REVIEW OF LITERATURE

Cervical cancer remains the seventh leading cause of cancer related deaths in women in the United States and is the number one cause of cancer related deaths in many developing countries. After breast cancer, cervical cancer is the second most common type of cancer in women worldwide (Elkas et al, 1998). In United Kingdom, invasive carcinoma of cervix is the sixth most common malignancy in women (Landis et al, 1999). The cervical cancer is very common in women between 25 and 50 years of age (Hunter, 1995).

Shift in the control mechanism that govern cell proliferation and differentiation is the
main characteristic of Cancer (Katzung, 1998). Cervical cancer is extremely rare amongst Jewish women and catholic nuns. Most of the cervical cancers are of squamous cell origin, with the remainder being adenocarcinomas. The majority of well-defined epidemiological information relate to squamous cell carcinoma of cervix.

Majority of squamous cell carcinomas emanate from precancerous cervical conditions. Such lesions are termed "cervical dysplasia" or "cervical intraepithelial neoplasia" (CIN). CIN is graded according to the degree of involvement of epithelium as CIN I, II or III, with CIN III representing full thickness neoplastic change of epithelium. The likelihood of progression to
invasive cancer is much greater with CIN III. Severe dysplasia and carcinoma-in-situ (CIS) have the same prognosis, so both are graded as CIN III. In one large study (Nasiell et al, 1986) of 555 patients with CIN I, 62% regressed to normal and 16% progressed to CIN III or invasive cancer. A study of 894 patients with CIN II reported regression in 54% and progression in 30% (Nasiell et al, 1983). The regression rate of CIN III is thought to be lower and the risk of progression to invasive cancer much higher (Peterson et al. 1956, McIndoe et al, 1984, Koss et al, 1963 and Mitchel M.F.1994). Adenocarcinoma in situ also is a well described lesion arising from the endocervical epithelium that is less common than CIN. Although less is known

Sexually transmitted factors or cofactors appear to be the cause of lesions of cervix. Agents such as herpes simplex virus 2 have been implicated
previously (Vonka V et al, 1984). The human papilloma virus (HPV) is currently considered most seriously the sexually transmitted factor in the development of cervical squamous carcinoma. Approximately 70 different types of HPV have been identified through DNA technology, with 20 of these affecting the woman’s genital tract. Only a few of these HPV have a strong association with high-grade CIN and therefore considered “high-risk” types (HPV 16, 18, 45, 56) (Lorincz AT et al, 1992). Other HPVs are either of intermediate or low risk degree.

While there is a strong evidence to support the aetiological role of certain HPV types, other factors or circumstances must also be at work in order for cervical neoplasia to occur. A large
percentage of women test positively for the virus, and yet only a small percent develop cervical neoplasia.

Initially using vaginal pool smears to study hormonal status, Dr. George Papanicolaou reported usefulness of the technique for detecting neoplastic cervical cells in 1941 (Papanicolaou GN et al. 1941). Ayre produced better samples by direct sampling (Ayre JE, 1947). The idea of Pap smear evolved into a technique to screen for cervical precancers that are then histologically confirmed and treated with the idea of preventing progression to invasive cancer.

The test involves cytologic interpretation of cells taken from the cervix and is subject to error

Colposcopy is used to evaluate a cervix following an abnormal Pap smear. Application of 3% to 5% acetic acid removes mucus, dehydrates the cells and accentuates the abnormalities such as mosaicism, punctuation and white epithelium. Although an improvement in screening sensitivity has been shown by combining the Pap smear and colposcopy, (Giles JA et al, 1988, Navrati E et al, 1958, Limburg H 1958, Olatunbosun OA et al, 1991) the use of the colposcope in a screening setting is
not practical due to cost and need for expertise.

Cervicography, originally described by Dr. Adolf Stafl in 1981, depicts what is seen through the colposcope as a picture (Stafl A, 1981), which may be sent to an expert for interpretation. The high rate of false positive and false negative reports and high cost make this method impractical.

The Schiller test consist of applying Lugol’s iodine to cervix during pelvic examination. Normal ectocervical tissue contains glycogen which turns a mahogany brown colour. Biopsy should be performed on pale areas, which are positive. However, false positive tests are too frequent to make this a useful screening test.

