DISCUSSION
CHAPTER V
DISCUSSION

5.1 BEFORE TREATMENT:

The earlier studies by Rohrborn et. al., (1973) and Jaju and Ahuja (1984) on the untreated Tuberculosis patients have ruled out the possibility of the bacterium Mycobacterium tuberculosis causing chromosomal aberrations. However, in the present study it was observed that the bacterium is capable of inducing chromosomal aberrations in the affected individuals. The observation indicating the clastogenic property of Mycobacterium tuberculosis has got wider implications. These observations are in good agreement with the other report on Mycobacterium leprae, the causative agent of Leprosy, belonging to the same family as Mycobacterium tuberculosis and which cause chromosomal aberrations (D' Souza and Thomas 1988). These results get supported by various other reports suggesting that bacterial and viral infections do cause chromosomal damage (Paton et. al., 1965, Aula and Nicholas 1967, Kudsin et. al., 1971, Bhatnagar et. al., 1984). Variations with regard to frequency of chromosomal aberrations observed by other authors could be due to various factors such as their small sample size.
In the present study the frequency of chromatid type of aberrations is much higher than that of chromosome type of aberrations. These results suggest that the DNA damage has been caused at the G or S phases, thus indicating that the bacterium acts as a S-dependent agent. These aberrations were not confined to any particular chromosome, and are distributed at random, but the larger chromosomes are more frequently affected than the smaller ones. In the present work, the damage seems to be related to the size of the chromosome, as the damage is more in larger chromosomes when exposed to any mutagenic agent. Similar results were reported earlier by Ahuja et. al., (1981), Madhuri et. al., (1981) and Manjula et. al., (1981).

The mechanism by which the bacterium induces chromosomal aberrations has not yet been understood. Slack and Synder, (1975) suggested that the bacterial enzymes act as DNAases and can induce lesions in DNA which ultimately result in chromosomal aberrations or sister chromatid exchanges (SCEs). In the present study also the same seems to be true, resulting in increased chromosomal aberrations.

There is a controversy regarding the inclusion of
gaps in the scoring for chromosomal aberrations. Stoain and Raiceu, (1975) have postulated that gaps are the result of either despiralization or loss of DNA and chromosomal proteins, which possibly can alter the normal functioning of chromosomes. In this context gaps assume significance, hence in the present study gaps were included in the analysis of chromosomal aberrations.

However, the other parameter, sister chromatid exchanges (SCEs), have not shown any increase. The mean SCEs/cell in the affected individuals is more or less the same as that in controls. This is in contrast to other reports that bacteria do enhance the frequency of SCEs (Ito Kuwa and Shigeji, 1984; D’ Souza and Thomas, 1988). The result of the present study do contradict the only other study on untreated Tuberculosis patients by Jaju and Ahuja, (1983) wherein they observed the SCE frequency was lower than in general controls, but no possible explanation was offered for this low frequency of SCEs by them. D’ Souza and Thomas, (1988) have suggested that the altered profile of lymphocytes as a result of depressed cell mediated immunity could be the reason for the increased frequency of SCEs in Leprosy. However, in the absence of well documented studies on
the immunological aspects of Tuberculosis, it is difficult to ascertain the possible reason for this variation in these studies. Significant differences between control and untreated Tuberculosis patients with regard to SCE frequency could be due to the reason that the disease is the expression due to a depressed immune mechanism, of a long standing infection.

On the other hand several authors have suggested that though SCEs are a sensitive parameter, for certain kinds of DNA damage they are not good indicators as compared to chromosomal aberrations (Kato and Sandberg, 1977; Wolff, 1977; Gebhart and Kappauf, 1978; Midro Alina, 1982; Bhatnagar et. al., 1984). Goth-Goldstein (1977) has proposed that SCEs are formed as a result of damage at the O6 position of Guanine, and in all probabilities these lesions constitute only a fraction of the total DNA lesions responsible for the manifestation of chromosomal aberrations. It is quite possible that the DNA damage caused by the bacterium does not fall in this category and hence no effect on the frequency of SCEs. Furthermore, these results clearly indicate that though the SCEs are considered to be more sensitive (Latt, 1974), in the present study chromosomal aberrations were more indicative of
chromosome damage. These results further strengthen the hypothesis that the possible mechanism of formation of chromosomal aberrations and SCEs are different and in any mutagenicity testing, one test system is not adequate enough to replace the other (Gebhart, 1981).

