# LIVER FUNCTION TESTS IN PATIENTS OF PULMONARY TUBERCULOSIS USING FOUR DIFFERENT DRUG REGIMENS

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*Background:* Chemotherapy is the basic approach to clinical tuberculosis control. Antituberculous therapy causes derangement of hepatic functions revealed by disturbed liver function tests. The incidence of side effects may vary depending upon a number of factors. The primary purpose of this study was to determine the relative and absolute hepatotoxicity of different antituberculous drug regimens in Pakistani population where majority of the tuberculous patients belong to poor socioeconomic status. *Methods:* One hundred patients between 30 to 70 years of age with newly diagnosed pulmonary tuberculosis were selected and divided into four groups on the basis of different drug regimens. Blood and urine tests of these patients were made. Liver function tests were performed before therapy and then after one. two. three, six and nine months of treatment. *Results <& Conclusions:* Antituberculous therapy causes derangement of hepatic function to a variable extent in patients of four different antituberculous drug regimens under study. Drug combination of Streptomycin. Isoniazid and Myambutol seem to be best tolerated of all the four regimens. Monitoring of the liver function in patients on antituberculous therapy indicated that liver dysfunction most frequently occurs during first three months of therapy. There is a tendency for enzyme values to return to normal inspite of continuous treatment. The mechanism underlying this adaptation to injury to the liver is unknown. Biochemical tests in the patients presenting with jaundice yielded the pattern of acute hepatocellular necrosis with high transaminases and moderately elevated Alkaline Phosphatase. None of the patients had hepatitis associated antigen in their serum.

## INTRODUCTION

Tuberculosis is the most common chronic disease of the world. Despite modern chemotherapy and large infusions of public money for its prevention and treatment, tuberculosis continues to match across the globe, singling out its victims whenever there is poverty, overcrowding and poverty.

Tuberculosis is a disease produced by infection with Mycobacterium tuberculosis Asia and South Pacific offer the most fertile breeding grounds for the tubercle bacillus. WHO estimates that in many Asian countries 60-70% of children up to fourteen years of age are infected with tuberculosis. Tuberculosis is almost always acquired through lungs by inhalation of an aerosol containing viable tubercle bacilli. In countries where tuberculosis of cattle is still prevalent the infection can be acquired by ingesting contaminated milk. Rarely tuberculosis is acquired by direct inoculation of bacilli usually through skin of hand. The tubercle bacillus is an intracellular parasite that usually lives in cytoplasm of macrophages'.

Chemotherapy is the basic approach to clinical tuberculosis control even if the social, economic, environmental or nutritional conditions are poor, chemotherapy can indeed assume cure of tuberculosis[4].

Treatment began at the turn of century with plenty of fresh air, sunshine and high protein diet. This was followed by an era of artificial pneumothorax, pneumo-peritoneum, phrenic crush and thoracoplasty. Then came drug regimen with Streptomycin. Para

Amino Salicylic acid and Isoniazid to be replaced later by Myambutol, Pyrazinamide, Cycloserine, Ethionamide, Capromycin and Viomycin with passage of time[4].

Isoniazid is regarded as the most valuable antituberculous drug. It is metabolized primarily by acetylation to acetyl isoniazid mainly in the liver. Acetyl isoniazid is markedly hydrolyzed by humans and rats to yield free hydrazine derivatives[6]. Metabolic activation of liberated hydrazine produces a chemically reactive acylation agent which appears to be responsible for hepatic damage in animals'.

Age appears to be an important factor in determining the risk of hepatotoxicity due to isoniazid. Severe liver damage is observed rarely in patients under twenty years of age. Incidence of hepatotoxicity increases age[8].

Ethambutol hydrochloride (Myambutol) has attained wide acceptance as first line of drug for initial treatment of tuberculosis. It is absorbed rapidly after oral administration and accumulates at significantly higher levels in tissues'.

Intracellular concentrations of Myambutol are sevenfold greater than the extracellular levels. This is well above the minimum bactericidal concentration for most strains of tubercle bacilli and is achieved rapidly by alveolar macrophages and has significant bactericidal activity against phagocylyzed tubercle bacilli as well as extracellular mycobacteria. Myambutol is a drug virtually free from side effects, well tolerated, simply administered and very acceptable to patients[11].

Pyrazinamide has been shown to be an important drug in short course chemotherapy that eliminates special bacterial population that is not rapidly eliminated by other antituberculous drugs. Incidence of side effects

especially hepatotoxicity is particularly high in groups of patients containing pyrazinamide in their drug regimens[4].