HPV DNA testing also has been studied

Treatment of cervical cancer consists of chemotherapy, radiotherapy and surgery. The mode of treatment depends upon the age & general condition of the patient and the extent and stage of cancer cervix. The object of treatment is to arrest the neoplastic activity, reduce the size and area of malignancy and prevent metastasis.

Chemotherapy is the method of choice in most patients with early stages of malignancy. In general chemotherapy consists of introducing
chemical substances into the body which act specifically against pathogens causing the illness. Apart from killing or arresting the growth of the pathogenic agent, a successful chemotherapeutic regimen should not interfere with the activities and growth of the normal host cells. In other words, chemotherapeutic agent should have specific action and yet not cause “side effects”.

Chemotherapy has been described in ancient Indian scriptures specially in Charak Samhita written in 8th century BC. Cancer is described as “arbuda” or uncontrolled tissue growth. The treatment suggested is chemicals extracted from plants and their roots. Nagarjuna, in 6th century AD suggested treatment of cancer with chemicals
derived from heavy metals, in form of “Bhasma”.

The concept of modern chemotherapy was originated by Paul Ehrlich 1854-1915. Since then different scientists have introduced various chemical substances for treatment of a host of pathological conditions. Lissaus, in 1865 advised use of arsenite in cancer.

Primary or neoadjuvant chemotherapy is employed to reduce the size of tumor prior to resorting to radical hysterectomy or radiotherapy. Antineoplastic agents are often used in combination (Frei, 1972; Haskell, 1995). There are several significant limitations to single-agent chemotherapy which led to use of a multidrug approach. The combination chemotherapy has become a standard
method of management of many tumors, thus increasing the efficacy of the regimen and yet reducing the side effects. The knowledge of cellular kinetics, drug metabolism, drug resistance and tumor heterogeneity, all have contributed to use of combination chemotherapy.

Use of different drugs with different cellular kinetic characteristics reduce the tumor mass more effectively than a single drug. Moreover, there are more chances of developing drug resistance with the use of single drug. A particular chemotherapeutic agent acts in a particular phase of the tumor cell cycle. A minor tumor response is achieved by using a cycle non-specific agent which is followed by tumor regrowth and finally no impact
on survival. A cell specific agent will affect cells coming into cell cycle only. By using different cell cycle specific agents in combination and sequences, log kill can be enhanced substantially and a cure can be achieved.

A less than satisfactory response to chemotherapy means other methods of treatment has to be considered before it is too late. Chemotherapy has to be considered also where other means, like surgery or radiotherapy are not feasible i.e. recurrent or metastatic diseases.

The commonly used chemotherapeutic agents in cervical cancer are Cisplatin, Bleomycin and Methotrexate. All of these drugs, though potent antineoplastic, are nephro and hepato-toxic.
Nephro-toxicity of Cisplatin was found to be limiting factor by Higby et al, (1974) Rossof et al, (1979). Rozencweig et al, (1977) found that cis-diaminedichloroplatinum (CDDP) was anew class of cytotoxic agent with less nephrotoxicity. Dentino (1978) studied long term effect of CDDP on renal function. Blood urea and serum creatinine were found to be raised. Madrias reported dose related toxicity of cisplatin. Fleming et al, (1979) in their study did not find any change in serum creatinine level with treatment. They suggested 'adequate hydration during cisplatinum treatment to prevent nephrotoxicity. In their study of renal function and serum electrolyte estimation in patients receiving cisplatin, Schilsky et al, (1979), reported it leads to
hypomagnesemia due to renal tubular defect.

Blachley and Hill (1981) found that serum creatinine concentration is raised due to loss of body muscle mass. Hypomagnesemia, hypokalemia and hypocalcemia are all associated with cisplatin treatment. Bitran et al, (1982) studied the effects of a single dose of cisplatin on kidney function in 14 patients. Serum magnesium and calcium levels declined in 48 hours within start of therapy.