Though Perry and Evans, (1975) have observed good correlation between chromosomal aberrations and SCEs, in the present study no such correlation was observed.

Inter chromosomal distribution of SCEs showed similar results as that of chromosomal aberrations. The larger chromosomes are more frequently affected than the smaller ones and again no particular chromosome is affected with distribution of SCEs being at random.

The cell cycle was observed to be significantly lower in untreated Tuberculosis patients compared to controls at 48 hr. incubation. However, in general the cell proliferation rate was much slower, and this could be attributed to the disease condition. These results contradict the earlier study on Tuberculosis by Jaju and Ahuja, (1983) but are supported by the study on Leprosy, wherein a depressed cell proliferation was observed in untreated Leprosy patients (D' Souza and Thomas, 1988).
Gebhart, (1978) has observed an association between the anti-clastogenicity of a given chemical and depression in cell proliferation rate, but the results of the present work suggest, on the contrary, an association between the clastogenicity and depressed cell proliferation.

On the other hand, at 72 hr. incubation, the cell cycle was much faster compared to controls. Herrmann (1978) has suggested that some chemicals are capable of accelerating the cell proliferation. Likewise in the present study also the bacterial toxins can accelerate the cell proliferation rate. When the cells are incubated for a longer period, this effect could be more pronounced and hence the differences observed at the two different incubation periods.

It is observed in the present work that mitotic index in general was low in untreated Tuberculosis patients compared to controls, and this could be the result of the disease process. Studies with 3H-thymidine have revealed that there is a direct relation between mitotic index and blast cell formation. Wadee et. al., (1981) have observed that when peripheral blood monocellular cells were inactivated by mitogen in the
presence of *Mycobacterium tuberculosis*, a significant suppression occurred in the uptake of 3H-thymidine. The depressed blast cell formation in the untreated Tuberculosis patients was reported to be due to the overwhelming infiltration of bacteria into the body tissues, which affects one or two steps of the immunological chain reactions, thus subsequently hampering the rejection of foreign substance. This impairment of the immune system was suggested to have reflected in the depressed lymphocyte transformation (Jaju and Ahuja, 1983).

Similar results were also observed by earlier investigators with regard to untreated Leprosy patients and a significant reduction in the T cell number in Lepromatous Leprosy was suggested to be the reason for a depressed mitotic stimulation in these affected individuals (D' Souza and Thomas, 1988).

5.2 AFTER TREATMENT:

In the present study an attempt has been made to evaluate the mutagenic potential of four anti-tubercular drugs that are commonly used in combination in India. These four drugs are used, in three different combinations during the intensive phase and one
combination during the continuation phase. These different combinations of drugs are selected keeping in mind their efficacy in the treatment of Tuberculosis and were tested for their effects on genetic material. Of the four drugs that are used in this study, three drugs, Isoniazid (INH), Streptomycin (SM), and Rifampin (RIF) have been extensively studied, but no information was available on the fourth drug Pyrazinamide (PZI) with regard to its effects on the genetic material.

All the three drug combinations given in the intensive phase i.e., 2 SHRZ, 2 HRZ and 2 H2R2Z2 have induced chromosomal aberrations in the patients under treatment, thus suggesting the mutagenic potential of these drug combinations. However, there are significant differences among these combinations, 2 HRZ being a highly potential inducer of chromosomal aberrations, while 2 H2R2Z2 was the least effective. These results clearly indicate the fact that though the number of drugs are the same and are identical in both groups, the duration of the drug given determines the mutagenic potential of a given combination. 2 H2R2Z2 combination, wherein the three drugs are given twice weekly, inspite of an increased dosage, proved to be less harmful than the daily combination of 2 HRZ with normal dosage.
These observations are further strengthened by the fact that the two drug combination of 4 H2R2 given during the continuation phase is also observed to be highly clastogenic. Even though only two drugs are given twice weekly, during this phase, the frequency of chromosomal aberrations was still significantly higher compared to the frequency before treatment. Though, no significant differences were observed when the frequency of chromosomal aberrations, after intensive phase, were compared with the frequency after continuation phase, the frequency remained high, even after withdrawal of two drugs, in the continuation phase. Literature survey on the drug profiles revealed that none of the drugs employed in the present study are retained in the body for more than 24 hrs, hence the possibility of residual effects of these drugs during the continuation phase is ruled out. This suggests that the two drug combination of 4 H2R2 given during the continuation phase, followed by any one of the three regimens in the intensive phase, is capable of inducing chromosomal aberrations. Based on these results, it can be suggested that the two drugs Isoniazid and Rifampin in combination are highly mutagenic, and the high incidence of chromosomal aberrations observed during the intensive phase also could be due to the action of these two drugs alone.
However, one interesting observation is that, the drug combination 2 HRZ during intensive phase, followed by 4 H2R2 during continuation phase, reduced the frequency of chromosomal aberrations significantly, when only two drugs are given during the continuation phase. This is quite in contrast to the observation after intensive phase. During intensive phase, 2 HRZ combination has induced a high incidence of chromosomal aberrations compared to other regimens. This combination has also induced a significant depression in cell cycle kinetics at both 48 and 72 hrs. during the intensive phase. Due to this delay in cell cycle duration, the number of cells entering the cell division is less and perhaps this could be the reason for the decreased frequency of chromosomal aberrations after continuation phase.