Rifampicin is a semisynthetic antibiotic derived from cultures of Streptomyces mediterranei. It can penetrate into phagocytic cells and kills microorganisms that survive in intracellular environment". Some of the patients show hepatic toxicity due to rifampicin [13].

Thiacetazone the most active of the thiosemicarbazones against mycobacterium tuberculosis is an extremely inexpensive and moderately effective antituberculous drug. The most common side effects of thiacetazone include anorexia, nausea, vomiting and fairly high incidence of jaundice suggesting that it is hepatotoxic[14].

Streptomycin was the first potential antituberculous drug recognized and still remains an important first line agent. It acts by interfering with normal protein synthesis of bacteria[15]. Auditory and vestibular dysfunction, rash and fever are the side effects in some patients treated with streptomycin[16].

Antituberculous therapy causes derangement of hepatic functions revealed by disturbed liver function tests. The incidence of side effects may vary depending upon a number of factors including population distribution, kinds of regimens and drug combinations used, frequency and dosage of drug administration. The primary' purpose of this study was therefore to determine the relative and absolute hepatotoxicity of different antituberculous drug regimens in Pakistani population where majority of the tuberculous patients belong to poor socioeconomic status.

## MATERIALS AND METHODS

One hundred patients between 30 to 70 years of age with newly diagnosed pulmonary tuberculosis were selected and were divided into four groups on the basis of different drug regimens and are shown in table-1.

Blood and urine examination of these patients were made. Liver function tests were performed before therapy and then after one, two, three, six and nine months of treatment. Liver function tests included serum bilirubin, alkaline phosphatase (ALP) Gama Glutamyl Transferase (GGT), Aspartate Transaminase (AST) and Alanine Transaminase (ALT). Serum was also tested for hepatitis B Surface antigen (HbsAg) to exclude hepatitis as a possible cause of disturbed liver functions. Twenty-five healthy persons of the same age group were included as controls.

## RESULTS

The results are-given in tables 2-6.

## DISCUSSION

In present study the antituberculous therapy resulted in disturbance of liver function to a variable extent. These results are in agreement with many workers who concluded that liver functions are disturbed in patients on antituberculous therapy[7,9,20].

As shown in tables 2-6 a slight but significant rise was seen in serum levels of bilirubin, ALP, ALT, AST and GGT in patients taking streptomycin, isoniazid and myambutol. Upper limits of normal were not crossed over inspite of a significant rise in level of these parameters. Hepatotoxicity in this group is attributed to isoniazid alone, as myambutol is known to be virtually free from hepatotoxic side effects[21]. In present study 16% of patients in this group presented with elevation in serum levels of AST, ALT, ALP and GGT without hyperbilirubinemias during first three months of therapy. The levels tended to decline with continuous treatment. These results are in good agreement with Black et al.,[22] and Mitchill et al.,[23] who have reported asymptomatic elevation of transaminase with moderately elevated ALP values without jaundice.

**Table-1: Subject Groups based upon drug regimens**

| GROLP | DRUG REGIMEN | DURATION |
|---|---|---|
| I | Streptomycin, Isoniazid and Myambutol Isoniazid, Myambutol | Daily for initial three months.<br>Daily for next six months |
| II | Streptomycin, Isoniazid. Pyrazinamide | Daily for initial three months |
| IIII | Streptomycin. Isoniazid and Rifampicin Isoniazid, Rifampicin | Daily for initial three months.<br>Daily for next six months. |
| IV | Streptomycin. Isoniazid and thiacetazone Isoniazid. Thiacetazone | Daily for initial three months i Daily for next six months |

