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BIOCHEMICAL STUDIES ON SOME TRYPTOPHAN METABOLITES IN PULMONARY TUBERCULOSIS

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Changes in carbohydrates[6)7)], lipids[9)], proteins[8)] and amino-acid metabolism have been described in tuberculous patients. It has been found that some indole derivatives are tuberculostatic both *in vitro* and *in vivo*[2)~5)].

Accordingly this work was directed to the study of the metabolism of some indole compounds in tuberculosis; namely serum total indoles, serotonin level in blood and urinary 5-hydroxy indole acetic acid (5-HIAA).

EXPERIMENTAL

Seventy eight patients represent the subjects of this study, 58 were pulmonary tuberculous patients having different stages of the disease, 15 cases (11 males and 4 females) with minimal lesion (stage I), 16 patients (11 males and 5 females) with moderately advanced lesions (stage II), and 16 male patients with far advanced pulmonary lesion (stage III). The classification of stages was followed according to The National Tuberculous Association of U. S. A.[18)]. Another 11 male tuberculous patients, with other associated lesions, were examined. These associated lesions were; minimal pleural effusion (3 patients), tuberculous lymphadenopathy (3 patients) and diabetes mellitus (D. M. 5 cases). Twenty normal control individuals, 15 males and 5 females, were also examined.

Fasting serum total indoles[17)], fasting blood serotonin[11)], and urinary 5-HIAA[23)], were measured before the beginning of treatment, and after 6 & 12 months from the start of treatment. All patients received the classical antituberculous treatment; streptomycin, isonicotinyl hydrazine and paraaminosalycilic acid.

RESULTS

Results are shown in the following tables (1~5).

Table 1. Tryptophan Metabolites in 20 Normal Subjects

	Serum total indoles μg/ml	Blood serotonin μg/ml	Urinary 5-HIAA mg/24hrs
Mean	12.33	0.128	0.443
St. D±	1.45	0.020	0.780
St. E±	0.32	0.006	0.203

The three indole derivatives were shown to increase in all stages of tuberculosis. Serum total indoles increase was significant in stages II & III.

Blood serotonin increase was significant in 3rd. stage. Urinary 5-HIAA increase was significant in all 3 stages.

Treatment for 6 months lowered the three indole derivatives. The levels were normalized after one year treatment. Also table 5 showed that treatment of tuberculous diabetics tends to gradually normalize the indole

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Table 2. Serum Total Indoles in Different Stages of T.B. μg/ml
Before and after treatment

	Stage I		Stage II		Stage III		After one year treatment
	Before	6 months after	Before	6 months after	Before	6 months after	
No. of cases	15	10	14	10	16	10	20
Mean value	13.61	12.65	14.92	13.55	18.40	16.07	12.53
St. D. ±	2.41	1.91	4.63	2.2	5.15	2.61	2.02
St. E. ±	2.47	0.66	1.23	0.69	1.28	0.82	1.57
P	>0.05	>0.05	<0.05	>0.05	<0.05	<0.05	>0.05

Table 3. Blood Serotonin in Different Stages of T.B. μg/ml
Before and after treatment

	Stage I		Stage II		Stage III		After one year treatment
	Before	6 months after	Before	6 months after	Before	6 months after	
No. of cases	13.00	13.00	13.00	13.00	13.00	13.00	13.00
Mean value	0.136	0.131	0.144	0.135	0.161	0.146	0.128
St. D. ±	0.056	0.028	0.040	0.038	0.042	0.040	0.030
St. E. ±	0.015	0.007	0.011	0.010	0.012	0.010	0.008
P	>0.05	>0.05	>0.05	>0.05	<0.05	>0.05	>0.05

Table 4. Urinary 5-HIAA tn Different Stages of T.B. mg/24 hrs
Before and after treatment

	Stage I		Stage II		Stage III		After one year treatment
	Before	After	Before	After	Before	After	
No. of cases	15	14	16	16	16	16	15
Mean value	2.893	2.50	4.359	3.66	5.400	3.759	2.391
St. D. ±	1.06	1.15	2.85	1.81	1.56	1.22	0.73
St. E. ±	0.27	0.30	0.714	0.45	0.39	0.03	0.18
P	>0.05	>0.05	<0.05	<0.05	<0.05	<0.05	>0.05

Table 5. Comparison between the Three Indole Levels of Pulmonary Tuberculous Patients Stage I and Pulmonary Tuberculous Patients Having Associated Lesions (Before treatment & 6 months after treatment)

Mean	Pulmonary T.B.		Pulmonary T.B. +Pleural effusions		Pulmonary T.B. +Lymphadenopathy		Pulmonary T.B. +Diabetes melitus	
	Before	After	Before	After	Before	After	Before	After
Serum total indoles μg/ml	13.61	12.65	14.08	12.80	13.30	12.00	8.81	10.06
Blood serotinin μg/ml	0.136	0.131	0.144	0.128	0.146	0.129	0.095	0.122
Urinary 5-HIAA mg/24 hrs	0.893	2.500	2.468	2.126	2.824	2.400	1.710	2.000

levels.

Discussion

The levels of tryptophan metabolites tested were generally increased in all stages of tuberculosis than the normal controls. Serum indoles were also found to be increased in tuberculosis by Stepenian[21)22)], Mastenni-

kova[16] and Abdel Kader et al.[8].

The normal levels of these three indole derivatives are rather kept constant by different specific homeostatic[12][15][19] processes namely hormonal and enzymatic. The pathological increase in the indole derivatives may be attributed to increased destruction of lung tissue proteins and their further hydrolysis into amino-acids including tryptophan and its indole derivatives. The degree of rise in the tryptophan metabolites was found to be proportional to the advancement of the disease. The increase in levels was highest and always statistically significant in stage III.

Another contributing factor for biochemical aetiology of this rise may be hormonal imbalance as well. Insulin overactivity was found to increase plasma tryptophan by releasing it from the liver[24]. This insulin overactivity was found to be present in non-diabetic tuberculous patients[6][7]. Abdel Kader, et al.[6][7] found a persisting hypoglycaemia after glucose tolerance test in tuberculous patients which was attributed to insulin overactivity. Insulin overactivity would evoke tryptophan release from the liver and accordingly affects its increase in blood. Suprarenal cortical insufficiency was found in tuberculous patients[10][14][20].

Abdel Aziz et al.[1] found diminished level of cortisol in blood and no more secretion on ACTH administration. Glucocorticoids were found to induce tryptophan pyrrolase in the liver[13]. The latter is a key enzyme for the catabolism of tryptophan leading to destruction of the ring and subsequent change in indole metabolism.

Pulmonary tuberculous diabetics showed highly significant lower levels of all three indole compounds tested than in non-diabetic tuberculous patients having the same extent of pulmonary lesion or having the same extent of the disease associated with minimal pleural effusion or tuberculous lymphadenopathy. This significant lower levels of the three indole compounds in diabetic tuberculous patients may probably be due to the relatively more potent glucocorticoids in diabetics where the antagonistic action of insulin is decreased. So glucocorticoids might be more active in potentiating the tryptophan pyrrolase leading to more destruction of indole ring and hence lowering of indole ring-containing compounds.

Treatment of non-diabetic patients with traditional anti-tuberculous drugs, caused gradual lowering of the serum total indole, blood serotonin and urinary 5-HIAA. After 6 months of treatment the three levels were lowered. After one year treatment normalization of all three levels occurred; which ran parallel with the clinical response to treatment. This finding could possibly be attributed to inhibition of tissue breakdown, with concomitant tissue repair and shift of the biochemical mechanisms towards normal hormonal control.

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