Though there are no significant differences observed between the two drug combinations 2 SHRZ and 2 HRZ, the latter combination induced more number of chromosomal aberrations compared to the former one. Similar results were observed by other authors in their earlier studies. This could be due to a mild protective action of SM observed by many authors. Dubinin et. al., (1961, 1983) have reported that SM reduces or suppresses
the mutations induced by other agents. Borodkin, (1972) stated that SM decreased the chromosomal aberrations in humans by 25 - 30 %, when it is given after irradiation. Jaju and Ahuja (1983) reported from their studies on the anti-tubercular drugs that the triple drug combination involving SM has induced less number of aberrations compared to double drug combinations without SM. Based on these reports and on the results of the present study it can be concluded that SM does exhibit a mild protective action when given in combination. The four drug combination 2 SHRZ has also induced a high frequency of chromosomal aberrations in spite of the presence of SM. This suggests that the combined effect of the other three drugs INH, RIF and PZI is stronger than the mild protective effect of SM.

Of the four anti-tubercular drugs used in the present study INH has been extensively studied on various systems. In a co-ordinated study in Germany, 13 laboratories have studied the effect of INH on various test systems and majority of them have concluded that INH is not mutagenic (Rohrborn et. al., 1978). The other two drugs SM and RIF are also observed to be non-mutaginic when used individually, either in vivo or in vitro (Neu et. al., 1965; Obe, 1970; Vogel, 1973; Jaju
and Ahuja, 1983). However, with regard to RIF, there are contradictory reports. It has been reported that RIF blocks the DNA dependent RNA polymerase (Mauro et al., 1969) and hence is a potential clastogenic agent in vitro (Roman and Georgian, 1977).

While most of the anti-tubercular drugs have been reported to be non-mutagenic, their combinations were observed to be potential mutagenic agents. Schroeder and Stahl-Mauge, (1979) reported a high frequency of chromosomal aberrations when lymphocytes of patients with Fanconi's anaemia, a DNA repair defect condition, were treated with INH. Jaju and Ahuja, (1983) also observed that INH when given in combination with various other anti-tubercular drugs induces chromosomal aberrations. INH in the presence of alkylating mutagen N-methyl-N-nitrosourea has been observed to inhibit the post-replication repair (Klamerth, 1978) which was later stated to be long term excision repair (Klamerth, 1979). These results prompted Vogel, (1978) to suggest that INH is not a mutagen by itself but acts as a co-mutagen and aggravates the damage caused by another mutagen. It is quite likely that in the present study INH aggravated the effect of other anti-tubercular drugs. It is quite possible that in the present study, INH when given in
combination with other anti-tubercular drugs, interferes with some repair process as suggested by Jaju and Ahuja (1983), which results in induced chromosomal aberrations. Further, it is clearly indicated that INH, though not a mutagen by itself, induces chromosomal aberrations when given in combination with other drugs. This could be due to the synergistic action of these drugs.

When RIF was given in combination with INH to Tuberculosis patients in vivo, Roman et. al., (1983) have observed a high frequency of chromosomal aberrations. RIF when given in combination with DDF to Leprosy patients, was observed to increase the frequency of chromosomal aberrations (Beiguelman et. al., 1975; Roman and Georgian, 1977; Heckel and Beiguelman, 1985). However, Peters et. al., (1983) and D' Souza and Thomas, (1988) have reported to the contrary that RIF in combination with DDF and/or CLF did not increase chromosomal aberrations. From these results it can be deduced that RIF alone or in synergistic action with other drugs can induce chromosomal aberrations. Our results with the two drug combination of 4 H2R2 during the continuation phase, suggests that RIF alone or in synergistic action with INH is capable of inducing
chromosome damage, but in the face of such contradicting reports, it is difficult to draw a definite conclusion, until the issue is probed in detail.

