CHAPTER 7

DISCUSSION

7.1 Patient demographics

In this study, in which one hundred and sixty patients were enrolled, of whom seventy one were study patients with active newly diagnosed pulmonary tuberculosis, and eighty nine were control patients with other medical diseases/conditions other than tuberculosis, 85% were black, 13% were of mixed race, and 1% each were white and Asian (Table 1). This is a reflection of the dominant race grouping served by the hospital.

The mean age in both groups reflected a younger population of patients (Fig.1) and in the case of the study group was similar to those reported in other developing countries in patients with tuberculosis (Corbett et al 2003). Most of the patients in both groups resided in the sprawling Soweto township and the mixed race township which are in close proximity to the hospital (Table 3).

Occupations (Table 2) varied in both groups, with “unskilled” (labourers) constituting 36.6% and 40.4% of the study and control patients, while the “semi-skilled” (e.g. factory workers, drivers) represented 25.4% and 15.7% respectively. There were more skilled workers (e.g. teachers, technicians and clerical staff) in the control group than in the study group. There were
more unemployed patients in the study group than in the controls. This may reflect the fact that tuberculosis is rampant among the unemployed or low income groups, or among the uneducated or poorly educated in society (tuberculosis is thought to be a disease of the poor). This trend is seen both in developed and developing countries with large numbers of tuberculosis cases in the South East Asia region, African region and Western pacific region (Fatkenheuer et al 1999, Dye et al 1999, Churchyard and Grant 2000, Corbett et al 2003). The demographic profiles of the two groups were otherwise similar.

7.2 Behavioral features

In the control group, 60.7% of the patients were smokers compared with 39.4% in the study group (Table 4) of whom the majority were male (88.8% in the control group and 89.2% in the study patients respectively). A proportion of 79.6% and 57.1% smokers in the control and study patients had less than 10 pack years. Alcaide et al (1996) have demonstrated the risk of active pulmonary tuberculosis in association with cigarette smoking. They also found a close response relationship between the number of cigarettes smoked daily and the development of active pulmonary tuberculosis. Environmental cigarette smoke exposure was also noted as a risk associated with the development of active pulmonary tuberculosis. Reports by Kollapan and Gopi (2002), Maurya et al (2002) and Yach (2000) have associated smoking with the development of
pulmonary tuberculosis. Den Boon et al (2005) also observed an association between cigarette smoking and the development of tuberculosis in their study in Cape Town.

Alcohol consumption was greater in the control group than in the study group (93.7% and 69.7% respectively); males were again dominant in both groups (approximately 85% in each). The majority of patients in both groups consumed below 1.5 liters of beer per day or its equivalent. Those who consumed heavily were also noted to smoke heavily. The majority of alcohol consumers were generally low income earners (indicated by occupational class). Maurya et al (2002) noted a direct relationship between tuberculosis and alcohol consumption.

The nutritional history obtained in the study included intake of protein, consumption of fruits and other nutrients. All patients in both groups consumed one or other kind of meat, on average four times per week. Fruit consumption was universal. Despite this rather good nutritional history, it is to be noted that later in the clinical evaluation, most patients in the study group were noted to be malnourished. Previous work has demonstrated a correlation between tuberculosis and malnutrition (Getz et al 1951, Mayer 1971, Ikeogu et al 1997, Le Roux et al 1991, Hemila et al 1999, Byrd et al 2002). In their study Strachan et al (1995) also found an association between vegetarian diet and the risk of tuberculosis in

7.3 Presenting symptoms in study patients

The universal presenting symptoms in the study group were cough and fever (Table 7). All patients had a productive cough with night sweats. All the males had a history of weight loss compared with 43.7% of the females. 40.8% of the males had difficulty in breathing and 38.0% had pleuritic chest pain versus 36.6% and 21.1% of the females respectively. 9.8% males and 5.6% females had haemoptysis. The mean duration of symptoms was approximately six weeks in both males and females. The delay in presentation could be due to several reasons including lack of financial resources, patients downplaying symptoms, patients unaware of tuberculosis, self medication, alternative medication (traditional healers), the fear of HIV testing and the potential social stigma tuberculosis still carries. Some of these factors were noted by Hudelson (1996) in his review of the role of socio-economic and cultural factors in tuberculosis.
7.4 Nutritional indicator

The mean body mass index (BMI) in the study group was 18.29 ± 3.8 and in controls 23.20 ± 5.35 Kg / M² (p < 0.01). 40 patients in the study group had low BMI compared to only 6 in the controls. The BMI range in the study group was 11.72 to 32.05 Kg / M², while in the controls it was 15.57 to 44.96 Kg / M². Clinical evidence of wasting was found in 97% of study patients with only 1% in the controls. The low BMI and the near universal wasting found in the study patients would be due to the tuberculosis infection and / or malnutrition. It has been documented previously that malnutrition has a direct bearing on the pathogenesis and final outcome of tuberculosis infection. Mayer (1971) noted susceptibility to tuberculosis infection from malnutrition. In an East African study, Niyongabo et al (1999) found significant malnutrition in HIV positive tuberculosis patients. Karyadi et al (2000) also found poor nutritional status of patients with active pulmonary tuberculosis compared with healthy subjects, while Schwenk and Macallan (2000) reviewed the role of malnutrition in tuberculosis.

