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LESSONS FOR FUTURE TREATMENT FROM 472 FATALITIES IN DIABETIC CHILDREN*

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Our diabetic children are living a great deal longer than formerly, yet they still die prematurely and as a rule unnecessarily. We were much encouraged to learn that the average duration of diabetes in the 135 children who succumbed in 1944-9 exceeded the average duration in those dying in the previous six-year period, 1937-43, by approximately eight years, and that they were eight years older when they died. However, we were much discouraged to learn that tuberculosis and coma played a far more important part in mortality than among all our cases, young and old. In fact, these two preventable complications caused 21.5% of the deaths. Furthermore, an analysis of the cardiorenal-vascular group, which accounts for 56.3% (revised 59.3%) of the deaths, showed 37% (revised 51.9%)

age, up to the end of 1949, 472 were dead, 2,381 living, and only 20 untraced at January 18, 1950. This table is compiled in conformity with all our previous records. It is based upon causes of death reported by the family physician or recorded on death certificates. Table II, discussed in detail later, gives what we consider a more accurate classification of causes of death, because this is derived from a detailed reinvestigation of the last illness and the utilization of ante-mortem records. These figures appear in the text as revised percentages. The changes in diagnosis relate almost exclusively to the cardiorenal-vascular group. Justification for such changes and a few others is mentioned below but cannot be explained in each instance because of lack of space.

TABLE I.—*Causes of Death of Child Diabetics. Number and percentage of Deaths from Selected Causes by Eras of Treatment. Experience of E. P. Joslin, 1898 to Date**

Causes of Death	Pre-insulin Era 1898-6/8/22		Insulin Era							
			Banting 7/8/22-31/12/36		Hagedorn 1/1/37-31/12/43		Chas. H. Best 1/1/44 to Date		Total 1898 to Date	
	No.	%	No.	%	No.	%	No.	%	No.	%
Diabetic coma, primary	135	86.0	56	56.6	22	27.2	13	9.6	226	47.9
Cardiorenal-vascular, total .. .	1	0.6	5	5.1	14	17.3	76	56.3	96	20.3
Arteriosclerotic	—	—	2	2.0	14	17.3	76	56.3	92	19.5
Cardiac	—	—	—	—	3	3.7	21	15.6	24	5.1
Angina pectoris or coronary diseases ..	—	—	—	—	2	2.5	14	10.4	16	3.4
Nephritis	—	—	2	2.0	10	12.3	50	37.0	62	13.1
Apoplexy	—	—	—	—	1	1.2	3	2.2	4	0.8
Gangrene	—	—	—	—	—	—	2	1.5	2	0.4
Other circulatory and rheumatic heart diseases	1	0.6	3	3.0	—	—	—	—	4	0.8
Infections:	10	6.4	23	23.2	20	24.7	10	7.4	63	13.3
Respiratory	7	4.5	10	10.1	5	6.2	5	3.7	27	5.7
Kidney	—	—	—	—	1	1.2	3	2.2	4	0.8
Others	3	1.9	13	13.1	14	17.3	2	1.5	32	6.8
Tuberculosis	—	—	8	8.1	8	9.9	16	11.9	32	6.8
Cancer	—	—	—	—	—	—	1	0.7	1	0.2
Accidents	1	0.6	2	2.0	5	6.2	6	4.4	14	3.0
Suicides	—	—	—	—	1	1.2	2	1.5	3	0.6
Other diseases and conditions .. .	9	5.7	5	5.1	9	11.1	7	5.2	30	6.4
Unknown	1	0.6	—	—	2	2.5	4	3.0	7	1.5
All causes	157	100.0	99	100.0	81	100.0	135	100.0	472	100.0

* Deaths reported up to January 18, 1950.

to be renal. The future holds even greater promise for diabetic children, because we believe not only that the number succumbing to tuberculosis and coma can be reduced but that progress can be made towards decreasing the large number of deaths now resulting from complications in the kidney. A similar optimistic view has come from Boulin's clinic.

In Table I the causes of death of 472 children are recorded in successive periods from 1898 to 1949. Of the 2,873 diabetic children seen, with onset before 15 years of

It is true that the incidence of deaths due to diabetic coma has steadily dropped from 86% in the pre-insulin era to 9.6% since 1944, while the frequency of cardiorenal-vascular disease has steadily risen from 0.6% to 56.3%.

Inspection of the cardiorenal-vascular group discloses that only two cases of renal disease were recorded prior to 1937, but recently the figure has risen to 37%. Angina pectoris or coronary disease, likewise, did not appear until 1937, but since that time has risen from 2.5% to 10.4%. Apoplexy was observed only once among these children before 1944 and in only three cases since that time. As for gangrene, only two deaths were noted among the total number.

