I N T R O D U C T I O N

AND

AIM OF WORK

Benign and malignant tumours of the urinary bladder are considered to be predisposing factors for urinary tract infections due to impaired immune response and partial or complete obstruction to urine flow (Ries and Kaye, 1976).

Among the most common organisms involved in urinary tract infections are Gram -ve bacteria (especially, E.coli, Pseudomonas and Klebseilla) and Gram +ve bacteria (especially Staphylococcus aureus and Streptococcus foecalis) (Apri and Renneberg 1984).

Fishman and Armstrong 1972, reported that, Pseudomonas, Klebseilla and proteus were among the most common organisms in patients with cancer bladder. Morever, Hablas 1977, studied urine cultures from 80 Obilharzial patients and found 30 patients showing significant bacteriuria and the common organisms isolated were, Pseudomonas, E.coli, proteus and Staphylococcus aureus.

The aim of the present study is to identify the different bacterial organisms causing urinary tract infection in patients with cancer bladder as compared with patients suffering from simple urinary tract infection.

Urinary Tract Infection

Bacteriology of the normal urinary tract:

if present in large no. is considered pathogenic

The flora of normal urine arranged in order of frequency, are Micrococci, Diphtheroilds, Streptococcus foecalis, ∝-Streptococci, Staphylococcus albus, E.coli and Pseudomonas. It is probable that up to 1000 microorganisms may be found per ml. in normal urine due to unavoidable contamination from urethera during urination or catheterization (Schulte 1939).

The Urethera:

Beeson 1955, reported that the meatus being on the surface of the body and contagious with the skin can be populated with bacteria,

The urethera is normally sterile or may contain few Micrococci, Diphtheroids etc. The decreased number of organisms being attributed to the acidity of urine and its mechanical flushing effect. However the presence of microorganisms within the urethera is not unusual. Helmhols 1950, recovered bacteria at a depth of five cm. in the uretheras of 50% of normal males.

The normal male urethera may contain Staphylococci, Streptococcus foecalis, Diphtheroids, E.coli, Streptococcus viridans and Proteus species (Shackman and Messent 1954).

Leishman 1939, tested for E.coli in the urethera of normal adult females and it was detected only in four out of 25. Hirshfeld et.al. 1941,found different bacterial organisms in the uretheras of about 50% of 114 normal pregnant women.

The bladder and upper urinary tract:

Helmholz and Millikin 1922,found that even with the most carefull techniques including thorough washing of the meatus that, they got positive cultures in the bladder urine in one third of a group of normal infants. They concluded that the chances of contamination were so great that the presence of organisms in urine did not Prove that they had come from the kidneys.

Handley et.al.1938, compared bladder urine cultures of 50 normal women and 50 pregnant women. Positive cultures were obtained from 32 of the former and 22 of the latter groups. E.coli was encountered in only nine of the 54 positive cultures and most of organisms

found are of doubtful pathogenicity e.g. Staphylococcus ulbus, Streptococcus Viridans, Diphtheroides and yeast. Roberts 1983, reported that most bacteria that cause urinary tract infection possess adhesive properties that make bacteria be able to attach to uromucoid or uroepithetial cells. Kaijser et. al. 1977 , stated that Coliform bacteria possess K (capsular) antigens, that may increase invasiviness and interfers with opsonization and phagocytosis and O antigens contained in the bacterial polysaccharide (endotoxin) that has an effect on the smooth muscles leading to a decrease or cessation of uretheral peristalsis.

The exact site of infection is one of the most important factors in the managment of the patient with urinary tract infection. The clinical diagnosis which is based upon symptoms and signs was a poor giude to the site of infection. The site of infection was determined on the basis of bacterial counts in the serial catheter specimens collected from the bladder. Renal infection was assumed to be present when the timed specimens collected 20-30 minutes after bladder washout contained more than 3000 bacteria per ml. and in addition , this 20-30 minutes specimen contained more

than 5 times as many bacteria, as were present in the final bladder washout specimen. Bladder infection was assumed to be present when the final timed specimen (20-30 minutes after bladder, washout) was sterile, (Fairley et.al. 1971).

Hutch 1963, stated that the clearance of bacteria from the bladder is due to the defense mechanism of the bladder which may be divided into two parts. One is a mechanical factor consisting of complete emptying of the bladder. This eliminates most of the bacteria leaving only those in the small amount of urine wetting the vesical mucosa. The second mechanism is an antibacterial factor present in the vesical wall. The bacteria that remain in the bladder after complete voiding are in close contact with the vesical surface, so that the antibacterial factor can exert its maximal effect. Thus the bacteria are destroyed by an intrinsic bladder defence mechanism, with each voiding the bacterial count in the urine drops and soon the urine becomes sterile. So, if the bladder fails to empty completely, chronic infection results.

Local immunoglobulin and Antibody production was evaluated by Hand et.al. 1970, in the urinary bladder and

lymphatic tissues following lower urinary tract infection. The increase in protein and immunoglobulin production by the infected bladder was detected by the tenth day after infection, and was most significant from day 14 to day 129. IgG synthesis was 20 times greater than normal in bladders of animals studied from day 14 to day 129 of infection and comprised 31% of synthesized protein. No increase, in IgA synthesis occured in infected bladders and only a small increase in IgM was noted. Production of specific anti.E.coli antibody by the infected bladder was detected by day 11 and accounted for 4-11% of IgG synthesized. No specific antibodies in the IgAor IgM classes could be detected. An increase in IgG synthesis occured in spleens and lymph nodes from animals with lower urinary tract infection. However specific antibody production was demonstrated in the spleen from only two animals and lymph nodes from only one animal. These studies demonstrate that a significant local immune-response occurs in the bladder following urinary tract infection. IgG is the principal Ig. produced with IgA and IgM playing minor roles.

excretion

Epidemiologic aspects of bacteruria and urinary tract infection:

Kunin 1969, stated that, the numerous studies of

the distribution and frequency of bacteruria among populations, may be divided into those which have been conducted in hospital or clinic populations, and those which attempt to survey a community or specifically defined populations. Such differentiation appears to be important, since the very high frequncy of bacteruria among hospitalized patients may have a profound infleu-nce on comparative studies of bacteruria & pyelonephritis encountered at autopsy , while those studies conducted in defined and more general populations perhaps better reflect the long term natural history of this phenomena.