The low BMI could also be due to co- infection with HIV, the rates of which are much higher in developing countries. Patients were, however, not routinely tested for HIV infection, but those whose status were known were recorded. The presence though of lymphadenopathy (48%) and oral
thrush (15.5%) in the study group could suggest possible co-infection with HIV.

7.5 Laboratory data

The laboratory data (Table 11) obtained were tests done by the patients doctors in the ward, which if available were recorded. These included haematology, biochemistry, serum enzymes and liver function tests. In the study group the mean leukocyte count, haemoglobin and mean cell volume were significantly lower than in the control group. Mean leucocyte count for the study patients was 8.66 ± 5.44 × 10^9/l versus 11.0 ± 4.49 × 10^9/l (p = 0.018), mean haemoglobin 9.56 ± 1.59 gm / dl versus 12.92 ± 2.34 gm / dl (p < 0.01), mean cell volume 82.7 ± 7.53 versus 87.72 ± 7.87 (p = 0.001). Mean platelet and ESR values were higher in the study group, 369.2 ± 190.8 × 10^9/l and 67.2 ± 39.8 mm/hr compared with the controls, 295.9 ± 94.6 × 10^9/l and 2 mm/hr respectively. The low haemoglobin, white cell count and mean cell volume may be related to the chronic tuberculosis infection, but may also be a reflection of malnutrition in these patients. Co-infection with HIV may be a contributing factor as well. The findings in the control group suggest that there were healthy individuals before admission.

The mean sodium levels were lower in the study group than in controls, 132.56 ± 4.78 mmol/L versus 138.81 ± 3.35 mmol/L (p < 0.01), but there
were no differences in the serum urea, creatinine, potassium, phosphate, calcium, or magnesium between the two groups (Table 12). The low sodium levels in the study group could be attributed to inappropriate secretion of antidiuretic hormone (ADH) which is a feature of pulmonary tuberculosis. Other electrolytes and parameters were similar in both groups which could be attributed to the design of the study which excluded those with premorbid disease. Mean CRP was greater in the study group. There was a lower mean serum albumin in the study group, 24.94 ± 5.68 gm/ L versus 37.33 ± 8.75 gm/L for the control group (p< 0.01). The low serum albumin may be due to malnutrition and/or tuberculosis infection.

Twenty four of the study patients were known to be HIV positive, while one patient in the control group was noted to be HIV negative. This study, however, did not specifically evaluate the HIV status of the control or study patients.

7.6 Core research laboratory results

In this study, plasma and white cell vitamin C were found to be decreased in both the study and control groups. Over 95% of control patients and 93% of study patients had decreased plasma vitamin C levels whereas about a half of patients in each group had decreased white cell vitamin C levels. The decreased vitamin C levels are in conformity with previous reports (Getz et al 1951, Awotedu et al 1984, Plit et al 1998, Madebo et al 2003, Bakaev et al 2004). The decrease in the study patients could be due
to accelerated turnover secondary to increased oxidative stress, shifts in plasma concentrations, increased collagen formation and tissue repair and decreased intake (Plit et al 1998). The possible explanation for the decrease in the control group could be related to smoking (the percentage of which was higher in the control group). Smoking induces oxidative stress which accelerates vitamin C turnover. Another consideration is that it is possible that Africans may generally have low levels of vitamin C for reasons that are not apparent.

The serum cortisol levels in both groups were generally normal. A proportion 80% of control and 76% of study patients had normal cortisol levels while 10% of controls and 16% study patients had increased serum cortisol levels. These results are in contrast to the low levels of serum cortisol reported previously (Ellis and Tayoub 1986, Prasad et al 2000, Sarma et al 1990).

Vitamin C has been reported to be involved in optimal steroid hormone function or steroid synthesis mechanisms (Hornsty et al 1985, Goralczyk et al 1992). Decreased plasma vitamin C levels and involvement of adrenal glands by tuberculosis infection could therefore concurrently lead to decreased serum cortisol levels. However in the current study cortisol levels were normal in the majority of the cases. The reasons for this could be that vitamin C has a limited role in steroid-genesis mechanisms and/or
that the involvement of adrenal glands with tuberculosis is partial, since clinical features of adrenal insufficiency appear only when 90% of the glands are destroyed (Sarma et al 1990). Other abnormalities of adrenal function have also been reported including changes in diurnal rhythm and synacthen stimulation (Keven et al 1998, Rook et al 1996, Venter et al 2006), which were not investigated in the current study.