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Fatal infections rose from an incidence of 6.4% before insulin to a peak of 24.7% in 1937-43, but since the introduction of specific chemotherapeutic agents and antibiotics they have fallen to 7.4%.

The children lived for so short a time prior to the discovery of insulin that none was recognized as dying from tuberculosis until the period 1922-36; and, indeed, until this present detailed follow-up of all our cases was made we really did not appreciate that since the use of insulin the deaths from this cause were as high as 8.1% from 1922 to 1936, 9.9% from 1937 to 1943, and 11.9% from 1944 to 1950.

Deaths before 1944 are really "water over the dam," but there is plenty to discuss about the most recent deaths.

Causes of Death of Juvenile Diabetics, 1944-9

A comprehensive review of the ante-mortem clinical records of the 135 patients whose deaths occurred in 1944-9 has just been completed (Table II). This detailed study was

TABLE II.—*Revised Table of Causes of Death of Juvenile Diabetics, 1944-9, Based on Ante-mortem Clinical Records*

Causes of Death	No. of Cases	%
Diabetic coma, primary ..	12	8.8
Cardiorenal-vascular:		
Cardiac	8	5.9
Nephritis	70	51.9
Apoplexy	2	1.5
Infections	8	5.9
Tuberculosis	15	11.2
Cancer	1	0.7
Accidents:		
Suicide	1	0.7
Others	6	4.5
Miscellaneous	5	3.7
Unknown	7	5.2
Total	135	100

very revealing, and was particularly informative in those 76 cases (Table I) in which death was attributed primarily to cardiorenal-vascular causes, of which only 50 were recorded as renal. There were 13 such deaths assigned to cardiac disease because of statements on death certificates. However, we have definite evidence that severe renal diseases had existed for many years before the patients' sudden exitus. Most probably this was quite unknown to the physician signing the death certificate, for he may never have seen the patient before the terminal incident or not even until after death.

Two of the deaths reported on the certificate as due to previous gangrene were really due to advanced renal disease. Likewise, two of the cases classified under deaths due to infections were actually severe infections of the kidney superimposed upon a chronically diseased renal apparatus. Three other cases—reported as suicide (based upon suspicion), coma, and apoplexy—were in fact renal deaths. Other changes in our revised classification included one case which we deducted from the tuberculosis group because the osteopath who signed the death certificate told one of us he had included tuberculosis on the certificate on hearsay evidence only. Four others were similarly erroneously reported, but the errors were perpetuated statistically. Our final revisions appear in Table II.

The information disclosed by this critical analysis of the fundamental disease of the patient, as contrasted with the reported terminal event assigned on the death certificate, we believe to be of great significance. Among the diabetic children the true complication which we must combat is renal rather than cardiac. The early signs and symptoms for which we must be ever alert, and for which prophylaxis and newer therapeutic aids may be helpful, are those of

complications in the kidney. These observations are in conformity with those published by Fanconi, but they lead us to hope that Boulin, with his group of cases of, as yet, shorter duration, may be justified in his more optimistic attitude.

Tuberculosis

Of the 135 fatal cases among children in 1944-9, there were 15 (11.2%) whose lives ended in tuberculosis. In all of our patients, young and old, tuberculosis never has caused more than 4.9% mortality in any period, and since 1944 it has been 2.5%. With children the previous highest rate was 9.9%, none of the deaths up to 1922 having been caused by it, presumably because before insulin the life-span of a diabetic child was so short. We are uncertain of how many of our living children have tuberculosis.

Six of these 15 deceased children were seen but once, either at a single visit to our office or upon their first and only stay in hospital. Two of them already had advanced tuberculosis. Most of these 15 cases should have been discovered earlier. One had tracheo-bronchial adenitis and another had calcified bronchial glands at their first visit, and two others had findings suggestive of old healed tuberculosis. Having known formerly that one in five of our patients who recovered from diabetic coma developed tuberculosis within five years, we should have supervised more closely the six cases with a history of coma. The diagnosis in six cases was first made by us. In nine cases x-ray examination was not carried out at the first visit or during the first stay in the hospital. In fact, six of the cases saw us within six months of the detection of the tuberculosis, and we have no comforting assurance of a negative radiograph in our files.