Kaitz and Williams 1960, investigated 309 unselected ward patients for bacteruria and urinary tract infection and revealed that bacteruria was present on admission in 17% of all patients usually without urinary tract symptoms. Patients without bacteruria on admission did not acquire clinical urinary tract infection, unless bacteruria developed in association with genitourinary tract instrumentation , where 32% instrumented patients developed urinary tract infection.

Blandy 1979, stated that every new incident of

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Ban et.al. 1972 aspirated bladder urine from patients with no uretheral instrumentation or other manipulations and found that, bladder urine was sterile aerobically and anaerobically.

The normal urinary tract is sterile above the neck of the bladder, the presence of even one bacterium per ml. above the vesical neck constitutes a urinary tract infection (Stamy et.al. 1965).

The term urinary tract infection describes aspcet-rum of clinical entities ranging from asymptomatic bacteruria to frank urosepsis (Burbige et.al.1980).

Tanagho 1981, stated that urinary tract infection may be specific or non specific. Specific infections are usually caused by specific organisms each of which causes a clinically unique disease e.g. T.B., gonorrhoea and actinomycosis, but non-specific infections are a group of diseases having similar manifestations and caused by Gram -ve rods (e.g. E.coli and Proteus Vulgaris) and Gram +ve cocci as Staphylococci and streptococci. In acute infections, a single organism is usually found, but in chronic stages, mixed infections are often seen.

Urinary tract infections are of major importance because they are very common and they may be the source of invasion of bacteria or their products into the blood stream, this may lead to renal damage, dissiminated infection, the syndrome of Gram -ve sepsis and considerable morbidity. These infections often originate during hospitalization and constitute the largest single cause of Gram -ve bacterial sepsis in hospitals (Kunin 1980).

A study made by Teles & Rocha 1969, about the prevalence of bacteruria among male and female subjects and found that urine specimens from female, subjects showed significant bacteruria than those from male subjects with a proportion of 25: 1 . The predominatnt organisms were , coliform bacteria, Staphylococci and Proteus species.

Bacteruria occurs most commonly in pregnant women causing pre-partum or post-partum Pyelonephritis. Bacteruria has been involved in the mechanism and pathogenesis not only of pyelonephritis but also of hypertension, prematurity and perhaps of other disorders (Kass et.al. 1966).

Bacteruria in pregnant women has an effect on the maturity of the foetus. Perinatal mortality due to prematurity in untreated bacterurics was strikingly high when companed with non-bacterurics or with treated bacterurics. Also, the relationship between bacteruria and hypertension had been studied in surveys of defined populations in Wales and in Jamica, blood pressures were determined with a standardized technique. Beyond the age of 30 years, the blood pressures of bacterurics were significantly elevated over the blood pressures of non-bacterurics (Kass 1962).

Younes 1975 , stated that bacterial infection of the urethera is one of the causes of uretheral syndrome. Other causes include sexual intercourse, cold weather, emotional stress, allergy , bubble bath, detergents and pinworms. On the other hand Gray and Pingleton 1956, described uretheral syndrome as being, frequency and dysuria with negative urine findings and attributed it to nervous tension.

Organisms causing urinary tract infection:

Tanagho 1981, stated that, the most common invaders of the urinary tract and organisms found in urine are, Garm -ve bacteria, particularly E.coli Enterobacter Aerogenes, Proteus Vulgaris and Mirabilis and Pseudomonas

patients in whom urine contained more than 100,000 organisms per ml. E.coli infections were the commonest and were confined to the bladder in most cases whereas almost all Proteus species infections were renal.

Shaheen et.al. 1963, stated that, the commonest organisms isolated from cases of urinary tract infections with marked pyuria were cloiform bacilli, Pseudomonas pyocyaneas, and staphylococcus aureus. These organisms were also isolated from the urine of urological patients without the presence of marked pyuria, where pus cell count was in the range of 10/H.P.F.

Eykyn and Bultitude 1974, ~~decided~~ stated that, ther is no doubt that, the coagulase -ve Staphylococci and in particular those classified as ~~Micrococcus~~ Staph. epidermidis sub-group 3 could be important pathogens in the urinary tract infection especially in the female.

A study made by Fader & Davis 1982, on klebseilla pneumenia - induced experimental pyelitis using a female sprague- Dawley rats , including the effect of piliation on infectivity. The effect of bacterial piliation on the infectivity of klebseilla pneumonia in the renal pelvis was examined by means of piliated and non piliated

phase variants, derived from a single parent strain. Piliated phase variants were significantly more infective as indicated by viable counts of bacteria isolated from the kidneys at the time of sacrifice. Kidneys infected with the piliated phase organisms exhibited greater tissue damage both in the magnitude of tissue alterations observed and in the number of kidneys affected. Thus it is concluded from this study that, the piliation contributes to the ability of k-pneumoniae to infect the renal pelvis following reflux from the bladder. Also, bacterial pili (fimbriae) were first implicated as serving an attachment function in the urinary tract when following an electron microscopic examination of kidneys infected with proteus mirabilis.