Serum creatinine and blood urea nitrogen levels were not affected by five courses of cisplatin therapy, in a study undertaken by Buamah et al, (1982). Feaux de Lacroix et al, (1983) found that use of doxorubicin, bleomycin, vinblastin cause
fatal hepatic necrosis. Fall in glomerular filtration rate, rise in serum creatinine and blood urea nitrogen have been observed by many workers including Meijer et al, (1983), Fjeldborg et al, (1986) and Groth et al, (1986).

Meijer et al, (1983) in their study noted that main toxic effect of cisplatin therapy, either induction or maintenance is impairment of renal function. Even at the end of maintenance therapy after one year the serum levels of creatinine were found to be raised. They concluded that the initial damage was done in the first month and there was no recovery even after one year.

Myelosuppression was found to be the side effect of cisplatin therapy in moderate doses by
Ozols et al, (1984). With higher doses renal damage was observed by them. Doll et al, (1985) reported haemolytic anaemia following extended periods of treatment. This appears to be the result of direct damage to the red cell membrane.

A study was conducted by Gioccone et al, (1985) on 281 patients treated with cisplatin. Serum urea values of 60 mg/dl or higher were detected in 21 subjects. Higher levels of serum creatinine (up to a maximum of 2.3 mg/dl) were found in 28% cases. Long term effects of cisplatin treatment were studied by Sorensen et al, (1985). Creatinine clearance was significantly decreased from initial average of 108 ml/min/1.73m2 (p<0.01). None of the patients showed increase in serum
creatinine or proteinurea before or 6 months after termination of treatment.

Wertheim et al (1985) reported disease free survival for two years at the rate of 82% among 32 patients treated with postoperative radiation and cisplatin plus bleomycin therapy. It led to randomized trial of postoperative radiotherapy alone and radiotherapy plus 5-fluorouracil and cisplatin concurrently.

Effect of high dose of cisplatin (100 mg/m² daily for 5 days) were studied by Dauggard et al, (1988). Decrease in serum creatinine and proteinurea were noted, perhaps due to muscle wasting. Changes in albumin and IgG were also seen.
Rettenmaier et al (1988) studied the combination treatment of cisplatin and radiotherapy in recurrent cancer cervix patients. They concluded that combination therapy was justified as it led to minimal biochemical changes.

The initial experiences with the use of mitomycin C as a single adjuvant in 16 patients with stage 1B carcinoma of cervix who had undergone Wertheim radical hysterectomy were reported in 1989 by Sivanesaratnam and Jayalakshmi. Myelosuppression was reported in 25% cases resulting in severe drop in haemoglobin and platelet count. There was transient elevation of serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT) in one
patient. A follow up for a period ranging from 16 to 36 months have shown 14 patient to be free from disease.

Sardi et al, (1990) used chemotherapy and radiotherapy in combination in 67.5% cases and radiotherapy alone in 37.5% cases before surgery. They reported 2 year disease free survival rate in stage II and III of 79% and 50% respectively. Similarly Panici et al, administered chemotherapy before surgery or radiation. A 3 year disease free survival rate of 100%, 81% and 66% was achieved for stages I, II and III respectively.

Cisplatin induced nephrotoxicity has been the subject of many studies. The acute tubular damage appears to be dose related. There is
progressive biochemical changes such as urea, creatinine elevation and proteinuria.

Platinum accumulation in kidney and changes in creatinine clearance during chemotherapy with cisplatin were reported by Uozumi et al, (1993).

Schwartmann et al, (1994) found acute and chronic liver toxicity with methotrexate. They found elevation of liver enzymes and hyperbilirubinaemia after administration of high doses. They also reported biochemical changes like hypomagnesaemia which often leads to hypocalcemia.

Similar changes were the observation of Nagai et al, (1996). Their study reported decrease in
glomerular filtration rate and increases in serum creatinine and blood urea nitrogen levels. Hypomagnesemia, hypocalcemia and hypokalemia were also found after administration of CDDP.

The results of a study undertaken by Reisinger et al, (1996) showed rise in serum creatinine, creatinine clearance, bilirubin and SGOT levels. According to Young et al, (1996) there is moderate elevation of transaminase (SGOT & SGPT), alkaline phosphatase and bilirubin levels with many anticancer drugs but they resolve soon after treatment is stopped.

Merouani et al, (1997) noted increased nephrotoxicity of taxol and cisplatin combination than cisplatin alone. There was significant decrease
in creatinine clearance six months after completion of treatment.