A special, and warning, lesson is to be learned from the three cases which were at an excellent charitable tuberculosis preventorium long before the tuberculosis was recognized. Certainly they were studied for tuberculosis while there, but after leaving the institution they were not sufficiently followed up. We cannot help wondering what will be the fate of the boys and girls who outgrow the sheltering care of any diabetic children's home. Only two of the fifteen children were ever treated in a diabetic summer camp. All the cases save one came from especially underprivileged families. Four of these patients married; three of them did so before the onset of tuberculosis. One patient married two years after the onset of her tuberculosis and later had one child. In one case pregnancy was interrupted at seven months because of tuberculosis, and another had a nephrectomy for a tuberculous kidney.

Yet there is a hopeful aspect to the picture of these 15 deaths due to tuberculosis in that the average duration of diabetes at death was 13.2 years, though the duration of diabetes since the appearance of tuberculosis was much less. If diabetic children can live 13 years *with* tuberculosis, how much longer should they live *without* it!

Diabetic Coma

Twelve (8.8%) of the 135 deaths in this group of juvenile diabetics were directly attributable to diabetic coma. Five males and seven females, three of whom were married, comprised the group. Six of these patients were known to have relatives who were also diabetic. The average age at onset of diabetes in these 12 patients was 7.9 years and the average duration of the disease before the fatal attack of coma was 10.0 years. Thus the fatal complication occurred in the group at an average age of 17.9 years.

No attacks of coma had occurred during the interval between diagnosis of diabetes and the fatal episode in seven

of these cases. One patient had been grossly neglectful and was repeatedly treated for coma before his final attack. Information was inadequate in another case. One patient had suffered two attacks, and two other patients had each been in coma on one occasion between the onset of their disease and their fatal attack of coma.

It was impossible to determine definite precipitating factors in seven of these cases of fatal coma. One patient, having previously been in coma, omitted her insulin for three days because of an upper-respiratory infection; coma in one of the cases was reported to have been precipitated by complications of pregnancy. Dietary excesses alone or associated with the omission of insulin were responsible for the onset of coma in two other cases. Advanced bilateral pneumonia, unsuspected clinically, was first found at necropsy in one case treated at another hospital. This patient received much glucose intravenously during the course of treatment of her coma and was found to have a post-mortem blood sugar of 700 mg. Two of the children were severe behaviour problems, one of whom had associated epilepsy and died at a State mental hospital. Four of the children attended the diabetic camps during one or more summer sessions, but six of the group saw us only once. Not one of these 12 patients was treated at the New England Deaconess Hospital or seen by any one of our staff during their terminal illness. Only three patients were seen within twelve months of their final coma, and only two others had been seen within three years of their fatal illness. Nine of the deaths occurred during the second decade of life, two between the ages of 20 and 30, and one past the age of 30.

The usual variety of associated conditions was seen in these patients: thus one case each of epilepsy, necrobiosis lipoidica diabetorum, retarded growth, nocturnal diarrhoea, retinitis with generalized arteriosclerosis, xanthomatosis, and insulin lipodystrophy were seen.

Arteriosclerosis

In general, arteriosclerosis when present in one part of the body will manifest itself in the vascular system throughout. As a result of this and its major incidence after 50 years of age the tendency in the past has been to group together all patients showing degenerative vascular disease under the general heading of deaths due to arteriosclerosis. However, a discriminating review of the clinical records of the 135 fatal cases in this series has revealed the presence of ante-mortem renal damage of considerable degree in at least 70 cases, or 51.9% of the entire number. There were 15 post-mortem examinations in the group of 70 fatal cases. The clinical data accumulated on the other 55 patients before their deaths clearly indicate that, despite various other death-certificate classifications, death was in reality due primarily and chiefly to renal disease. The majority of these 55 cases showed all three of the most frequently seen ante-mortem clinical manifestations of vascular nephritis—namely, proteinuria, oedema, and hypertension. Twenty-six of these 55 had shown frank uraemia. Records available indicated that retinitis was an associated manifestation in at least 60% of this group.

It was noted consistently in those cases having adequate follow-up examinations that the proteinuria invariably preceded the elevation of blood pressure, thus strongly supporting the thesis that the condition was primarily renal in origin rather than attributable to the onset of essential hypertension.

Most post-mortem examinations of children dying with diabetes mellitus reveal a mixture of several types of renal pathology, including pyelonephritis, intercapillary

glomerulosclerosis, and arteriolosclerotic and arteriosclerotic disease. This was strikingly true in the 15 necropsies in this group. An exception to this general finding was, however, a case in which careful microscopical analysis failed to show evidence of any kidney lesions other than those of chronic glomerulonephritis, despite the fact that before her death the patient showed the classical symptoms of vascular nephritis and was in clinical uraemia terminally. In this case no arteriosclerotic renal changes were evident, although atheromatous changes were described in the aorta and coronary arteries.