Routes of urinary tract infection:

There are 4 major routes:

(A) Ascending infection: there is increasing evidence that ascending infection is the most common cause of urinary tract infection. The incidence of urinary infection judged by age group and sex, permits certain interferences, where urosepsis is common from birth to age 10. At least 80% of cases are in females, and the incidence of pyelonephritis

is relatively high. However during the first six months of life , infection predominates in the male because of the presence of posterior uretheral valves. New infections are seldom seen from this age untill age 20 at which time urinary infection again becomes commen. Again, the great majority are in women and the incidence parallels the years of sexual activity. This high incidence appears to be related to the short urethera of the female which often harbours urinary pathogens that migrate from the perineum to the vaginal vestibule. Most of these infections involve the bladder only. At the age of 60 and beyond, the incidence, of infection again increases due to the possibility of bladder neck obstruction and the inevitable vesical residual urine (Tanagho 1981).

Robets 1983, stated that, in man, it is accepted generally that the most urinary tract infections occur via an ascending route. Hutch 1963, et.al. reported that, the ascending route of urinray tract infection is the most common route especially in female due to short urethera.

Vivaldi et.al., 1959, studied the pathogenesis of pyelonephritis on experimental rats and found

that, when bacteruria was induced in rats by installation of Proteus Vulgaris into the urinary bladder, pyelonephritis is produced by ascending infection in the abscence of demonstrable obstruction in the urinary tract . Kidneys with ligated ureters are more susceptible than unaffected kidneys to spread of the organism.

(B) Haematogenous spread: Tanagho 1981, described haematuria genous route as being uncommon pathway of bacterial invasion of the genitourinary tract. During the course of many infections eleswhere in the body, bacteria are apt to enter the blood stream. These invaders are usually destroyed by normal body defenses, however if the number of bacteria is great, if they are virulent and particularly if the field is receptive e.g. renal stone, infection of the genitourinary tract may occur. In the view of the possibility that infections of the kidney may take place via the blood stream, the bacteraemia of uretheral instrumentation probably represents one of the ways in which infection is transferred from lower to upper urinary tract (Powers 1936).

Beeson 1955 reported that bacteria which happen

to escape from the bowel may be carried to the kidney to the blood and they find conditions suitable for growth and, establishment of a new infection.

(C) Lymphatogenous spread: There is evidence that infection can spread to the urinary tract through the lymphatic channels, but this probably occurs rarely. A few infestigators believe that infections spread from the large bowel to the urinary tract through the lymphatics. Others thought that cervicitis may cause vesical or renal infections by the spread of bacteria via the periureteral lymph vessels (Tanagho 1981).

Constipation is often present with pregnancy that favours transport of enteric Organisms from the colon to the kidney via the lymphatic anastmoses (Beeson 1955).

In a study made by Gallagher et.al. 1965 on 130 patients investigated, for urinary tract infection, he found that obstruction or urinary retention was an important cause of infection and could have been contributary factor in only nine patients.

Urinary tract infection occurs in about 2% of pregnant women usually during the second half of pregnancy where obstruction of the ureters by pregnant uterus occurs, leading to dilatation of the ureters epecially the right one and kidney pelvis resulting in stagnation of urine that favours infection (Beeson 1955). Also, urinary tract infection may occur immediately after labour due to trauma of the genital tract during labour (Gallagher et.al. 1965). A symptomatic bacilluria occurs in about 7% of women in pregnancy. The incidence of bacteruria does not seem to be affected by age of the patient, it appears to increase with increased parity (Turner 1961).

There is a high incidence of reflux in chronic urinary tract infection and is perhaps the mechanism responsible for extension of infection from the bladder to the kidneys in patients with long standing bladder infection e.g. in paraplegic individuals

with indwelling catheters,also individuals who already have incompetent valves may develop upper tract infection because of this defective barrier (Bumpus 1924).

(B) Presence of foreign body:

The urinary catheter is avaluable instrument when used for proper indications and when aseptic managment is enforced. When improperly used, it acts as a foreign body and it becomes the major source of serious Gram-ve infections in hospitalized patients (Kunin 1980). Jackman and Chisholm 1975, stated that, there was a significant correlation between the high incidence of infection and the duration of pre-operative catheterization.

In general, single catheterizations are associated with much lower frequency of infection than are the indwelling types. Nevertheless a definite risk of infection exists with any form of catheterization (Sullivan et.al. 1972, and Truck et.al. 1962).

The danger of indwelling catheter is more than of simple catheter due to the production of a sheath of mucopurulent excudate around the catheter providing

The association between the infection of the urinary tract and urinary calculi had been studied by Rocha and Santos 1969, who reported that calculi enhance the susceptibility of urinary tract to infection and infection can predispose to stone formation. Relapse or reinfeetion is the role, this suggests that colculi may serve as a nidus of infection in which bacteria are protected from the action of antimicrobial drugs.

Bran et.al. 1972, postulated that cystitis occurs in women during the first few days of marriage in association with trauma to the urethera such as occurs with sexual intercoucse, due to inward uretheral milking (Honeymoon cystitis).

Urine for laboratory examinations should be taken as mid-stream specimen and should not be taken by catheter to avoid contamination. Whene catheterization is to be used or unavoidable, subsequent examination of urine is important for the early recognition and treatment of infection (Brumfitt et.al. 1961).

(C) Continuous source of infection:

This can occur from fistulas communicating between skin or bowel and urinary chunnels (Tanagho 1980).

Also, indwelling uretheral catheter results in persistance of infection in the bladder and urethera (Shackman and Messent 1954).

Leishman 1939, studied the relationship between diarrhoea and urinary tract infection espcially in female where he found that, 19 urine cultures were positive for E.coli among 36 women with diarr-eal disease, and only one positive among 16 men with diarhoeal disease. Also, Leishman 1939, made a similar study on patients with constipation, and found that they did not differ from the control group, so, constipation has no role in the pathogenesis of urinary tract infection.

(D) General body resistance:

The presence of a chronic underlying disease prodisposes to infection as described by, Beeson 1955, in diabetes. Diabetics are more vulnerable to urinary tract infection than non-diabetics, due to their susceptibility to infection glycosuria that favours growth of bacteria and frequent catheteri-zation due to frequent hospitalization especially

during sever acidosis of diabetic coma.