Seckl et al, (1999) studied patients of small cell carcinoma of cervix. There was high concentration of serum insulin along with hypoglycaemia. Liver function tests revealed high serum concentration of alkaline phosphatase. Thomas (1999) was of the opinion that both chemotherapy and radiotherapy showed good result in cancer cervix patients. The advantage of concurrent chemotherapy is only theoretical over the use of radiotherapy alone.

Pattersalt (2001) opines that combined chemo-radiation therapy have led to a change in the standard of care. They found higher response rate in
patients suffering from prolonged disease. Vermorken et al, (2001) reports that bleomycin, methotrexate and cisplatin induce a significantly higher response rate than cisplatin alone.

To assess the presence and extent of drug toxicity, some of the enzymatic changes can be used as indirect markers. Preventing and combating nephrotoxicity needs vigorous hydration and urine alkalization.

For long radiotherapy has been the mainstay in treatment of cancers along with chemotherapy. The idea of radiotherapy is to cure or control the disease process by destroying the malignant cells that are capable of proliferating in an uncontrolled fashion and at the same time not
damaging the normal tissue that surround the tumor.

Electromagnetic and particle rays are used in radiotherapy to treat diseases like malignant tumors. It is of great use in treatment of cervical cancer. The cure rate in cervical squamous cell cancer is 70% for stage I, 60% for stage II, 45% for stage III and 18% for stage IV (Patterson, 1994). Radiotherapy has a special place in management of gynaecological malignancies. Sometimes it is combined with chemotherapy in an attempt to achieve better results (Young et al, 1996). The radiation can be applied either externally in the form of beams or internally as intracavity implants. The choice depends upon the type and site of malignancy. The radiation beams are targeted in
such a way that they destroy the cancer cells. During this process some of the normal cells in the vicinity of the tumor may also get injured. The extent of damage to normal tissue depends on the radiation dose and the nature of the organs. Some organs are more prone to get damaged than others i.e. the eyes, spinal cord and kidneys. The dose of radiation around these organs have to be kept low. The response of the malignant cells of different type of tumors are different to radiation rays. Therefore the treatment has to be planned, prescribed and delivered in appropriate way along with adequate patient monitoring. Initial evaluation of the general condition of the patient is important before the treatment is planned. Conditions such as anaemia,
nutritional deficiencies and systemic diseases should be ruled out. Normally to a patient of IIb cervical cancer is given 6500 cGy dosage of radiation for 6½ weeks. The dose for IIIa patient is 5500 cGy for 5½ weeks.

The biological effects of an absorbed dose of radiation vary with the type of radiation, pattern of energy release, constituent processes and other biological factors. Ionizing radiation in sufficient doses will produce cell death. Ionizing radiation produces free radical formation, which disrupts the reproductive integrity of DNA and produce mitotic death. The target of radiation is the cells which attempt to undergo mitosis. After subjecting the cell to radiation it undergoes a limited number of
mitosis, but it can not reproduce indefinitely, leading to its death. Though the target of radiation are the diseased cells, the interaction with matter occurs both with normal and neoplastic cells in the path of the radiation beam. This undesired interaction with normal cells is responsible for acute and chronic complications following radiation.

Aimed at getting the benefits of both, radiation and chemotherapy, a combination is often developed. This improves the control of primary tumor more effectively, decreases the secondary distant metastasis and enhances the survival rate, without excessively increasing normal tissue injury. The two regimens may be synergistic in action leading to faster killing of tumor cells, thus reducing
the course of therapy and minimizing the chances of proliferation.

The benefits of concurrent radiation and administration of chemotherapy has been documented in the studies of Piver et al, 1977 and Hreshchychyn et al, 1979. The cytostatic agent is of limited activity on its own in cervical cancer but was believed to be a possible radiation sensitizer. Choo et al, in 1986 have claimed that the radiation response of the tumor cells improve if weekly injections of CDDP are given during radiation. High local response was observed when six courses of cisplatin, bleomycin and methotrexate were given concurrently with conventional radiotherapy.