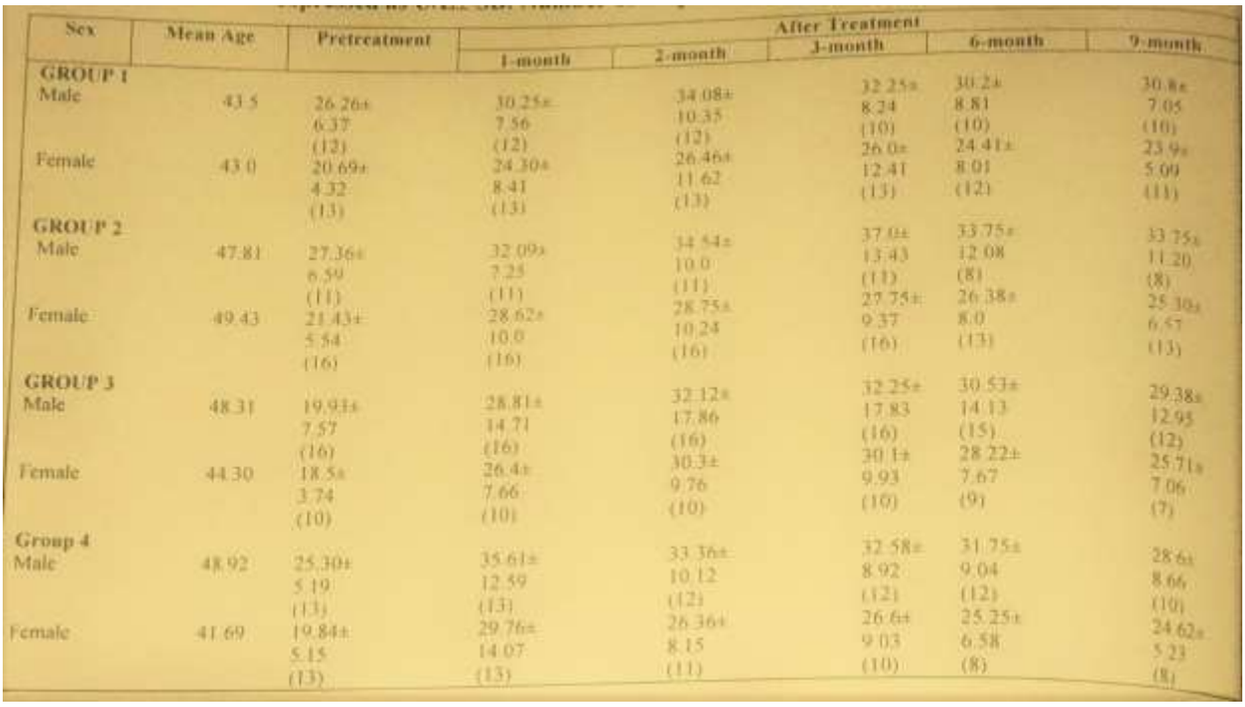
**Tablc-2: Serum bilirubin in patients of pulmonary tuberculosis. Results shown are expressed as mg/dl i SD Number of subjects is shown in parentheses.**

| Sex | Mean Age | Pretreatment | After Treatment | | | | |
|---|---|---|---|---|---|---|---|
| | | | 1-month | 2-month | 3-month | 6-month | 9-month |
| **GROUP 1** | | | | | | | |
| **Male** | 43.5 | 0.4± | 0.461 | 0.5 5± | 0.53± | 0.49± | 0.49 ± |
| | | 0 12 | 0,14 | 0.21 | 0.14 | 0.08 | 0.12 |
| | | (12) | (12) | (12) | (12) | (12) | (12) |
| **Female** | 43 | 0.4± | 0.461 | 0.5± | 0.5± | 045± | 0.45± |
| | | 0.1 | 0.14 | 0.15 | 0.15 | 0.13 | 0.12 |
| | | (13) | (13) | (13) | (13) | (12) | (11) |
| **GROUP 2** | | | | | | | |
| **Male** | 47.81 | 0 38± | 0.47± | 0.53± | 0 67± | 0.5± | 0.46 ± |
| | | 0.08 | 0.2 | 0.33 | 0.54 | 0.16 | 0.13 |
| | | (11) | (11) | (11) | (11) | (8) | (8) |
| **Female** | 49.43 | 0.39± | 0.591 | 0.58± | 0.53± | 0.51± | 0.50 ± |
| | | 0.07 | 0.52 | 0.43 | 0.25 | 0.15 | 0.17 |
| | | (16) | (16) | (16) | (16) | (13) | (13) |
| **GROUP 3** | | | | | | | |
| **Male** | 48.31 | ().45± | 0.56i | 0.65± | 0.64± | 0.581 | 0.55± |
| | | 0.11 | 0.18 | 0.39 | 0.32 | 0.2 | 0.18 |
| | | (16) | (16) | (16) | (16) | (15) | (12) |
| **Female** | 44.3 | 0.37± | 0.501 | 0.71± | 0.85± | 0 53 ± | 0.50 ± |
| | | 40 | 0.22 | 0.39 | 1 | 0.15 | 0.12 |
| | | (10) | (10) | (10) | (10) | (9) | -7 |
| **GROUP 4** | | | | | | | |
| **Male** | 48.92 | 0.49± | 0.991 | 0.71± | 0.72± | 0 64 ± | 0.57± |
| | | 0.16 | 0 70 | 0.39 | 0.39 | 0.16 | 0.16 |
| | | (13) | (13) | (12) | (12) | (12) | (10) |
| **Female** | 41 69 | 0.441 | 1.05i | 0 62± | 0.61± | 0.56 ± | 0.55± |
| | | 0.12 | 0.94 | 0.28 | 0.22 | 0.16 | 0.14 |
| | | (13) | (13) | (11) | (10) | (8) | (8) |