Disturbance in bladder innervation also plays a role in the genesis of urinary tract infection where a study made by Talbot and Bunts 1949, on a group of 331 patients with paraplegia. It was found that 10 of these were found to have vesico-ureteral reflux that predisposes to urinary infection.

Infections in the immuno suppressed cancer patients are caused by a wide variety of bacteria, viruses, fungi and protozoa , many of these in normal individuals, are saprophytes but will cause disease in the immunosuppressed patients often with failure of treatment (O'Loughlin 1975).

Hashem ? 1962, described the mode of infection in bilharziasis where the bilharzial ova are excreted in water through the urine or foeces. An intermediate aquatic snail host is invaded by the meracedium where it develops into cercaria. These are set free in water and enter the human host through the skin and occasionally through the mucous membrane of the alimentary tract meanwhile discharging their tails. The cercarial bodies burrow into the lymphatics, part of them is destroyed in the lymph glands , the rest reaches the lungs through the blood stream. In the lungs they are temporarily arrested then the infective forms known as (Schistosomioles) pass through the pulmonary capillaries to the left side of the heart and these reach the general circulation there, they are mostly arrested in narrow vessels where they excite thrombosis. Effective fixation of the growing worms takes place in the intrahepatic branches of the portal vein where they attain, sexual maturity. The few cercariae that find their way into the portal circulation are the only ones that mature. The female worms start to lay eggs in 6-10 weeks after infection. The coupled worms travel in the portal system against the blood stream until the lumens of the veins allow no further progress. The female worm then leaves her partner, and travels in the veins to reach a suitable place for the deposition of its ova. This is usually

a hallow viscus as the bladder or the intestine. This allows for further propagation of the disease by voidance of eggs into water containing snails. It is well known that, schistosoma haematobium mainly affects the urogenital tract , while schistosoma mansoni & japonicum mainly involve the digestive organs.

Hashem 1962, described the general pathology of schistosomaiasis as being divided into 3 stages:

1. Stage of infilteration: Ova deposited in the submucous tissues soon disintegrate and the toxic products released from the disintegrated meracidia excite a cellular reaction forming small tubercle-like, firm nodules 1-2 mm in diameter, that is called the follicular bilharzial lesion. There may be diffuse thickening of the affected parts,a picture called, the diffuse bilharzial reaction. When a very heavy bilharzial ova deposition occurs in the submucous tissues, these get devitalized by the mechanical and heavy toxic effects of the ova and so, they become necrotic and present little or no reaction. The bilharzial ova found in the dead tissues also die and get calcified and remain densely aggregated amongst the remaining connective tissues. This gives rise to the bilharzial sandy patches which are

common in bilharziasis of the bladder and ureters and rarely in the mucosa of the larg gut. Bilharzial lesions in the muscle coat occur in heavy infections of the urinary bladder. Heavy deposition of eggs and various bilharzial lesions occur between the muscle bundles and particularly between the circular muscle bundles of the sphincter with ensuing fibrosis and much destruction of the muscle itself. In some cases the eggs are scanty & yet there is a diffuse infilteration of lymphocytes, plasma cells and eosinophils in the stroma between the muscle bundles with definite involvment of the muscle itself (El-Gazayerli 1962).

2. Stage of ulceration: In this stage, the granulation tissue papillomata fall away giving rise to multiple ulcers. Two factors are encountered with ulceration. In the first place, the continious cellular infilteration & fibrosis in the pedicle or the base of the papillomata leads to constriction of the vessels at the base of the papillomata, resulting in cutting of nutrition, thus necrotizes & falls away. Secondly, infection with microorganisms that causes slouphing away of the papilloma.

3. Stage of repair: Most of the cellular bilharzial

granulomatous tissue in time is transformed into scar tissue which goes on contracting, causing narrowing of the lumena of hallow organs such as the bladder, and of tubular structures as the ureter. So, the resultant pathological lesions, according to Salem 1962, depend upon, the age of the individual, duration of infection, number of worms and eggs in the human body, amount of exposure to reinfection, and the nutritional status of the individual.

Abdel-Halim 1984, suggested the following scheme for the categorization of bilharzial patients on the basis of their symptomatic presentation in order to detect complicated cases at an early stage:

Category (I): Including patients with fresh infection who present with characteristic symptoms of the acute stage (terminal haematuria and, burning micturition). They almost alaways have bilharzial ova in their urine. For this group , antibilharzial treatment is enough, unless it is a case of repeated infection, when follow up is indicated.

Category (II): Including patients with a past history of urinary bilharziasis who present with symptoms of obstruction (e.g loin pain and dysuria), malignancy (e.g. sever haematuria and necroturia) and for renal failure. They may or may not have bilharzial ova in

their urine. This group should, have antibilharzial treatment and be referred to the urology clinic.

Category (III): Including patients with a past history of repeated infection with urinary bilharziasis who present with non-urological symptoms. Usually they don't have bilharzial ova in their urine. These patients should have regular examinations of the urine to detect early malignancy.

In a study made by Khalil et.al.,1977, on 122 young men (aged between 15-40 years old), they concluded that schistosomaiasis is still highly endemic in Egypt. The prevalence of the disease among the middle age group segment of the community is not related to job or educational status of the patient, the infection being contracted early in childhood. Parasitological examination alone is not sufficient to assess the proper endemicity of the disease, it should be complemented by serodiagnosis using indirect haemagglutinating tests.

Another study made by Rifaat et.al. 1966, on 882 cases, their age varied from 3-65 years. The infection percentage ratio among males and females was nearly4:3. Exposure to infection being more among males whose

work offers a great liability to come in contact with infected water. It was found that, the rate rises with the increase of age to reach a peak at the age group of 10-19 years to decline gradually thereafter . The decline in older age group can be explained by the lower liability to exposure due to retiring, development of immunity, closed lesions & the effect of repeated treatment.