Minerals or trace elements like
magnesium, iron, calcium etc. are essential for metabolism (Mulay et al, 1971). They are also active part of enzymes (Schutte 1964). They have also been critically examined as a potential key factor in various diseases like cancers and cardiovascular diseases (Prasad et al, 1961). Though the trace elements are only a part of the total picture, they are important in relationship of nutrition and maintenance of health and prevention of diseases.

The body contains about 1 mol of magnesium which is mainly in the bone and tissues like liver, kidneys and muscle. Only about 1% of body magnesium is in the extracellular fluid. Kidneys are the main regulator of serum magnesium level. Hypercalcemia inhibits magnesium
reabsorption. Magnesium has an important role to play in the normal functioning of nerve and muscles. It is also an activator of various enzymes such as alkaline & acid phosphatase and creatinine kinase.

A study was done by De Jorge et al, (1964) about the serum magnesium levels of normal persons and inpatients of cancer. It was noted that magnesium level was significantly high in cancer patients while calcium was within normal range. Lyman et al, (1980) demonstrated administration of cisplatin in cancer patient lead to renal tubular dysfunction, which in turn resulted to hypermagnesuria, and eventually hypocalcemia.

Gonzalez et al (1982) observed hypocalcemia secondary to hypomagnesemia could
be fatal and could be controlled by administration of magnesium as supplement. The reports of Capel et al, (1982) were contradictory to the reports of De Jorge et al, (1964). Their findings showed a lower serum calcium level in cancer patients without any significant change in serum magnesium levels.

It was shown by Altintas et al, (1995) that serum and tissue magnesium, copper and zinc were of no significance in management of cervical carcinoma. Their levels in different stages of cancer were also not of any import. Tweigeri et al, (1999) reported sudden blindness in patients being treated with radiotherapy and cisplatin. The serum magnesium levels were found to be low in these patients and its correction reversed the ocular
problem.

Calcium content of the body is about 25 to 35 mol (1.0 to 1.4 Kg.) in adult. Bones and teeth are reservoir for over 98% of these. Although the extracellular fluid and plasma contain very little calcium but it is vitally important for neuromuscular transmission and for the activity of enzyme system, specially in blood coagulation.

Hypercalcemia is frequently seen in cancer patients (Mundi, 1978) an aggressive treatment of this condition may lead to remission of urogenital tumors (Lubensky and Gangai, 1979). Cancer patients rarely become hyocalcemic, which rather is a frequent accompaniment of terminal disease (Mundy, 1978).
The adult male body contains approximately 50 mg. of iron per kg. body weight. The amount in a female body is 40 mg. per kg. body weight. Physiologically active part of iron is about 75% and the rest is stored iron. More than 90% of iron is in the form of haemoglobin and about 10% as myoglobin. Various haem enzymes such as cytochromes and peroxidase contain less than 1% of total body iron. Small quantities of iron are present in plasma, bound to non haem enzymes like transferrin and ferritin.

Many cellular enzymes and coenzymes require iron. Iron is transported in serum, bound to the protein, transferrin. The iron binding capacity of serum includes amount of iron already bound to
transferrin (serum iron) and the amount of iron required for binding to the unoccupied binding sites of transferrin.

Fever, infection and acute stress are conditions which are commonly associated with cancer. All these conditions affect the serum zinc level. Trace element deficiencies are a common accompaniment of cancer, specially in advanced stages, due to weight loss, anorexia and changes in eating patterns. These deficiencies may not be apparent and are liable to be missed (Garofalo et al, 1979). These variables should be considered before evaluating the level of zinc in serum.

The DNA polymerase activity essentially need zinc. It is therefore particularly
important for the rapid cell proliferation, which is the hallmark of a growing tumor (Prasad, 1979; Aggett et al. 1979). Zinc deficiency is also associated with acuity of taste, which may arise during chemotherapy (Catalanotto, 1978).

In a study of serum zinc levels, Capel (1982), reported no change in the level between control and cancer patients. They also did not find any difference in serum zinc levels of patients of cancer before and after receiving radiotherapy during a 5 month follow up period. Sullivan et al. (1979) on the other hand reported a fall in serum zinc level in patients with malignancy as compared to normal controls.

