TUBERCULOSIS AS A COMPLICATION OF DIABETES MELLITUS

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During the nineteenth century, when the incidence of and the mortality from pulmonary tuberculosis were much greater than at present, a large percentage of sufferers from diabetes mellitus died of coma, and most of those who survived this died of pulmonary tuberculosis. Publications towards the end of that century indicate that 50% of diabetics succumbed to pulmonary tuberculosis. For example, Windle (1883) reported that of 333 diabetic cases coming to necropsy half had active tuberculous lesions. Naunyn (1906) found pulmonary tuberculosis in 264 out of 622 diabetics at necropsy. Despite the passage of the years, and even after the advent of insulin in the treatment of diabetes, the incidence of tuberculosis in cases of diabetes mellitus has remained significantly high. This was shown by Banyai (1931), who concluded from the available literature that pulmonary tuberculosis was three times commoner in patients suffering from diabetes mellitus than in the general population. These observations were confirmed by Root (1934) when he investigated the incidence of tuberculosis in 1,651 cases of diabetes. The frequent combination of these two diseases is, then, an accepted fact.

Root (1934) maintains that, despite the decline in the mortality from pulmonary tuberculosis in the general population, the morbidity from tuberculosis among diabetic patients is steadily increasing. This would indicate that the longer the patient has diabetes the greater is the possibility that he will ultimately develop tuberculosis. In view of this, and on account of an apparent increase in the incidence of pulmonary tuberculosis among patients attending a diabetic clinic, it was considered important to review the subject in more detail locally.

Review of a Series of Cases

This paper describes 17 cases of diabetes mellitus and tuberculosis encountered during the supervision of 717 patients suffering from diabetes over the period 1932–46. Among these were 60 deaths—11 from pulmonary tuberculosis after 1936, with eight such deaths during the war years. A review in 1945 showed that of 657 patients alive at that time 239 were males and 418 females; 12 were under 15 years and 236 between 15 and 45 years of age; and 387 were under insulin treatment. The cases considered here are summarized in Table I.

In all cases the patients were definitely diabetic, and the diagnosis of tuberculosis was verified by isolation of the tubercle bacillus. In 11 cases the diabetes preceded the onset of tuberculosis by periods of up to 13 years, while in the other six cases the diagnoses were made simultaneously. Fourteen patients were males and three females. The diabetic condition was detected on an average at 40.18 years of age, and the tuberculosis at 44.23 years. In the greater percentage of cases the tuberculosis made its appearance in the fifth decade, whereas the majority of cases of tuberculosis in the general population occur in the second or third decade. This suggests that tuberculosis developed on account of pre-existent diabetes mellitus. That tuberculosis is a complication of severe diabetes will be seen from Table II. These observations agree with those of Himsworth (1938). Only those cases in which the diabetes preceded the tuberculosis have been used in compiling these figures.

TABLE I

Case No.	Sex	D.M. Diag.		Control of D.M.	Tb. Diag.		Stage of Tuberculosis	Signs Suggesting Tb.	Remarks
		Age	Date		Age	Date			
1	F.	33	1933	Fairly good	46	5/46	Fibro-caseous bilateral apical	Nil	Died of coronary thrombosis at 46
2	M.	43	8/43	Poor	44	5/44	Infiltrative L. apex	Yes	Died 7/45
3	M.	17	11/32	,,	26	5/41	Infiltrative with cavity R. apex—extensive	,,	Died 4/42
4	M.	32	6/35	Fairly good	35	2/38	Tb. meningitis	,,	Died 15 days after diagnosis
5	M.	39	7/43	Fair only	42	5/46	Extensive filtration L.	,,	Condition improving. Diabetes under control
6	M.	12	1935	Repeated comas	20	12/43	Fibro-caseous, with cavitation L. apex. Infiltration R.	,,	Died 4/44. Bronchopneumonic spread
7	M.	63	8/41	—	63	8/41	Fibro-caseous bilateral apical	,,	Died 2/44. Bronchopneumonic spread
8	M.	51	5/39	? Good	55	9/43	Fibro-caseous bilateral, with cavitation	,,	Died of pulmonary embolism from phlebothrombosis L. leg 9/43
9	M.	48	1938	Fair only	55	2/45	Fibro-caseous bilateral, with cavitation	,,	Condition improving. Diabetes under good control
10	M.	29	7/33	Fairly good	41	1/45	Infiltration apical L., with cavitation	Nil	Patient died 9/46. Coronary thrombosis. Chest condition improving
11	M.	65	8/39	—	65	8/39	Fibro-caseous with cavitation—L.	Yes	Died 12/40
12	F.	46	4/45	—	46	4/45	Infiltration apical R., with cavity L.	,,	Condition improving. Diabetes under good control
13	M.	40	12/37	Unknown	46	4/43	Fibro-caseous bilateral, extensive, with cavitation	,,	Condition improving. Diabetes under good control
14	F.	41	10/36	—	41	10/36	Bilateral fibro-caseous, with bronchopneumonia	,,	Died 11/36
15	M.	37	1928	Unknown	39	4/30	Bilateral infiltration	,,	Fairly well
16	M.	48	1/33	—	48	1/33	Infiltration with cavitation R.U. and M. lobes	,,	Under good control
17	M.	39	10/36	Fair only	40	11/37	Tb. bronchopneumonia R. lung	,,	Died 12/37. Skiagram of chest 10/36 showed no abnormality