Of the three drug combinations that are studied during the intensive phase, two combinations 2 SHRZ and 2 HRZ have induced SCEs while, the other combination did not induce SCEs. Once again these results clearly suggest the fact that its the duration and dosage of drugs that determine the mutagenic potential of a given combination. The four drug combination of 2 SHRZ and three drug combination of 2HRZ given daily have induced SCEs while the other three drug combination of 2 H2R2Z2 given twice weekly did not induce any SCEs. Furthermore, even the two drug combination of 4 H2R2 given twice weekly for four months during the continuation phase also induced SCEs, suggesting the importance of the duration and dosage of these drugs in evaluating their mutagenic property. Though no significant differences were observed when the frequency of SCEs after intensive phase are compared with the frequency after continuation phase, the frequency of SCEs remained high during continuation phase. As is the case with chromosomal aberrations, here also, the two drug combination of 4 H2R2 also seems to be capable of
inducing SCEs.

As is the case with chromosomal aberrations, a mild protective action of SM is evident even with regard to SCEs. Though no significant differences were observed with regard to SCE frequency in the groups 2 SHRZ and 2 HRZ, the later combination without streptomycin induced relatively more number of SCEs compared to the former.

With regard to the effect of these drugs on the induction of SCEs, not much information is available. Stahl-Mauge, (1979) has reported that INH did not induce SCEs in the chromosomes of normal individuals. Jaju and Ahuja, (1983) reported that INH in combination with various other drugs also did not show any increase in the frequency of SCEs. RIF in combination with DDS was shown to increase SCE frequency in Pauci-bacillary Leprosy patients by D’ Souza and Thomas, (1988). However, in the present study the SCE frequency was increased with only two drug combinations.

The other drug combination 2 H2R2Z2 induced only chromosomal aberrations but not SCEs. This could be due to the differences in the mechanisms of formation of chromosomal aberrations and SCEs. Jaju and Ahuja,
have proposed that the combination of anti-
tubercular drugs induce two types of lesions, one
leading to SCEs and the other to chromosomal
aberrations. They also suggested that only few
individuals are susceptible to the kind of damage
leading to SCEs and this susceptibility could be the
result of slow acetylation phenotypes of INH.

As in the case of chromosomal aberrations and SCEs
in untreated Tuberculosis patients, even the drugs also
show an association between the extent of damage and the
length of chromosome or its DNA content. The larger
chromosomes are affected more often than the smaller
chromosomes.

With regard to cell cycle/cell proliferation
kinetics at 48 hrs, except for the 2 HRZ combination,
the other two combinations did not show significant
differences compared to untreated patients. The drug
combination 2 HRZ has considerably depressed cell
proliferation rate in the patients. Jaju and Ahuja,
(1983) reported that SM when used in combination
depresses the cell proliferation rate. However, in the
present study the drug combination 2 SHRZ with SM did
not show any depression in cell cycle kinetics. A
stronger synergistic action of the other three drugs could offset the effect of SM, and hence there is no effect on cell cycle kinetics.

However, at 72 hrs, the cell cycle was depressed significantly with all drug combinations. The difference observed at the two incubation periods can be attributed to the longer duration of culture time at 72 hrs, wherein there is an accumulation of cells with chromosomal aberrations, which normally do not enter cell division, hence the effect is more at 72 hrs.

Similarly, the two drug combination of 4 B2R2 given during the continuation phase, followed by 2 HRZ combination in the intensive phase also induced cell cycle delay. This delay could be due to the high incidence of chromosomal aberration induced by this combination during intensive phase. These cells with aberrations normally do not enter the cell cycle, hence this delay is seen even during the continuation phase.

One interesting observation was that mitotic index was improved considerably with drug combination 2 SHRZ at both incubation periods. These results are quite contrary to the earlier reports. Subramanyam and Reddy, (1975) and Sahai, (1981) have reported that SM
depressed the mitotic index in their studies on various animal systems. Leurs and Obe, (1971) observed that INH in physiological concentrations did not inhibit the mitotic index in human peripheral blood lymphocytes. Though SM is reported to have depressed the mitotic index in their studies, Jaju and Ahuja (1987) also reported that the mitotic depression was not significant in combinations with and without SM. They suggested that the difference could be due to the presence of other drugs. In the present study, the enhanced mitotic index in the four drug combination suggests that this improvement could be due to the synergistic action of all the four drugs.

