DIABETIC COMA AND PULMONARY TUBERCULOSIS.

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The susceptibility of the diabetic to the development of pulmonary tuberculosis has occasioned comment by all students of the diseases. The outstanding facts have been (1) that diabetes precedes the development of the active tuberculosis in the great majority of cases. (2) That forms of turberculosis other than pulmonary do not occur with this heightened frequency. (3) That the development of tuberculosis seems to occur chiefly in cases of uncontrolled diabetes, especially coma cases, and its course is greatly affected by the degree of successful treatment of the diabetes.

Recently in reviewing 245 cases it appeared that although tuberculosis mortality rates are falling in the community at large, the incidence of tuberculosis among diabetics is increasing in spite of the lessened frequency of contact. One needs to consider that diabetes is steadily increasing in importance because of the increasing number of older people in the community. In fact, in 1933 there were 22 cities in the country in which the diabetic death rate exceeded the death rate from pulmonary tuberculosis. In Massachusetts tuberculosis hospitals, in April of this year, one in every 100 patients was a diabetic, a proportion three times as great as the proportion of diabetics in the State at large.

It appears that the study of diabetic patients with tuberculosis affords a rich field for the study of metabolic and chemical conditions as they affect the development of tuberculosis. The greatest deviations from normal occur in diabetic coma, formerly universally fatal, but now, thanks to insulin, both preventable and curable. It is now for the first time possible to observe the aftercourse of cases of coma for long periods. This paper reports 25 cases of diabetic coma later developing pulmonary tuberculosis of the adult type.

INCIDENCE. Coma and tuberculosis frequently occur in the same patient, contrary to the old idea that coma was rare in the

tuberculous diabetic. Coma appears repeatedly in the histories of tuberculous diabetics. Hirsch-Kauffmann describes the development of tuberculosis in a 16-year-old girl who had had coma more than once. Labbé *et al.* describe a woman whose diabetes began in pregnancy at 21 years of age. After two attacks of coma, pulmonary tuberculosis involved both lungs, requiring double pneumothorax. Rosenberg's case, also treated by pneumothorax, after diabetes of 20 years' duration, developed a fresh exudative process. Acidosis was severe, as indicated by urinary ammonia of five grams and beta-oxybutyric acid of 32 grams. Most striking is Bertram's statement that seven out of 13 deaths following recovery from coma and discharge from the hospital were due to pulmonary tuberculosis. Among 76 cases treated at the New England Deaconess Hospital, with coma so severe as to be accompanied by a lowering of the plasma CO_2 combining power below 20 volumes per cent, six or eight per cent developed active pulmonary tuberculosis within three years. These cases left the hospital prior to February 1, 1929. In later coma series sufficient time has not elapsed to allow a statement, but we are now checking up the later cases by routine X-Ray and can report later. The above does not fairly represent the frequency of acidosis and tuberculosis in the same patient. In addition to the 25 shown in the table 16 cases had coma at home or in other hospitals. Among our 245 cases of pulmonary tuberculosis reported in January, 1934, 37, or 15 per cent, are known to have had coma. This is five times the incidence of coma in diabetes routinely admitted to the New England Deaconess Hospital. In ten cases coma was terminal. Ten per cent of 500 living diabetic children have had coma at the Deaconess, to which may be added an unknown number who may have had coma at home. This comparison is not entirely fair, since many of the 245 tuberculous cases lived in the period before the discovery of insulin, when coma caused from 60 to 75 per cent of all diabetic deaths. The fact that in only six out of 62 deaths, prior to insulin, was coma given as one of the causes of death, probably indicates that the patient with advancing tuberculosis is less likely to die of coma than of tuberculosis. This difference emphasizes again the tendency of diabetes to encourage tuberculosis and the opposite effect of progressing tuberculosis upon the incidence of diabetic coma.

AGE AND SEX. Males numbered 13 and females 12. The ages at onset of diabetes varied from 6.7 to 66.2 years. Nine cases developed diabetes before the 20th year and 11 developed tuberculosis before the 30th year. Acidosis was observed at periods varying from a few months to 17 years after the onset. Only one case was observed at autopsy. Fourteen are dead. Of these deaths four occurred in coma and one of carcinoma. Nine are living, of whom five have had diabetes eight to 12 years, with onset in childhood.

In four cases was family exposure known, and in a fifth, after X-Rays, six members of the family were negative. A positive sputum was obtained from his employer.

CHEMISTRY OF THE BLOOD. The average blood sugar on the first days of acidosis in 36 analyses was 0.40 per cent, whereas the average blood sugar in the last 42 cases of coma at the Deaconess Hospital averaged 0.47 per cent. Similarly the average plasma CO_2 in 28 cases was 14 volumes per cent in contrast to the average of 42 non-tuberculous coma cases of 12 volumes per cent. The degree of acidosis was the same in both groups. In eight instances the non-protein nitrogen was above normal. Renal function was so seriously disturbed in Case No. 4232 that anuria was present for 24 hours and the non-protein nitrogen of the blood rose to 139 milligrams.