**Table-3: Serum alkaline phosphatase in patients of pulmonary tuberculosis. Results shown are expressed as U/L± SD. Number of subjects is shown in parentheses.**

| Sex | Mean Age | Pretreatment | After Treatment | | | | |
|---|---|---|---|---|---|---|---|
| | | | 1-month | 2-month | 3-month | 6-month | 9-month |
| **GROUP 1** | | | | | | | |
| **Male** | 43.5 | 30.66± | 35.58± | 40.08± | 39.66± | 37.2± | 36.4± |
| | | 6.22 | 5.82 | 10.44 | 8.43 | 6.98 | 6.09 |
| | | (12) | (12) | (12) | (12) | (12) | (12) |
| **Female** | 43 | 33.38± | 37.15± | 40.46± | 39.23± | 39.25± | 38.45± |
| | | 5.38 | 8.75 | 12.19 | 6.93 | 8.88 | 9.1 |
| | | (13) | (13) | (13) | (13) | (13) | (13) |
| **GROUP 2** | | | | | | | |
| **Male** | 47.81 | 26.54± | 33.36± | 34.63± | 39.54± | 34.62± | 34.25± |
| | | 9.74 | 9.28 | 12.7 | 13.6 | 9.53 | 8.94 |
| | | (11) | (11) | (11) | (11) | (11) | (11) |
| **Female** | 49.43 | 33.75± | 38.93± | 38.93± | 38.68± | 37.23± | 36.8± |
| | | 5.6 | 12.13 | 12.46 | 10.84 | 10.36 | 8.4 |
| | | (16) | (16) | (16) | (16) | (16) | (16) |
| **GROUP 3** | | | | | | | |
| **Male** | 48.92 | 32.46± | 44.38± | 42.16± | 39.0± | 39.0± | 38.2± |
| | | 5.85 | 12.95 | 11.31 | 9.59 | 8.67 | 8.67 |
| | | (13) | (13) | (13) | (13) | (13) | (13) |
| **Female** | 44.3 | 27.4± | 35.4± | 39.9± | 38.6± | 35.66± | 35.57± |
| | | 6.03 | 9.55 | 3.91 | 11.07 | 9.32 | 8.34 |
| | | (10) | (10) | (10) | (10) | (10) | (10) |
| **GROUP 4** | | | | | | | |
| **MALE** | 44.31 | 32.0± | 39.18± | 42.25± | 39.75± | 37.93± | 36.69± |
| | | 8.29 | 14.67 | 16.9 | 14.99 | 12.78 | 9.52 |
| | | (16) | (16) | (16) | (16) | (16) | (16) |
| **Female** | 41.69 | 29.53± | 38.76± | 35.18± | 35.3± | 35.5± | 34.5± |
| | | 7.96 | 14.04 | 9.41 | 9.84 | 8.07 | 7.91 |
| | | (13) | (13) | (13) | (13) | (13) | (13) |

**Table – 4 Serum gamma glutamyl transferase in patients of pulmonary tuberculosis. Results expressed as U/L ± SD. Number of subjects is shown in parentheses.**



