٣,٢٤٣٠٦	٦٦,٦٦	
Median				٥,٨١٨٧١٥	٦		Median				١٠,٢٢٨٥٧٥	٦٨	
Range				٠,٠٥١٢٣-١١,٥٨٦٢	٤-٨		Range				١,١٨٥١-١٩,٢٧٢٠٥	٨-١٢٨	
a-	٥,٣٠٧٠٣٣٥١						a-	٢,٢٣٤٠٣١					
b-	٠,٢٢٨٢٢٦٣٤						b-	٤,٨٦٥٣٨					
r-	٠,٥٦٣٤٧٩١٦٧						r-	٠,٨٤٦١٥٤					

t	١,٧٤٩٠١١٤	t	
Equation	Y=٥,٣٠٧٠٣٣٥١+٠,٢٢٨٢٢٦xi	Equation	Y=٢,٢٣٤٠٣١+٤,٨٦٥٣٨xi

الخلاصة ..

درس تأثير الشيخوخة على الكلوبيولين المناعي البولي لمرضى التهاب المجرى البولي . وتحقق مثل هذا التقويم عن طريق استخدام :

١- عينة بول واحدة ذات حجم (٧) مل، ٢- تركيز الكلوبيولين البولي باستخدام الكلايكول متعدد الاثيلين ، و ٣- التلازن البكتيري لكل من ٥٣ مصاب بالتهاب المجرى البولي من الشيوخ و ٢٥ مصاب من الشباب ..

هذا وقد فصل الكلوبيولين البولي باستخدام ٦ % اثيلين كلايكول متعدد التركيز والعيار حدد في كل من الشيوخ والشباب كمجموعة سيطرة.اضهرت الدراسة اختلافات معنوية في حالات الاصابة بكل من البكتريا المعوية،اشريكيا القولون ،الزوائف الصديدية و المكورات العنقودية التبروية. وتم الكشف عن مؤلفة حساسة لثاني مركبتو ايثانول واخرى مقاومة لهذه المادة اثناء التفاعل المصلي بين محاليل الكلوبيولين المناعي ومستضدات المسببات المشاركة ويتوقع ان تكون هذه المؤلفة الحساسة راجعة لجزء مصلي متنا ضح للمجرى البولي .. اثبتت الدراسة ان عيار الضد عند الشباب أكبر من العيار لدى الشيوخ بحوالي من ٢-١١اضعاف ..

لهذا يمكن ان يستخدم الكلوبيولين المناعي البولي كمجس للإصابة في الكبار كما في الشباب . ومن الجدير بالذكر ان الشيخوخة من المحتمل ان تحث الى حد ما فعل تثبيطي في الاستجابة الخلطية والمخاطية كما في فعلها التثبيطي لدى مرضى التهاب المجرى البولي في الشيوخ .

تاثيرشيخوخة ذكور البشرعلى الاستجابة المناعية المخاطية للمجرى البولي أثناء الخم

رسالة مقدمة إلى

مجلس كلية العلوم ، جامعة بابل

وهي جزء من متطلبات نيل درجة

ماجستير علوم

في

علوم الحياة / علم الأحياء ا لمجهرية

من قبل:

زينب خضر احمد