Shokeir,et.al.1972, studied the relationship between bilharziasis and urinary tract infection. They reported that schistosoma ova can act as a predisposing factor to urinary tract infection,since the passage of schistosoma ova through the urinary passages may break the mucous membrane barrier against secondary bacterial invasion. This was especially evident in chronic bilharzial cystitis, bilharzial polypi , granulomata, stone and chronic prostatitis. However in cancer bladder and stricture of the ureter the incidence of infection was high even in the abscence of living ova in urine. This was explained by the possibility that , the predisposing factor to infection here is no more the passage of ova , but it is malignancy and obstruction. The lesions in which more than on type of bacteria was detected were, bilharzial cystitis, ulcer of the bladder, bilharzial polyps, stricture of the ureter, cancer bladder, bladder neck obstruction, stones and

infection by various microorganisms which establish the themselvesin the different parts of the mucous membrane especially in the bladder and pelvis of the kidney. These microorganisms alone and in the abscence of any other complications may be however,responsible for the persistance of the above mentioned symptoms after the disappearance of bilharzial ova from the urine following specific treatment.

A recent study made by Lehman et.al. 1973, on 200 patients hospitalized for documented urinary schistosomaiasis showed a bacteruria prevalence of 39% and half of these patients with bacteruria had concomittent bacteraemia.

Laughlin et.al. 1978, did an epidemiologic survey to assess the prevalence of bacteruria in urinary schistosomaiasis which was carried out in a region endemic for urinary schistosomaiasis in Egypt. In this endemic population, bacteruria was found in 6.5% of active egg excretors and 2.3% of non-egg excretors.

Cancer Of The Urinary Bladder

Carcinomata of the urinary bladder is the commonest solid tumour among adult males in Egypt (El-Sebai, 1961).

The association between bladder cancer and urinary bilharziasis, determines distinct clinicopathological behaviour in which most of the cases were seen at an advanced stage and are usually of the squamous cell type (El-Boulkany et.al., 1972).

Morrison and cole, 1976 discussed the predisposing factors encountered in cancer bladder as follows:

1. Occupational exposures: dye stuffs, rubber and leather workers, cookers and kitchen helpers have an increased bladder cancer risk.

2. Tobacco use: This occurs among cigarette smokers and heavy smokers of cigars and cigarillos. Few data exist on bladder cancer risk in relation to tobacco chewing or snuffing.

   Kerr et.al., 1965 reported that cigarette smoking increased the urinary excretion of tryptophane metabolites which are experimental carcinogens.

3. Schistosoma haematobium:

   Hinder and Schmaman 1969, stated that in a series

of cases from South Africa, 68% of subjects with Squamous cell carcinoma of the bladder had schistosoma haematobium ova in their bladder wall. However only 19% of the patients with the transitional cell carcinoma were so infected.

4. Tryptophane metabolites:

Tryptophane derivatives that have been found to be carcinogenic are, 3-hydroxykynurenine, 3-hydroxy-anthranilic acid and 2-amino - 3-hydroxyacetaphene.

5. Pelvic irradiation:

Women who recieve pelvic irradiation usually for dysfunctional uterine bleeding are at a two to four fold increased risk of bladder cancer.

6. Coffee drinking:

It was found thatwomen who drank more than one cup of coffee per day had a relative risk to develop cancer bladder, for men the relative risk is slightly decreased.

7. Analgesic abuse:

Persons who ingest larg amounts of analgesics containing phenacetin over prolonged periods are at increased risk of developing transitional cell carcinoma of the renal pelvis.

8. Stasis and urinary tract infection:

discussed before.

Pathology of cancer bladder:

ElGazayerli 1962, described the pathology of bladder cancer concerning the gross and histologic types of this neoplasm.

Gross appearance:

1. The protuberant variety:

Most cases are of the squamous cell type. They project into the cavity as coarsely nodular masses. They lack the fonded appearance of the papillary corcinomata occuring in non-bitharziol countries. They may fill completely the vesicol cavity and slowly invade the wall of the bladder. On section they show the characteristic flacked yellow appearance of keratinization.

2. Diffuse infilterative Variety:

Here the bladder wall is diffusely thickened. Most of these cases belong to the undifferentiated (anaplastic) transitional & squamous cell types.

3. "Ulcerative" Variety:

It ulcerates early and tend to penetrate deeply into the wall of the bladder. Some of these cases are of adenocarcinomatous variety.

4. "Papillary" variety:

It is similar to the common form seen in non bilharzial countries.

Histologic types and Grading:

1. The commonest type of bladder cancer in Egyptian material is the squamous cell variety which forms about 60% of the total. About 3/4 of them are of the low grade type and the rest are of the high grade.

2. Transitional cell cencinomata forms only $\frac{1}{3}$ of cancer bladder in this country. The low grade variety forms also about $\frac{3}{4}$ of this type.

3. Adenocarcinomata forms about 5% of the cases and the mucoid type is commoner than the non-mucoid.

4. Sarcoma is exceedingly rare.

Urinary Bilharziasis and Cancer of Urinary Bladder

Hashem 1961, reported that, there is multiple evidence to indicate that there is an aetiological relationship between cancer of the bladder and bilharziasis of this organ, while no relation could be found between bilharziasis and cancer of colon, liver, lungs, pancreas or other organs commonly affected by bilharziasis. The reason is that cancer of the bladder appears to be dependant for its initiation on specific humoral carcinogenic factors directly or indirectly related to bilharzial infection which are secreted in urine. These act on the specially predisposed bladder epithelium due to local infection to evoke cancer.

Elem and Purohit 1983 suggested that the overall severity of schistosomal infection is unlikely to be the sole factor in the pathogenesis of carcinoma of the urinary bladder.