TABLE II

	Cases
Mild, requiring less than 20 units of insulin daily	2
Moderate, requiring 20–40 units of insulin daily	1
Severe, requiring over 40 units of insulin daily	8

All except two patients had symptoms suggestive of tuberculosis some months before the verification of the presence of a tuberculous lesion. Most of those complained of productive cough with loss of weight. Many gave a history of recurrent colds, or perhaps of a head cold which was persistent. Physical signs of pulmonary tuberculosis were present in 14 of the cases at the time of diagnosis.

Table III shows an analysis of the extent of the tuberculous process when first diagnosed and the course of the disease in these cases. The most striking feature is the number of patients with the disease already far advanced at the time of diagnosis. There are several possible reasons for this. The patients were almost without exception under poor or uncertain control, accounting possibly for their greater susceptibility, and also perhaps for the rapid spread

of the disease. The majority of the affected cases were most irregular attenders, and adequate checking was almost impossible. The early symptoms of tuberculosis simulate those of diabetes so that errors in diagnosis are easy. And, finally, of course, the physical signs of pulmonary tuberculosis are seldom more than minimal until the disease is well advanced. In six patients the pulmonary disease remains arrested. In point of fact, seven are shown as arrested in Table III, but of these one died of coronary thrombosis.

TABLE III.—*(Excluding the Patient who died from Tuberculous Meningitis)*

	Unilateral		Bilateral		Total
	Without Cavitation	With Cavitation	Without Cavitation	With Cavitation	
Cases ..	2, 5	3 (A.P. failed), 10, 11, 16, 17	7, 15	1, 6, 8, 9, 12 (A.P. failed), 13, 14 (A.P.–Tb. empyema)	16
Stationary, arrested	5	10, 16	15	9, 12, 13	7
Progressive	—	11, 17	3	2 (A.P. failed), 6, 7, 14	7
Death ..	—	10 (died coronary thrombosis), 11, 17	3	1 (died coronary thrombosis), 2, 6, 7, 8, 14	10

Discussion

The patient under poor diabetic control is more prone to the complication of tuberculosis. Root (1940) showed that patients who have suffered from coma are the most likely to develop pulmonary tuberculosis. Moreover, he has shown that patients on a free diet yield a far greater percentage of tuberculosis than those subject to careful dieting. It should be remembered, however, that the patients on free diet are on the whole less well-off economically. Consequently, this introduces an environmental element which renders direct comparison between the two groups an unjustifiable procedure. Conversely, Himsworth (1938) in a series of 300 diabetics under good control found that only two developed tuberculosis. These facts are largely borne out in the present series of cases. On the experimental side Steinbach and his colleagues (1935) have produced some evidence to show that dogs rendered diabetic by removal of the pancreas were less resistant to a known dose of tubercle bacilli than a control group of healthy animals. This suggests that the increased susceptibility of the diabetic dogs to the tubercle bacillus may be due to faulty carbohydrate metabolism.

This fact forms the basis of the most frequently accepted hypothesis, which is that hyperglycaemia favours the growth of the tubercle bacillus in the body. Joslin and others (1940) stated that this is due to the hyperglycaemia impairing the normal reparative tissue processes and the resistance to infection—statements which are not accorded universal agreement (Richardson, 1933, 1935). Long (1930) suggested that the primary cause was an upset in fat metabolism with an increased availability of glycerin, which, of course, is one of the best nutrients for acid-fast organisms.