Out of the three combinations studied in the intensive phase, 2 H2R2Z2 showed a depressed mitotic index compared to the other two drug combinations. The triple drug combination of 2 H2R2Z2, given only twice weekly, though less clastogenic and and though it did not induce SCEs, seems to have no remedial effect on the mitotic index.
SUMMARY
SUMMARY

Tuberculosis is a chronic infectious disease, affecting primarily the lungs, and secondarily the skin, bone and other tissues. Based on this knowledge, this present study aims at finding out whether there is any damage done to the genetic material by the tubercle bacilli, *Mycobacterium tuberculosis*, and also to study the effect of multidrug treatment on the genetic material of these patients.

A total number of 188 cases is studied and the breakup of the cases studied is as follows:

Group I: This group consists of age and sex matched controls from the general population.

The number of cases studied in this group is 28

Group II: This group consists of untreated tuberculosis patients, with no history of tuberculosis in the past and no habits of smoking, alcoholism and pan chewing.

The number of cases studied in this group is 95

Group III: This group consists of patients who had completed the two months intensive phase of chemotherapy. Depending on the drug regimens administered these patients were further classified into three sub groups. They are
Sub Group A: Patients who had completed the two months intensive phase of short term chemotherapy regimen 2 SHRZ (S - Streptomycin 0.75/1g, H - Isoniazid 300 mg, R - Rifampin 450 mg Z - Pyrazinamide 1.5 g per day regularly).

The number of subjects studied is 20

Sub Group B: Patients who had completed the two months intensive phase of short term chemotherapy regimen 2 HRZ (drugs and dosage are same as in sub group A, except for the withdrawal of Streptomycin)

The number of subjects studied is 15

Sub Group C: Patients who had completed the two months intensive phase of short term chemotherapy regimen 2 H2R2Z2 (H - Isoniazid 600 mg, R - Rifampin 900 mg, Z - Pyrazinamide 1.5 g, twice a week instead of every day)

The number of subjects studied is 20

Group IV: This group consists of patients who had completed the continuation phase (next four months) of the above three regimens. During this continuation phase the patients were administered a regimen 4 H2R2 (H - Isoniazid 600 mg and R - Rifampin 900 mg twice a week for four months)

The number of subjects studied in this group is 15
Peripheral blood lymphocyte cultures are set up using a modified method of Arakaki and Sparkes (1963). Fluorescence plus Giemsa (FPG) staining was done according to the method of Perry and Wolff (1974) with slight modifications. Chromosomal aberrations are scored from 100 first cell cycle metaphases per subject. For scoring of chromosomal aberrations ISCN (1985) criteria are used. Twenty five second cycle metaphases are scored from the 72 hr cultures for scoring Sister chromatid exchanges (SCEs). For cell cycle kinetics 100 metaphases are scored at random from both 48 and 72 hr cultures. For mitotic index 1000 cells are counted at random from both 48 and 72 hr cultures.

BEFORE TREATMENT:
Chromosomal aberrations: The frequency of chromosomal aberrations is higher in the untreated group compared to that of controls. Chromatid gaps and breaks are more in number compared to the chromosome type of aberrations.

Sister Chromatid Exchanges: The frequency of sister chromatid exchanges did not differ much in both the groups.
Cell cycle kinetics: Cell cycle is significantly depressed in the untreated TB patients compared to controls at 48 hr. incubation. On the other hand the cell cycle is significantly accelerated at 72 hr. incubation compared to controls.

Mitotic Index: Mitotic index in general is low in patients, when compared to that of controls. Mitotic index is depressed in case of untreated patients at both 48 and 72 hr cultures.

Chromosomal aberrations: Patients, who have completed the intensive phase of short term chemotherapy regimens 2 SHRZ, 2 HRZ and 2 H2R2Z2, have shown a high frequency of chromosomal aberrations compared to the Untreated TB patients. Even patients who had completed the full course of chemotherapy (4 H2R2) have also shown a high frequency of chromosomal aberrations compared to the untreated group.

Sister Chromatid Exchanges: Patients who had undergone the intensive phase of short term chemotherapy regimens 2 SHRZ and 2 HRZ and full course of chemotherapy (4 H2R2) have shown a high frequency of SCEs per cell
compared to the untreated TB patients. But the other group who had undergone the short term chemotherapy regimen 2H2R2Z2 have not shown any increase in the frequency of SCEs.