Freguson 1911, studied the relationship between bilharziasis and cancer of the bladder and found that, the ova of schistosoma Haematobium irritates the epithelium lining the bladder. The infleunce as an irritant, of bilharzial ova on the epithelium of mucous membrane, beneath which they are being deposited in larg numbers

is an important factor to bear in mind in considering the frequency of association between this condition and malignant disease. In simple cases of bilharziasis of the ureter, it is the rule to find that the surface epithelium is considerably increased in thickness and that columns or clynders of epithelium continuous with that of the surface pass some distance downwards among the connective tissue and other cells of the specific inflammatory new formation.

Dolbey and Mooro 1924, belived that the"alkaline sepsis" of an inflammed bilharzial bladder . was responsible for the production of this carcinoma.

El-Gazayerli 1962, stated that the marked affection and destruction of the muscle coat in bilharzial cystitis would certainly interfer with the normal function of the bladder-namely complete evacuation - as a result of which stasis of urine is apt to occur in bilharzial cystitis and so the carcinogens responsible for the development of cancer in any urinary bladder would have a better chance for a prolonged action on the bladder mucosa in bilharzial bladders. This explains the high incidence of urinary bladder cancer in bilharzial countries as compared with that in non-bilharzial.

This explanation was evidenced by Aboul-Nasr 1962, who stated that retention if present, will provide the necessary prolonged contact time between carcinogenic factors and the bladder epithelium.

In 1953 ashour, directed the attention to the possible hazardous effect of urinary retention. Moslem who constitute the vast majority of the rural population have to perform their ablutions before prayers and so they prefer to retain their urine as long as possible. This daily retention of urine added to bilharziasis in the long run predisposes to cancer.

El-Aaser et.al. 1979, discussed the possible role of urinary B-glucourinidase enzyme in the aetiology of bilharzial bladder cancer since they found increased level of B-glucourinidase activity in urine of bilharzial and bladder cancer patients compared to that of normal patients urine. Urinary B-glucourinidase is derived from tissues affected mostly with bilharzial infection such as, the liver, kidney bladder mucosa, and leucocytes associated with inflammatory process. Another main source is the bacteria, especially E.coli and Pseudomonas that are alaways associated with bilharzial infestation. They concluded that, elevation of urinary B-glucourinidase due to organ damage or bacterial infection associated with bilharziasis

together with other cofactors such as vitamin A diffi-cency has to be considered as a factor in the aetiology of bilharzial bladder cancer. Bacterial infection is one of the major fatal complications in cancer patients. Many factors operate to predispose cancer patients to infection. Some are related to the underlying malignant disease and the tumour mass itself. Tumours may obstruct drainage from the genito-urinary tract as in cancer bladder or they may erode blood vessels resulting in extreme haemorrhage that provides the site for infection. As tumour masses enlarge they may outgrow their blood supply become necrotic and secondarily infected. Also the susceptibility of cancer patients to infection also varies considerably upon the underlying disease and surgical and / or medical treatment used. Nutritional differencies generally decreases the capacity of an individual to resist the occurance and the consequences of infection. Cancer patients are particularly suscepti-ble to certain less common types of infections. Organisms that cause infection in the neoplastic patients are usually referred to as "opportunists", where, these Organisms are non-pathegenic, but in cancer patients they are potentially lethal, (Dionigi et.al. 1980).

Infection and malignancy

Armstrong et.al. ,1974, stated that patients suffering from neoplastic disease are highly susceptible to infection by less viruleut but more antibiotic resistant Gram -ve bacteria and Gram +ve bacteria. Most people live in Symbiotic or commensal relationship with these organisms, but this balance is upset in patients with neoplastic disease by the following three mechanisms:

1. Altered host resistance due to the basic disease.
2. Altered host resistance due to therapy given.
3. Increased inocula of organisms due to therapy and the hospital environment.

The most Common Gram -ve organisms encountered in malignant disease are , E.coli, Klebseilla , Proteus and Pseudomonas. The most Common Gram +ve Organisms encountered are, Staphylococci, Streptococci, P neumococci and Clostridia.

A study made by Fishman and Armstrong 1972, on pseudomonas bacteraemia complicating chronic diseases. Many general views have shown that Pseudomonas bacteraemias are increasing now, accounting for 10-20% of all Gram -ve bacteraemias. Patients developing Pseudomonas

bacteraemia include those patients whose defensive mechanisms, are altered by malignant disease and for immunosuppressive measures, patients with extensive burns and infats both premature and those with congenital disease.

The incidence of malignant disease both carcinoma and sarcoma as a sequel to the irritation of the terminal spine of bilharzial ova in the foul and alkaline bladders of cystitis is extremely common. The alkalinity and sepsis of an inflammed bilharzial bladder is partly responsible for the development of carcinoma of that organ (Dolbey & Mooro, 1924).

Chernick et.al. 1973, studied the central nervous system infection in patients with a malignant disease and they concluded that, Fungi and Gram -ve rods commonly infect cancer patients than the general population. Also, abscess formation relative to meningitis was more common in patients with neoplasm than the general population. Most of these infections were opportunistic, invading either immuno-suppressed host or those with fistula between the control nervous system and the environment.

Treatment of Urinary Tract Infections

The choice of siutable agents for the treatment of urinary tract infection, is governed by bacteriological and pharmacological factors. The agents must be active against organisms commonly responsible for urinary infection and it is generally felt preferable that they should be bactericidal. Though there is no direct evidence that this property infleunces the comparative performance of different agents. As in other infections the toxicity of the compounds should be low, particularly if they are to be used for long term therapy or in patients with impaired renal functions. The mode of handling by the kidney should ensure that adequate concenterations are available at the site of infection and an effective concenteration in the urine itself should be attained. In many infections confined to the bladder or perhaps to the renal pelvis, it is enough to sterilize the urine itself, so, as soon as the tissues lining them cease to be bathed in a fluid teaming with bacteria, they can look after themselves (Garrod and O'Grady, 1972).