| Sex | Mean Age | Pretreatment | After Treatment | | | | |
|---|---|---|---|---|---|---|---|
| | | | 1-month | 2-month | 3-month | 6-month | 9-month |
| GROUP 1 | | | | | | | |
| Male | 43.5 | 26.26± 6.37 (12) | 30.25± 7.56 (12) | 34.08± 10.35 (12) | 32.25± 8.24 (10) | 30.2± 8.81 (10) | 30.8± 7.05 (10) |
| Female | 43.0 | 20.69± 4.32 (13) | 24.30± 8.41 (13) | 26.46± 11.62 (13) | 26.0± 12.41 (13) | 24.41± 8.01 (12) | 23.9± 5.09 (11) |
| GROUP 2 | | | | | | | |
| Male | 47.81 | 27.36± 6.59 (11) | 32.09± 7.25 (11) | 34.54± 10.0 (11) | 37.0± 13.43 (11) | 33.75± 12.08 (8) | 33.75± 11.20 (8) |
| Female | 49.43 | 21.43± 5.54 (16) | 28.62± 10.0 (16) | 28.75± 10.24 (16) | 27.75± 9.37 (16) | 26.38± 8.0 (13) | 25.30± 6.57 (13) |
| GROUP 3 | | | | | | | |
| Male | 48.31 | 19.93± 7.57 (16) | 28.81± 14.71 (16) | 32.12± 17.86 (16) | 32.25± 17.83 (16) | 30.53± 14.13 (15) | 29.38± 12.95 (12) |
| Female | 44.30 | 18.5± 3.74 (10) | 26.4± 7.66 (10) | 30.3± 9.76 (10) | 30.1± 9.93 (10) | 28.22± 7.67 (9) | 25.71± 7.06 (7) |
| Group 4 | | | | | | | |
| Male | 48.92 | 25.30± 5.19 (13) | 35.61± 12.59 (13) | 33.36± 10.12 (12) | 32.58± 8.92 (12) | 31.75± 9.04 (12) | 28.6± 8.66 (10) |
| Female | 41.69 | 19.84± 5.15 (13) | 29.76± 14.07 (13) | 26.36± 8.15 (11) | 26.6± 9.03 (10) | 25.25± 6.58 (8) | 24.62± 5.23 (8) |

**Table – 5: Serum alanine aminotransferase (ALT) in patients of pulmonary tuberculosis. Results shown are expressed as U/L ± SD. Number of subjects is shown in parentheses.**

| Sex | Mean Age | Pretreatment | After Treatment | | | | |
|---|---|---|---|---|---|---|---|
| | | | 1-month | 2-month | 3-month | 6-month | 9-month |
| **GROUP 1** | | | | | | | |
| **Male** | 43.5 | 18.0± 9.01 (12) | 25.46± 15.56 (12) | 31.08± 30.4 (12) | 29.58± 27.28 (12) | 29.5± 23.6 (10) | 27.0± 15.56 (10) |
| **Female** | 43 | 20.15± 5.31 (13) | 27.3± 18.06 (13) | 32.84± 30.15 (13) | 30.92± 23.97 (13) | 28.91± 19.91 (12) | 25.69± 14.54 (11) |
| **GROUP 2** | 47.81 | 22.25± 12.0, (11) | 36.81 ± 26.45 (11) | 46.81± 38.71 (11) | 44.81± 37.3 (11) | 38.12± 44.51 (8) | 36.5± 46.62 (8) |
| **Male** | | | | | | | |
| **Female** | 49.43 | 25.25± 9.06 (16) | 42.31± 30.08 (16) | 46.93± 33.79 (16) | 45.37± 32.56 (16) | 40.23± 30.6 (13) | 38.18± 26.20' (13) |
| **GROUP 3** | | | | | | | |
| **Male** | 48.31 | 29.25± 8.33 (16) | 41.75± 30.78 (16) | 46.56± 33.19 (16) | 44.31± 27.43 (16) | 43.33± 23.39 (15) | 42.53± 16.79 (12) |
| **Female** | 44.3 | 26.0± 8.04 (10) | 43.4± 23.36 (10) | 48.1± 27.81 (10) | 47.7± 29.87 (10) | 41.1± 21.56 (9) | 41.71± 22.63 (7) |
| **GROUP 4** | | | | | | | |
| **Male** | 48.92 | 21.76± 5.49 (13) | 44.92± 33.99 (13) | 43.76± 25.45 (12) | 43.08± 22.15 (12) | 41.33± 22.76 (12) | 40.8± 22.87 (10) |
| **Female** | 41.69 | 22.15± 6.98 (13) | 43.38± 33.51 (13) | 39.09± 29.5 (11) | 39.8± 26.9 (10) | 37.75± 20.81 (8) | 36.37± 19.01 (8) |