LIPEMIA. Lipemia is an evidence of tissue destruction in acidosis as well as of failure to utilize fat ingested. It is a common feature of diabetic coma. Thus, in this series, Case No. 2448, age 17.9 years at onset of diabetes, had a creamy plasma in acidosis at the age of 20 years and again lipemia with plasma cholesterol at 750 mgs. at the age of 23 years. One year later, when tuberculosis was far advanced, the plasma cholesterol fell below normal. Similarly Case No. 4232, female, during the years from 17 to 21, on several occasions was found to have an increase in the plasma cholesterol. She developed cataracts, arteriosclerosis and pulmonary tuberculosis. An abnormally elevated cholesterol is not *per se* so significant, but it indicates uncontrolled diabetes. As we understand the metabolic disturbance of diabetes, this implies overproduction of glucose from protein and fat not only derived from ingested food, but from body tissue.

MULTIPLE COMA. Repeated attacks of coma indicate prolonged periods of uncontrolled diabetes and often of acidosis. Variations in intensity occur with acute periods of rather brief duration.

TABLE II.
MULTIPLE ATTACKS OF COMA.

Case No.	Sex	Age at Onset Tbc.	Number of Times in Coma	Result Living or Dead	Cause
2448	M	19.6	5	dead	tbc.
2687	F	30.0	4	dead	tbc.
4232	F	22.0	4	living	
4287	F	59.0	2	dead	coma
8089	M	49.6	2	dead	tbc.
6287	F	16.8	6	living	
3750	F	38.7	3	dead	tbc.
4261	F	19.5	3	living	
7047	F	16.5	4	living	
7210	F	72.4	2	living	

In ten instances multiple attacks of coma occurred, six in one case, five in another, four in two cases, three in two cases, and two in the remaining two cases. In such patients one can be sure that other periods of less severe acidosis occurred, and that control of the diabetes was constantly lacking.

TYPES OF TUBERCULOSIS. Primary infection apparently occurs in childhood, in diabetics, with the usual incidence. Forty-seven per cent of diabetic children had positive Mantoux tests. In Cases 6287 and 5932, for example, routine chest films showed calified tracheobronchial glands, and in Case 4763 calcified abdominal glands from one to four years before the pulmonary tuberculosis developed. Films taken every four to six months, in Case 6287, enabled the site of the first minimal lesion to be definitely placed just below the right clavicle. The lower lobes were involved in four cases. Pleurisy, with effusion, occurred in Case 7210, six months after coma, at the age of 73 years. Miliary tuberculosis caused the death in Case 2687. Extensive exudative processes occurred in five cases. Cavitation was recognized in seven. Details as to the type are lacking in five cases.

Case No.	Sex	AGE: Onset of D.M.	AGE: Onset of Tbc.	AGE: At First Coma	Date Coma	Blood: Sugar	Blood: Plasma CO_2 Combining Power	Blood: Alveolar Air Co_2 mm.Hg.	Blood: Insulin Units	Results: Living or Dead	Results: Age Years	Results: Cause of Death
2448	M	17.9	19.6	18.8	1923	0.33	21	17	80			
					1923	0.27	31	31	125			
					1926	0.50	32	..	70			
					1928	0.51	34	..	40	Dead	24.1	Coma and Tuberculosis.
2687	F	24	30	24.3	1922	0.17	..	31	0			
					1922	...	..	29	0			
					1922	0.45	31	17	14			
					1923	0.23	25.7	18	75	Dead	30.1	Miliary Tuberculosis.
3143	M	16	18	17.5	1924	0.50	20.1	0	170	Dead	19.1	Pulmonary Tuberculosis.
3176	M	41	53	58.6	1923	0.31	34	30	15	Dead	56.6	Tuberculosis.
4232	F	14	22	17.0	1924	0.49	11	2	315			
					1925	0.35	..	23	107			
					1926	0.29	17	..	90			
					1928	0.29	14	..	70	Living	27.0	
4287	F	54	59	58.9	1923							
					1924							
					1924	0.40	..	..	110	Dead	63.2	Coma.
4763	F	16	22	16.0	1925	0.36	19	19	40	Living	23.3	
5632	M	35	34	35	1926	0.80	12	..	240	Dead	35.1	Coma, Nephritis, Laryngeal Tbc.
5932	M	14	19	19	1931	0.71	9	..	380	Living	21.5	
6511	F	48	50	50	1927	0.56	14	..	120	Dead	55	Recurrent cancer breast.
8435	F	40	20±	44	1932	0.74	3	..	510	Living	46.1	
9354	M	42	43	43	1930	0.46	12	..	125	Living	45.3	
11006	F	19	19	19	1932	0.60	2	..	520	Living	21.0	
1577	M	20.8	24.9	25.1	1922	0.27	12	..	..	Dead	25.2	Tuberculosis.
3775	M	49.5	63.8	62.5	1924	0.25	28.2	29	13	Dead	69.7	Tuberculosis.
8089	M	37.5	43.6	43.6	1929	0.42	..	..	90	Dead	44.4	Tuberculosis, Coma.
7486	M	26	36	33	1929	0.54	11	..	235	Living	37	