Cox, 1970, stated that the antibacterial spectrum and pharmacology of gentamicin are idealy suited for the

therapy of urinary tract infections. The following observations were noted about gentamicin in urinary infections:

1. 90-95% of the organisms (except enterococci) recovered from patients with urinary infections were susceptible to gentamicin.

2. Susceptible bacteria were inhibited by concenterations of gentamicin easily attainable in the serum and far below urinary concentrations.

3. Gentamicin is as effective or more so than polymyxins (polymyxin B and colistimethate) for Pseudomonas, E.coli, Klebseilla-enterobacter infections.

4. Gentamicin is more effective than kanamycin for infections caused by all Proteus species as well as for those caused by E.coli and klebseilla-enterobacter.

5. Gentamicin is effective but no more so that many other antibiotics for simple uncomplicated cases of urinary infections.

6. Gentamicin in selected cases, may be more effective than other agents in ~~causing~~ during recurrent or persistant urinary infection.

Glauser et.al. 1979, studied the accumulation of gentamicin in rat kidneys before infection with E.coli, prevented obstructed pyelonephritis despite heavy urinary tract infections in the obstructed pelvis. Thus the kidneys were protected against infection in the abscence of effective level of gentamicin in the urine. Despite the reduced activity, gentamicin storage might be usefull in the prophyloxis of kidney infection in patients with abnormalities of the urinary tract. In the treatment of established kidney infection, the dose of gentamicin could be reduced and the interval of its adminsteration increased for minimal toxicity.

Glanser et.al. 1979, treated rats with obstructive pyelonephritis due to E.coli for different intervals with ampicillin and gentamicin either alone or in combination, the combination of ampicillin and gentmicin was synergistic in vitro and significantly more effective in vivo than was either drug alone . After treatment for 10 days, the combination of ampicillin and gentamicin was the only regimen that sterilized all of the pyelonephritic kidneys. They found that 11of 12 strains of E.coli, isolated from the urine of patients were synergistically killed by ampicillin and gentamicin. In humans synergistic antibiotic combination may be usefull in the

treatment of obstructive pyelonephritis in humans. Many strains of Pseudomonas and Proteus mirabilis are susceptible to synergestic inhibittian by penicillin and aminoglycoside antibiotics.

A limited controlled study made by Kudinoff et.al. 1966,to determine wheather or not prophylactic chemo-therapy would be useful in decreasing the incidence of urinary infections associated with transuretheral prostatectomy. The results obtained with kanamycin (one week) or acombination of methonine and mandelic acid (5 weeks) were compared with those noted in untreated controls. The data indicated that, it was possible to reduce the incidence of bacteruria with methionine mandelic acid. Kanamycin treatment was less effective and was associated with a high incidence of posttreatment bacteruria due to Pseudomonas aeruginosa and staph. aureus.

The combination of trimethoprim with sulphamethoxazole has been safe and effective for the treatment and proph-ylaxis of urinary tract infections but can not be used in patients known to be allergic to sulphonamides. Patients showing a history of an allergic reaction to sulphonamides are better treated with trimethoprim alone,

which is also most effective when used as prophylactic against recurrent urinary tract infection (Light et.al. 1981).

Iravani et. al. 1983, suggested three days of sulfisoxazole therapy for acute uncomplicated urinary infections in young women was as effective as 7, 14 and 21 days. They concluded that, therapy for 3 days with sulfisoxazole, may not provide additional benefits in this patient population.

Gallagher 1965, used sulphafurazole in a dose of 1 gm. four times daily for 10 days to treat patients complaining of urinary infection due to catheter application. This treatment reduced further the chance of bacteria introduced by the catheter causing an infection in the urine.

Fair et.al. 1980, treated 60 patients with acute uncomplicated urinary tract infection for 3-10 days with penicillin G, or trimethoprim-sulphmethoxazole. At 5-14 days after therapy, the cure rates were 86% in the 3 days group, and 88% in the 10 days group.

Theoretically, high single doses of antimicrobials are efficacious in the treatment of lower urinary

tract infections, because of the production of high prolonged urinary concenterations. Other advantages include assured compliance, low cost, decreased selection of resistant strains and less side effects. A single dose of 50 mg/Kgm. amoxicillin in 18 girls with documented lower urinary tract infection, an additional 17 girls recieved 10 days of therapy. Of the 18 girls,14 (78%) were cured with a single dose. Of the 17 girls who recieved treatment for 10 days 15 (88%) were cured (Shapiro and Wald 1981).

Kastriotis and Dimopoulos 1983, tried once a day 500 mg amikacin for 7 days. With this treatment Schedule, all patients tried remained with negative cultures within two months after the end of the treatment and they were evluated as cured. They concluded that once a day 500 mg. amikacin for 7 days provides a susceptible and well tolerated treatment for the non-hospitalized patients with urinary tract infection.

Charlton et.al. 1981, reported that 3 and 10 days courses of amoxycillin in 116 non-pregnant women with complicated urinary tract infection rendered cure rates at one week after therapy of 81 and 85% respectively.

Waterbury et.al. 1965, studied the effect of nitrofurans on the suppression of cell wall synthesis in Staph. aureus and concluded that nitrofurans may interfere with the cell wall synthesis, but that the cell wall is not the primary site of action of nitrofurans, since nitrofurans produce inhibition of L-phase variants also.

In a study made by Turner 1961, on cases of bacilliuria among pregnant women two resistant cases responded to nitrofurans within 48 hours.