The immunoglobulins are antigen
binding proteins that are present on the B cell membrane and are also secreted by plasma cells. The immunoglobulins act as antibodies. The cell mediated immunoresponse is the basic defense of body against cancer (Lehner, 1972). The blocking or interfering phenomena characterizes the humoral component of immune system although cytotoxic antibodies have been described in humans (Hallstrom et al, 1973) and animals (Vaage 1973).

The basic structure of gamma-globulins was elucidated by Rodney Porter. Immunoglobulins chemically are composed of 82-96% polypeptide and 4-18% carbohydrate. The Ig molecule was cleaved by Portar et al, (1959) with proteolytic enzyme and found that it consisted of a
pair of heavy chain and a pair of light chain. Disulphide links bind these chains together. Each chain has amino terminal and shows marked variability in amino acid residues, called variable region (V-region) and a carboxy terminal portion with a similar type of amino acid residue for a particular class or subclass of Ig, called constant region (C region). Constant region has two basic amino acid sequences, Kappa and lambda. In humans 60% chains are kappa and 40% are lambda.

The light and heavy both chains are of same length in the “V” region, whereas in the “C” region heavy chain is nearly three times longer the light chain. The heavy and light chain of ‘V’ region is the sights for binding antigen. A monomeric Ig
molecule has two antigen binding sights. The heavy chain of a particular antibody determines the class of antibody: IgG, IgM, IgA. Each class can have either kappa or lambda light chains. Each class is distinguished by unique amino acid sequences in the heavy chain constant region, which determines the functional and structural differences among various isotypes.

Amongst various immunoglobulins IgG is the most well researched isotype, both at structural and at functional levels (Burton et al, 1985). Antibodies of this class are the major constituent immunoglobulin in blood. They are produced in abundance during secondary immune response. The Fc region of IgG molecule binds to
specific receptors in phagocytic cells, such as macrophages and polymorphonuclear leukocytes. It thereby increases the efficiency of the phagocytic cells to ingest and destroy the invading microorganisms, which have been coated with IgG antibodies, in response to the infection. The best known function of the IgG is complement activation via the classic cascade.

The only antibodies that can pass from mother to foetus are IgG molecules. Cells of the placenta that are in contact with maternal blood have receptors that bind the Fc region IgG molecules and mediate their passage to the foetus. This gives the foetus the main defense against infection in the first few weeks of life.
There are four subclasses of IgG in humans, IgG 1 through 4. The dominant subclass is IgG 1. The IgG 2 has been demonstrated to cross the placenta.

Immunoglobulin A or IgA are mainly found in body secretions like milk, saliva tears and respiratory & intestinal secretions. The IgA of external secretions, called the secretory IgA, consists of a dimer on tetramer, a J-chain polypeptide and a polypeptide chain called secretory component.

Based on differences in antigenic structure and variation in arrangement of interchain disulphide bridges, it has been possible to classify IgA antibodies in humans into two subclasses, IgA 1
and IgA2.

Since IgA is present near the external membranes, secretory IgA constitutes the first line of defense against micro-organisms present in the environment. IgA inhibits the adherence of micro-organisms to the surface of mucosal cells, thereby prohibiting their entry into host tissue. The property of IgA of having great greed for binding to antigens, is of special relevance in neutralization of viruses. IgA may also combine with certain antigens present in food, preventing their absorption and reducing the chances of allergic reactions.

The major class of antibody released in blood in the early stages of primary antibody
response is the glycoprotein IgM. It comprises of 5-10% of total serum immunoglobulins. It is expressed as membrane bound antibody on B cells. The secreted form of IgM is a pentamer composed of five chain units. IgM is more competent at complement activation than IgG. It does not cross the placenta and is confined to blood circulation. IgM is a minor component of secretory immunoglobins at mucosal surface and in breast milk. Immunodeficiency may occur in cancer due to malignancy or metastasis or because of chemotherapy and/or radiotherapy. It is universal to find immunodeficiency with advanced stages of disease. This gives chance to opportunist infections to set in, which may prove fatal. Primary
immunodeficiency may lead to cancer (Cunningham-Rundles, 1987) and certain tumors may develop in association with HIV infection (Krown, 1983; Davis, 1984). Untreated cancer may result into inverted ratio of CD4/CD8 ratio and raised suppressor cell activity (Livingston, 1987). Radiation may have a prolonged effect on immune system, whereas chemotherapy may produce transient suppression of immune response, which is known to be resolve (Katz, 1993). From the immunological perspective the cancer cells can be viewed as altered self cells that have escaped normal growth regulating mechanism.