1560	M	24	25	25	1919	0.33	..	32	..	Dead	25.2	Pulmonary Tuberculosis.
4626	M	48	50	50	1925	0.27	..	38	20	Dead	50.2	Pulmonary Tuberculosis.
6121	M	45.7	48+	48	1927	0.14	..	..	50	Dead	48.7	Pulmonary Tuberculosis.
6287	F	6.7	16.8	6.7	1927	0.74	21	29	85			
					1928	0.46	19	..	60			
					1928	...	18	..	95			
					1929	0.20	20	..	5			
					1929	0.62	13	..	140	Living	18.8	
4261	F	9.8	19.5	10.8	1931	0.30	14	31	74	Living	20.1	
3750	F	28.5	38.7	34.8	1929	0.39	2	2	230	Dead	39.7	Tuberculosis.
12385	F	9.4	14.4	11.4	1931	...	..	..	..	Dead	14.7	Tuberculosis.
7047	F	10.9	16.5	11.2	1928	0.40	14	..	60	Living	16.9	
7210	F	66.2	72.4	69.5	1931	0.52	9	..	335	Living	72.5	

DISCUSSION. The high incidence may not be explained as due to chance. The native resistance is not low as shown by (a) autopsy examinations in 120 cases.* These show abundant evidence of healing; (b) deaths from tuberculosis in diabetic children were made; (c) calcified glands are as frequent in diabetics as in non-diabetics. Tuberculosis develops and progresses chiefly in uncontrolled cases. However, coma produces chemical conditions favorable to the cultural needs of the tubercle bacillus, namely, excessive protein destruction with amino acid nitrogen set free and disturbance in fat metabolism with probably an excessive amount of glycerol.

These findings recall the experiments of Long.† He says that "on the theory that glycerol might be a controlling chemical factor on the growth of the bacillus within the body as well as outside, an attempt was made to decrease the resistance of a relatively refractory animal by increasing its glycerol content, and to enhance that of a susceptible animal by decreasing any naturally existing glycerol in its tissues. For the first purpose glycerol was injected intravenously into infected rats several times a day for a period of two months; similarly infected, but non-treated rats, served as controls. For the second purpose palmitic acid was fed in large quantities to infected guinea pigs, on the theory that in conformance with the low mass action, an excess of fatty acid would force the synthesis of any glycerol freed from fat in its metabolism back into the forms of neutral fat. The results were clear-cut as far as they went. The rats treated with glycerol developed a more rapid and extensive pulmonary tuberculosis than did the non-treated control rats. The guinea pigs treated with palmitic acid developed less pulmonary tuberculosis and of a more sclerotic type than the untreated control rats."

One conclusion is that diabetic children and young adults must be aggressively treated with insulin and diets, so as to control the diabetes. For this purpose the blood sugar and lipoids should be followed as fundamental guides. Tuberculin testing and repeated X-Rays are necessary, especially during adolescence, if incipient cases are to be discovered.

*Root, H. F., Association of Diabetes and Tuberculosis, N. E. Jour. Med. 210: Nos. 1, 2, 3, and 4, 1934.

†Long, E. R.: Arch. Path., 6, 1142, 1928.

First observations have a notorious tendency to be strongly positive, but incapable of repetition. Possibly a later report will not show so high an incidence of tuberculosis in coma cases. Indeed, it should not, if we consider the fact that the dietary management of later cases is so radically different. The development of tuberculosis should be reduced in later series for two reasons:

(a) Whereas in the majority of this series, old types of diet with relatively little carbohydrate and high fat were being used, in ten cases with active pulmonary tuberculosis treated during 1931 and 1932, the average diet was as follows: carbohydrate 157 grams, protein 83 grams, fat 116 grams, calories 2209.

(b) Realizing the danger, far greater efforts are being made to avoid acidosis and to maintain weight. Follow-up of coma cases by repeated X-Ray examinations is being carried out. Cases discovered with minimal lesions should be arrested. Three such cases, now under observation, have shown no progression in two years.