Ceftazidime is a new synthetic cephalosporin stable to beta-lactamase. In an open prospective randomised study, the safety and efficacy of Ceftazidime was compared to that of tobromycin. Fifty one patients were treated with either Ceftazidime or tobramycin for 7-10 days. Four patients were excluded from each treatment group, leaving 22 patients in the Ceftazidime group and 21 in the tobramycin group. Urine was defined as sterile 7-10 days after treatment. The cure rate for Ceftazidime was 73% and for tobramycin 62% . They concluded that ceftazidime is safe and efficient in the treatment of complicated urinary tract infection (Primodt-Møller and Madsen 1983). Ceftazidime has as broad spectrum as gentamicin in Vitro & Seems to be

especially affective against Pseud. aerug. (Brumfitt and Hamilton Miller 1981). Piperacillin is another new semisynsthetic penicillin derivative, it is a broad spectrum antibiotic active against Gram -ve aerobic bacilli particularly, E.coli, Klebseilla pneumoniae, Pesudomonas aeruginosa, Enterobacter species, Serratia marcescens and indole -ve and indole +ve Proteus. Bacteriodes fragilis and Gram +ve cocci especially strept. foecalis, also are sensetive to piperacillin in vitro. however penicillinase producing Staph. aureus are usually resistant (Sharifi et.al. 1982).

Gruneberg 1980, examined E.coli from hospital urinary tract infection. E. coli isolated showed increased resistance to ampicillin,amoxycillin, capholosporins and sulphonamides, but not to other drugs, including trimethoprim and co-trimoxazole. The declining position of ampicillin and the cephalosporins is due partly to an increased prevalence of more resistant bacterial species and partly to increasing resistance within bacterial species.

Gillenwater 1983, reported that, to prevent bacteruria, trimethoprim sulphamethoxazole, nitrofurantion, cinoxacin, cephalexin, or mandelamine should be used. In urologic

micturition

preoperative patients many prefer to give no antibiotics to prevent bacteruria if the urine cultures are sterile. When the preoperative cultures are positive, the appropriate antibiotic should be used to prevent preoperative sepsis.

Garrad and O'Grady 1972, stated that, failure of treatment of urinary tract infection is not due to emergence of a resistant mutant. This is very uncommon cause of failure except with streptomycin and in some series, nalidixic acid. Typically the organism remains fully sensetive and some patients respond to retreatment with a two weeks course of the same or another agent to which the organism is sensetive. if the patient again, relapses, there is a high chance that radiology will show some abnormality of the urinary tract or stones which may be surgically corrected. Therapeutically there are two approaches which may be usefull but have yet to be subjected to extended study. One is to continue convenintial dosage with water loading and frequent complete micturation for an extended period (6 weeks), on the grounds that final clearance of bacteria from the urinary tract is a slow process. The alternative is to treat patients intensively with high dose parenteral therapy in the expectation that inaccessible areas of

bacterial survival in the kidneys or eleswhere will be subjected to eradicative levels of antibacterial agents. Suitable agents are ampicillin, cephaloridine, or cephalothin, streptomycin or kanamycin. Dosage should be given frequently preferably by rapid i.v. infusion, and in the case of the penicillin or cephalosporins enhanced by probenicid. If sugery is undertaken (e.g. removal of astone) intensive therapy should begin at the time of operation. Patients who fail to these measures require long term suppressive therapy. Long term therapy has two main disadventages, which are, toxicity and superinfection with resistant organisms. These hazards may be minimized by choosing the least toxic agent and progressively reducing the dose to the effective minimum.

Gutman et.al. 1967, studied the cause of relapsing urinary tract infection due to Proteus mirabilis L-forms, and stated that, patients with L-forms in their urine during antimicrobial therapy often relapsed with the original infecting organism after antibiotic withdrowal. In contrast patients in whome L-form were not isolated, usually become infected with a new organism if relapse occured. Bacterial L-forms are usually sensetive to antibiotics which affect the cytoplasmic membrane and intermediary metabolism, e.g. kanamycin, erythrocin and tetracycline. They are usually resistant

to penicillin & its synsthetic analogues which inhibit cell wall synsthesis. The classical Proteus mirabilis was sensetive to ampicillin and resistant to erythromycin while the L-form was sensetive to erythromycin and resistant to pencillin (Gutman -et.al. 1967).

Kagan et.al. 1963, reported that, agents whose primary site of action is one the cell wall, have little or no affect on, L-phase variants. In contrast agents whose primary effect is within the cell markedly inhibit L-phase variants.

Parsons et.al. 1980, suggested that the transitional epithelium of the urinary bladder mucosa secretes and binds on its surface a glycosamino-glycan. The presence of this substance at the bladder surface markedly reduces the ability of microorganisms to adhere to the mucosa.

To avoid urinary tract infection due to indwelling catheter, Gillespie et.al. 1967, proposed the drainage of the catheter into a closed sterile container together with disinfection of the urethera and bladder when the catheter is inserted.

Jensen 1952, reported that, he could lower the

Dd.

incidence of complicating urinary tract infection following urological operation procedures by first reducing the bacterial content of the intestinal tract with antibiotic therapy.

Armstrong et.al. 1974, stated that , antibiotics are frequently administered preoperatively to patients with neoplastic disease or because of fevers which may or may not be due to infections. Treatment with penicillin for a week or more especially in high doses will result in suppression of much of the normal flora such as Diptheroides, Strept., susceptible Staph. and lactobacilli in the bowel. The latter bacteria along with bacteroides make up the bulk of the bowel flora. In the abscence of these organisms, the Gram -ve aerobic bacteria and fungi increase in numbers. A gastrointestinal tract ulceration is thus subjected to much larger inocula of these relatively avirulent organisms. A similar picture is seen with tetracycline, chloramphenicol and ampicillin. These broader spectrum antibiotics also suppress more of the normal Gram -ve flora, allowing resistant E.coli, Klebseilla, Proteus, Pseudomonas and fungi to flourish, infect and cause disease. On culture, patients treated for long periods with more than one antibiotic may grow predominately pseudomonas from the stool, throat skin.