A majority of patients in both the study and control group had normal or increased catecholamine levels. A total of 93% of control patients and 76% of study patients had normal dopamine levels. A proportion of 31.2% of control and 39% study patients had increased norepinephrine levels while high epinephrine levels were found in 53% and 48% of control and study patients respectively. Hafeiz et al (1992) previously reported increased catecholamine levels in patients with pulmonary tuberculosis, the mechanism of which involved induction of some of the enzymes in catecholamine synthesis such as tyrosine hydroxylase, dopamine, β–hydroxylase and phenylethanolamine – N – methyl transferase. On the other hand the role of vitamin C in catecholamine biosynthesis has been documented (Padayatty and Levine 2001). The stimulatory role of tuberculosis infection on the catecholamine synthesis countered by the low plasma vitamin C and adrenal gland involvement in tuberculosis infections sets the stage for varied catecholamine levels, with high levels if the stimulatory role of tuberculosis predominates. The possible reasons
for not overwhelmingly high levels of the catecholamines in the current study could be that the induction of the enzymes in the catecholamine synthesis by tuberculosis is not as significant as is purported to be, or that the patients’ selection did not include severely ill patients. On the other hand, the reasons for not having low catecholamine levels could be that the vitamin C role in catecholamine synthesis and adrenal involvement in tuberculosis infection is either minimal or not apparent.

In the study group, 95.8% had elevated CRP levels compared with 78.6% of the controls. Baynes et al (1986), Lawn et al (2000) and Sanchez-Moreno et al (2003) have previously documented high CRP levels in pulmonary tuberculosis patients which decreased after initiation of therapy. It was further noted that concentrations of CRP correlated with severity of the illness. This study confirms the elevated plasma CRP levels in the tuberculosis patients, but the small number which had normal CRP values could be related to less severe infections with tuberculosis. The elevated levels in the control group demonstrate that CRP levels are increased in different inflammatory disorders (Baynes et al 1986). Louw et al (1992) have previously observed a decreased leukocyte vitamin C levels in patients with increased CRP. In this study a weak correlation was found between plasma vitamin C and CRP with 88.7% in the study group and 76.4% in
the control group having low vitamin C and high CRP. The two variables signify the levels of oxidative stress.

A proportion of 90% of the study patients and 29.2% of control patients had high plasma levels of ferritin in keeping with previous reports (Morris et al 1989, Caso et al 1997 and Al-Omar and Oluboyede 2002). These investigators noted high ferritin levels in tuberculosis patients which decreased after initiation of tuberculosis treatment. The beneficial effect of ferritin in reducing toxic effects of iron and defense against pathogens are well known. Ferritin could be a marker of severity of the disorder as well as a prognostic factor (Caso et al 1997).

Bridges (1985) has reported interplay between ascorbate (vitamin C) and iron metabolism. This study however did not find any correlation between the two variables.

A total of 50% of the study patients and 53.4% control patients had high urine cotinine levels with cigarette smoking of 39.4% and 60.7% in study and control patients respectively. The disparity between the number of smokers and the urine cotinine levels in both groups could be due to the patients not declaring their smoking habits for fear of victimization, patients’ disease (patients were too sick to smoke), or patients being admitted to wards which did not provide for smoking (note the half life of
cotinine is 17hrs). Other reasons could be the role of environmental tobacco smoke exposure which could cause elevation of urine cotinine levels in non-smokers.

The role of cigarette smoking as a risk factor for tuberculosis has been reported before (Alcaide et al 1996, Yach 2000, Kolappan and Gopi 2002, Maurya et al 2002, Den Boon et al 2005). Further cigarette smoking (including environmental tobacco exposure) has been associated with decreased vitamin C and other anti-oxidants in the body (Dietrich et al 2003, Preston et al 2003).

This study did not show a correlation between urine cotinine and plasma vitamin C levels, neither was there a correlation with tuberculosis, probably because of the design of the study. However, an inverse correlation was noted between CRP and urine cotinine suggesting a role for the oxidative stress in smoking.

It is important to mention potential limitations of this study hormone. The total number of patients in the study was smaller than initially targeted mainly due to the costs involved in doing the laboratory investigations. Some laboratory results were missing as frequently happens in studies involving biological specimens. Strength of the study include, the fairly
large number of patients studied, with clinical data that was extensive and complete, and the quality of the laboratory data.