Serum immunoglobulins have been widely used to test the humoral immunity of cancer,
but the results have been contradictory.

The use of cytostatic agents, which does not bring about cure but can provoke good remission, has become increasingly common. The cytotoxic drugs though control the tumor cell proliferation but they also damage the normal cells. The use of cytotoxic drugs therefore, apart from reducing the tumor size, can reduce the immunological capacity of patient and increase the susceptibility to malignancies further (Almat et al, 1995). Stjernsward et al, I 1972 and Stjernsward, 1974, have inferred that radiotherapy in cancer patients may lead to increased mortality due to the immunosuppression it causes.

Exposure to radiation results into
reduction in the number and functional activities of lymphocytes. It also changes the ratio and subpopulation of the cells (Stjernsward et al, 1972; Blomgren et al, 1976; Cohorn et al, 1978). The duration of the cell reduction and changed ratio may be related to physiological turn over of the cells or a changed distribution of the cells in the body (Rotstein et al, 1985).

Vasudevan et al, (1971) studied the levels of IgG, IgA and IgM in 22 patients suffering from carcinoma cervix. They fell in two groups – 1. Untreated and 2. Treated with radiation. The method used for estimation was modified Mancini’s radical diffusion technique. Group 1 patients showed raised values for immunoglobulins and
group 2 patients the values reverted to normal. IgM was not affected in patients of either group.

Patients of breast carcinoma and cervical carcinoma were compared in a study conducted by Mc Credie et al, (1972). Following radiotherapy the total white cell count decreased to 1200 cells/ml during the first month of therapy in breast cancer, which did not improve later. In patients of carcinoma of cervix, the total count fell to one third, which increased after 24 months, yet in 23% cases it was below 1500 cells/ml.

Stjernward (1972) reported impaired immunological activity in irradiated patients. Lee et al, (1977) on the other hand reported that serum IgG level remained normal in cancer cervix patients and
were not affected by either chemotherapy or radiotherapy. Reduced survival rates were reported in irradiated patients, by Stjernward (1977), due either to immune suppression or cardiac complications. Dasaia et al (1979) were of the opinion that radiotherapy and chemotherapy both cause lowering of lymphocyte count and immunological deficiency is seen in every stage of every malignant process.

Depressed immunologic function in advanced cancer was also reported by Check et al. (1980). With advancement in stage of cancer both B-cell and T-cell count decreased significantly. In a study by Jenkins et al, (1980) patients of all the four stages of cervical carcinoma were included along
with normal controls. The results showed that there was decline in lymphocyte count during radiation treatment which gradually became normal after cessation of treatment.

Adelusi et al, (1981) studied serum immunoglobulin concentration in 19 cancer cervix patients. The IgG and IgA levels were found to be raised but the level of IgM was unaltered. Gupta et al, (1981) reported rise in IgA serum level in cervical carcinoma patients which reverted to normal values after surgery. The changes in IgG and IgM levels were insignificant. Vijaykumar et al, (1986) after his work on 172 carcinoma cervix patients, reported significant rise in serum IgG (p < 0.01) and IgA (p < 0.001) before start of treatment. IgA was
elevated in all the stages of carcinoma (p, < 0.001) but IgM was unaltered. Patients who were declared clinically cured showed normal values but those continuing treatment had very high levels of IgA. 

Pillai et al, (1991) in their study found that B-lymphocytes were low in number after radiation. By third month the number attained pretreatment level. In 1994 Juranic et al, studied immune reactive proteins in patients irradiated for cervical cancer. They studied stage IIB and stage IIIB during follow up. The IgA level, which was high prior to treatment slowly declined after radiotherapy and was normal at follow up. IgG values were low and continued to be so afterwards. IgM remained in the range of control values after the
treatment was stopped. Lauagie et al (1999) observed deep decline in the lymphocyte count at the initiation of radiotherapy and remained constant during the therapy.