The fact that diabetic coma often leads to the appearance of pulmonary tuberculosis or a flare-up of an already existing lesion is thought to be partly attributable to an over-supply of nitrogenous compounds which favour the growth of tubercle bacilli. In this connexion Keeton (1941) brought forward the suggestion that tissue resistance is lowered by acidosis, and Smithburn (1935) demonstrated experimentally that the virulence of the tubercle bacillus is increased by increasing the acidity of the culture. Furthermore, Root (1934) emphasized the possible importance of the reticulo-endothelial system. In poorly controlled diabetics the cells of this system are often found to be distended with fat, and it is recognized that any interference with these cells causes a decrease in the defence and resistance of the body.

There is another possible factor which has found much favour in recent American literature. It is well known that deficiency of vitamin A leads to specific changes in the mucosa of the respiratory system characterized by atrophy of the epithelium with associated disappearance of the ciliary function, proliferation of the basal cells, and replacement of the original epithelium by stratified keratinizing epithelium. That vitamin A deficiency exists in diabetes has been reported by Brazer and Curtis (1940) and confirmed by Freston and Loughlin (1942). Kimble, Germek, and Sevringhaus (1946), investigating the vitamin A and carotene metabolism in 116 unselected diabetics, found that 49% of the 59 males and 47% of the 57 females gave values for one or both substances outside the normal range. The predominant type of deviation in the series was low vitamin A and low carotene, and this was particularly noticeable among the older patients and those with infections. A control group of normals, however, also showed variations similar to the above, suggesting that hypovitaminosis A is not likely to be the sole factor, though it might easily be an accessory one. Vitamin A is normally stored in the liver, and its metabolism, as pointed out by Schneider and Widman (1944), is closely coupled with glycogen metabolism in the liver. With the disappearance of hepatic glycogen in uncontrolled diabetes it is obvious that the synthesis of vitamin A will break down with the appearance of hypovitaminosis A.

Prognosis of the Combined Lesions

Study of the mass of literature on the course of pulmonary tuberculosis in diabetic cases discloses a gloomy picture, and without doubt the prognosis is worse than in uncomplicated pulmonary tuberculosis. This may be attributed to (1) the lowered resistance, defence, and repair of the tissues of the poorly controlled diabetic relative to the tuberculous process and its spread; (2) the late stage at which the complication is usually discovered; and (3) complications such as arteriosclerosis, chronic nephritis, and coronary and myocardial degenerations. The prognosis depends on the extent of the tuberculosis when first detected. Since, in the past, the diagnosis has not been established until late it is not surprising that the mortality rate has been high. Lorenzen (1931), for example, reported 143 patients with the combined diseases, and of these only 16 lived more than three years after the tuberculosis was discovered. More recent papers give results which are less pessimistic, and Mark, Mosenthal, and Liu (1942) go so far as to state that it is their impression that with early diagnosis and adequate and careful control of the diabetes the prognosis of the tuberculosis approaches that in the non-diabetic. Certain other writers agree with this.

With regard to the present series 11 out of 17 patients are dead. Of these seven died within the first year, three within two years, and one within three years of the complication being recognized. In two cases the cause of death was coronary thrombosis, and in these cases the chest condition was stationary. In another, death was due to pulmonary embolism—a fortunate escape for a patient whose condition was irretrievable. Of those still alive three are in the critical phase of the first two years, which are well recognized as carrying the highest morbidity.

Treatment

Prophylactic.—The earlier the diagnosis the better the prognosis, and therefore continual anticipation of the

possibility of tuberculosis is to be strongly advocated. A diabetic patient beginning to show unusual features, and particularly in our experience recurrent colds or persistent head colds, should be submitted to *x*-ray examination of the chest; a search for tubercle bacillus in sputum and fasting-stomach contents should be made, and the blood sedimentation rate ascertained. All patients suffering from poorly controlled diabetes, due either to social circumstances or to therapeutic difficulties, should be submitted to radiological examination of the chest every six months, and all other diabetic patients at yearly intervals. Failure to diagnose the combined lesions in the early stages is due to lack of diagnostic consciousness, improper interpretation of symptoms directly or indirectly referable to the chest, and incomplete diagnostic investigation.