**Table-6: Serum Aspartate Aminotransferase in patients of pulmonary tuberculosis. Results shown are expressed as U/L± S. Number of subjects are shown in Parenthesis.**

| Sex | Mean Age | Pretreatment | After Treatment | | | | |
|---|---|---|---|---|---|---|---|
| | | | 1-month | 2-month | 3-month | 6-month | 9-month |
| **GROUP 1** | | | | | | | |
| **Male** | 43.5 | 17.83± | 22.83± | 32.25± | 28.66± | 27.5± | 27.9± |
| | | 6.39 | 10.64 | 31.37 | 25.41 | 18.73 | 15.73 |
| | | (12) | (12) | (12) | (12) | (10) | (10) |
| **Female** | 43 | 20.15± | 27.15± | 33.29± | 29.46± | 28.5± | 26.81± |
| | | 7.16 | 14.7 | 30.4 | 23.1 | 18.16 | 17.3 |
| | | (13) | (13) | (13) | (13) | (12) | (11) |
| **GROUP 2** | | | | | | | |
| **Male** | 47.81 | 25.63± | 35.81± | 26.90± | 45.18± | 37.12± | 34.87± |
| | | 10.30 | 20.18 | 36.74 | 31.79 | 21.86 | 19.31 |
| | | (11) | (11) | (11) | (11) | (11) | (8) |
| **Female** | 49.43 | 28.37± | 44.0± | 45.75± | 43.31± | 39.61± | 36.15± |
| | | (16) | (16) | (16) | (16) | (13) | (13) |
| **GROUP 3** | | | | | | | |
| **Male** | 48.31 | 25.68± | 42.62± | 46.56± | 44.62± | 41.53± | 41.92± |
| | | 9.25 | 29.73 | 33.74 | 29.93 | 24.77 | 20.15 |
| | | (16) | (16) | (16) | (16) | (16) | (15) |
| **Female** | 44.3 | 22.8± | 43.4± | 48.3± | 47.4± | 41.77± | 41.0± |
| | | 5.89 | 26.06 | 29.74 | 27.76 | 24.76 | 23.59 |
| | | (10) | (10) | (10) | (10) | (9) | (7) |
| **GROUP 4** | | | | | | | |
| **MALE** | 48.92 | 20.30± | 46.0± | 44.0± | 44.08 | 41.5± | 40.7± |
| | | 7.1 | 29.53 | 29.73 | 27.7 | 23.99 | 26.73 |
| | | (13) | (13) | (12) | (12) | (12) | (10) |
| **Female** | 41.69 | 22.61± | 43.92± | 39.18± | 38.18± | 37.12± | 37.37± |
| | | 6.91 | 32.13 | 28.68 | 27.22 | 26.37 | 24.63 |
| | | (13) | (13) | (11) | (10) | (8) | (8) |

Results shown in tables 2-6 clearly indicate that mean levels of scrum bilirubin. ALP. AST, ALT and GGT are increased after taking streptomycin, Isoniazid and pyrazinamide. In spite of highly significant increase in the level of serum bilirubin and significant increase in enzyme levels upper limits were not crossed in case of ALP and GGT while AST and ALT showed highly increased levels crossing the upper normal limit. In present study ten patients out of twenty-seven developed hepatocellular dysfunction manifested by abnormal liver function tests. One patient presented with jaundice after three months of treatment. These findings are in conformity with the findings of McDermott22 and Pembran et al.,2J.

Results shown in tables 2-6 indicate disturbed liver functions in patients taking streptomycin, isoniazid and rifampicin. A highly significant increase was observed but upper normal limits were not crossed over. Mean values of serum ALP and GGT showed rise to peak value after 2nd and 3rd months of treatment. Similar observations have been made by Girling2,1 and Ronaq et al.,"

Girdwood25 documented that rifampicin may interfere with bilirubin estimation due to its reddish colour but findings of the present study are not in agreement with this and no change in serum colour was observed in patients taking rifampicin. Treatment

of patients with streptomycin, isoniazid and thiacetazone also resulted in marked disturbance of hepatic functions, this is evident from highly significant increase in serum bilirubin and ail the enzyme levels as shown in tables 2-6. Peak values of these parameters were observed after one month of therapy. Three patients developed clinical jaundice after one month of treatment and drugs had to be withdrawn. Mean values of AST and ALT remained above normal limits throughout the treatment; these results are in agreement with Robson24.

Sex did not seem to influence the incidence of hepatotoxicity. Almost all the patients who showed derangement of hepatic function were above forty years of age. Present study suggests that abnormalities of liver function are most likely to occur within three months of treatment and less frequent monitoring thereafter should be suggested. Treatment should be immediately discontinued in patients who develop symptoms compatible with hepatic syndrome.

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