Cell Cycle Kinetics: No differences are observed between any of the groups studied except for the patients who had completed the short term chemotherapy regimen 2 HRZ at 48 hr. incubation. The cell cycle is significantly depressed in these patients when compared to untreated TB patients.

However, at 72 hr. incubation, the cell cycle is significantly depressed in patients who had completed the intensive phase of chemotherapy regimen 2 SHRZ and 2 HRZ, while it is accelerated in the other group who had completed the regimen 2 H2R2Z2. Patients who had completed the full course of treatment (4 H2R2) have not shown any significant differences compared to untreated patients.

Mitotic index: Mitotic index at 48 hr. incubation is significantly improved in patients who had completed the intensive phase of short term chemotherapy regimen 2 SHRZ compared to the untreated patients. However, the
other groups did not show any significant differences. Similar results are observed at 72 hr. incubation also.

One difficulty encountered during the study is to followup the patients. Since many of the patients do not turn up for regular medication, it is very difficult to get patients after treatment. Most of the patients are untraceable at their given addresses. Probably these patients gave purposefully wrong addresses as they are afraid of the social stigmata attached to the disease in the society. The fact that out of the 95 untreated patients taken for the study only 55 have so far completed the I phase i.e., the intensive phase and only 16 completed the continuation phase (full course) of chemotherapy, gives a clear indication as to the magnitude of the problem.

DISCUSSION:

In the present study the chromosomal aberrations in untreated tuberculosis patients are significantly higher when compared to controls. Though there are many reports both for and against viruses causing chromosome damage, very little information is available with regard to bacteria and their ability to damage the chromosomes. Mycobacterium leprae, the causative organism of leprosy,
belonging to the same family as *Mycobacterium tuberculosis*, is reported to cause chromosome damage in affected individuals. Our present study also indicates that these bacteria are mutagenic and cause chromosome damage.

Significant differences were observed with regard to cell cycle kinetics and mitotic index between the untreated TB patients and controls at both 48 and 72 hr. incubation. These differences could be due to the high incidence of chromosomal aberrations induced by the bacterium itself, and the cells with these aberrations might not enter the cell division. With increased incubation times, the number of damaged cells accumulates resulting in further depression of mitotic index and cell cycle durations. Hence the differences observed between the two incubation times.

The fact that no significant differences were observed with regard to the frequency of sister chromatid exchanges between the controls and affected individuals suggest that though the SCEs are a sensitive parameter in mutagenicity testing, *Mycobacterium tuberculosis* is not potential inducer of SCEs.

In the present study chromosomal aberrations are
significantly increased in all the patients undergoing chemotherapy, thus suggesting that the chromosomal damage caused by the bacterium is aggravated by the anti-tubercular drugs. Out of the three short term chemotherapy regimens studied in the intensive phase, the triple drug combination of 2 HRZ given daily for two months was observed to have more clastogenic activity. The four drug combination of 2 SHRZ was shown to be less clastogenic comparatively, though the differences are not statistically significant. These results are in accordance with earlier reported observations that the Streptomycin has got a mild anti-mutagenic and anti-clastogenic property, and when used in combination with other drugs, decreases the frequency of mutations. However, the triple drug combination of 2 H2R2Z given twice weekly for two months was found to be the least clastogenic.

Similar results are observed with regard to the induction of SCEs by these drugs. This suggests the fact that these drugs are capable of inducing both chromosomal aberrations and SCEs, but these effects can be minimised by giving an optimal dose, so that it can be more effective in curing tuberculosis disease and at the same time less harmful to the genetic material of
the affected individuals.

Another interesting observation is that another two drug combination of 4 H2R2 (dose is doubled) given twice weekly for four months in the continuation phase following the intensive phase, is also capable of inducing chromosomal aberrations and SCEs. Though only two drugs are given during this phase, the high frequency of chromosomal aberrations and SCEs suggests that the prolonged duration of treatment with high doses of these drugs is harmful to the genetic material.

CONCLUSIONS:

1) In the present study for the first time it is reported that Mycobacterium tuberculosis, the causative organism of tuberculosis disease is capable of inducing chromosome damage in the affected individuals.

2) The anti-tubercular drugs used in the treatment are capable of aggravating the chromosome damage caused by the bacterium.

3) Though the anti-tubercular drugs are capable of causing chromosome damage, it is possible to minimise their effects by manipulating the dosage and duration of
the drugs.

4) Streptomycin, as reported earlier, seems to have a protective effect when used in combination with antitubercular drugs.