Management of Cases.—(*a*) *Of the diabetes mellitus:* This has evolved through the same changes which have characterized the general trend in the treatment of the disease. Fishberg (1932) stated that patients on low-calorie diet certainly lose their glycosuria, but at the same time there is a rapid progress in the pulmonary tuberculosis. As a result of this a high-calorie diet with moderately high carbohydrate intake is generally advocated. According to Root (1940) the standard diet should consist of carbohydrate, 150 g.; protein, 80 g.; and fat, 100 g.; and a diet to increase weight should include carbohydrate, 250 g.; protein, 87 g.; and fat, 120 g. The advantages of high carbohydrate intake have been summarized by Keeton (1941) as follows: (1) the appetite is often capricious and carbohydrate is probably more appetizing; (2) fats are not well tolerated and resultant diarrhoea is prone to occur; and (3) the ketosis which is so frequently associated with the infection is best counteracted by high carbohydrate intake. Adequate vitamin concentrates should be given if indicated. The indications for the use of insulin are the same as in uncomplicated diabetes. Some authorities (Mosenthal and Mark, 1941) state that the clinical course of the combined lesions is more favourable with protamine-zinc-insulin. On the criteria for control there has been much controversy, but essentially it does not differ from that of the uncomplicated case.

(*b*) *Of the Tuberculosis.*—The indications and contra-indications for collapse therapy are the same for diabetics as for non-diabetics. Owing to the high percentage of cases showing exudative and fibro-caseous lesions, the accomplishment of an artificial pneumothorax is often unsuccessful and is frequently complicated by pleural effusion and empyema. On the other hand, patients who tolerate artificial pneumothorax well can be considered for ambulatory treatment as in uncomplicated tuberculosis.

Since most cases come under treatment late in the disease, it is not surprising that conservative treatment is the only possible form in many cases. Of this series only four cases were subjected to artificial pneumothorax. In three of these it had to be abandoned because of failure to collapse the affected area of the lung, and the fourth was complicated by tuberculous empyema.

Summary

Seventeen cases of diabetes mellitus complicated by tuberculosis are described.

Poorly controlled diabetes predisposes to tuberculosis and causes a rapid spread of the disease.

This may be due to a complexity of causes.

A high percentage of diabetic patients acquiring tuberculosis are not adequately treated until the disease is far advanced. This calls for a revision of the diagnostic approach to the problem by routine radiography and sputum examinations.

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A CASE OF VITAMIN C DEFICIENCY

BY

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The following case history presents certain unusual features of vitamin C deficiency and seems to be worthy of record.

Case Report

The patient, a spinster aged 38, employed as a housekeeper, was admitted on June 24, 1946, having vomited blood on three occasions during the previous two days. She volunteered a history of ulcer symptoms extending over six years. These included pain half an hour after meals, which was relieved by taking alkaline powders, and a fear of eating. The symptoms were periodic but had been present during the greater part of the preceding six years. She had adhered to a strict ulcer regime and had refrained from taking fruit and vegetables. A barium meal examination had been made in 1942, but had failed to reveal any abnormality in the gastro-intestinal tract. There was no history of melaena or previous haematemesis even on direct questioning. The bowels were regular and there was apparently no disordered function of the genito-urinary system, though a nephrectomy for tuberculous kidney had been performed in 1928.

The condition of the patient on admission was one of collapse and exsanguination (haemoglobin, 33%—4.6 g. %) necessitating an immediate transfusion. After two bottles of blood had been given, her general condition was greatly improved, but the haemoglobin was still only 33%. A further slow transfusion was started, four and a half bottles of blood being given over 36 hours, after which the haemoglobin was only 39%. Twenty-four hours later another transfusion was started, three bottles being given, after which it was found that the haemoglobin had fallen to 28%. On July 1 the patient vomited 1/2 oz. (14 ml.) of altered blood. In view of the dangerously low haemoglobin three more bottles of blood were given and the haemoglobin was raised to 37%.

The patient had now been in hospital for 10 days, and despite the transfusion of 13 pints (7.4 l.) of blood, the haemoglobin remained virtually unchanged. There had been no reactions to any of the transfusions; no rigors, no haemoglobinuria, and no sign of jaundice developing to suggest that blood was being lost through haemolysis due to any incompatibility. The stools were black from melaena but were well formed—not loose as though there was severe bleeding from the supposed ulcer at any time. During the 10 days that the patient had been under