Distribution of the cases according to sex seemed irrelevant, since 37 males and 33 females comprised the group. It was anticipated that there would be a considerable preponderance of females in this renal group because of the increased incidence of urinary-tract infections in these young girls. Infection, although playing some part in the pathogenesis of these renal complications, was far from being the entire explanation, though many of these cases revealed a history of previous severe urinary-tract or kidney infections, but without adequate follow-up studies.

Cardiac and Cerebral

Arteriosclerosis, as stated above, is seldom if ever confined to one organ, but in the 10 cases in which the changes were predominantly localized the heart was involved in eight and the brain in two. To say that the heart was not affected in the 70 cases of death due primarily to renal disease would be untrue, but the functional cardiac impairment was apparently of far less importance. Three of these cardiac patients showed also severe hypertension and proteinuria, and two of them had clinical nephritis before death. In one case at necropsy intercapillary glomerulosclerosis was present. These eight patients (five males and three females) died primarily of cardiac disease complicating their diabetes, which had been present for an average of 22 years. The two cerebral deaths were due to emboli, in one case after 26.3 years of diabetes and in the other case after 16.5 years of the disease.

Complications were numerous in the cardiac group. Pulmonary tuberculosis was suspected but never proved in two cases. Five cases had retinitis proliferans, and there was one instance of necrobiosis lipoidica diabetorum. Severe diarrhoea, presumably on the basis of diabetic neuropathy, had occurred in two patients. None of these patients died in a Boston hospital, and a necropsy was performed in only one case, thus emphasizing our ignorance of the exact nature of the final illness. Very little information was available for review regarding the terminal events in these 10 patients whose death resulted from occlusive cardiovascular phenomena. One was known to have been markedly hypoglycaemic for a considerable period before his terminal coronary occlusion. The youngest patient to have a fatal coronary attack was 21.9 years old, and this same girl was also the only patient having been seen within two years of her death. In all the other cases the patients were last seen at the office or hospital from 3 to 25 years before the final outcome.

Miscellaneous Deaths

As shown in Table II, 27 (20%) of the cases were the result of accidents, infections, and miscellaneous or unknown causes. In seven cases it was impossible to trace the cause of death.

The seven accidental fatalities included a fractured skull in an industrial accident, flame burn in a circus fire, a car accident, a deer-hunting accident, suffocation in bed during

an epileptic seizure, one drowning, and one suicidal death from gunshot wounds. One death resulted from carcinoma of the bladder.

Infections were responsible for eight deaths: pneumonia accounted for four, and systemic infections for the remaining four.

Conclusions

Above all else, these 135 deaths of diabetic children within the last six years—11.2% from tuberculosis, 8.8% from diabetic coma, and 51.9% from renal disease—show that the diabetic with onset of disease in childhood should be followed more closely. Only in this way can needless deaths be avoided. Continuity of treatment is essential. Roentgenograms of the chest should be taken yearly. A constant awareness for evidences or incipient signs of renal disease must be maintained. Research should be concentrated on the kidney in the young diabetic. The importance of post-mortem examinations cannot be too strongly emphasized.

To preserve in comfort and prolong the lives of diabetic children the need is paramount for inexpensive and attractive opportunities, in children's and adolescents' camps, and especially in hospitals, of reviewing their physical condition and promoting morale and zeal for the continuing control of their diabetes.

ERYTHROCYTE SEDIMENTATION IN ANAEMIA

BY

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In 1921 Robin Fahraeus introduced his method of measuring the erythrocyte sedimentation rate (E.S.R.) and, after describing the various disorders in which it was increased, discussed the factors involved. Most of his findings are still widely accepted, especially the view that anaemia had an accelerating effect on blood sedimentation. Others studied this problem and also became convinced that anaemia, *per se*, increased the E.S.R. (De Courcy, 1925; Meeker, 1925; Rubin, 1926; Hubbard and Geiger, 1928; Cherry, 1934). It was soon suggested that the E.S.R. was so dependent on the red cell count that it was wholly unreliable in anaemia (Hunt, 1929) and that small increases in the E.S.R. should be discounted in the presence of anaemia (Bannick *et al.*, 1937). With few exceptions further studies have been in agreement on the effect of anaemia and on the need for correction of the increased rate, differing only over the best method of making this correction.

The object of this paper is to give certain theoretical, clinical, and experimental reasons for believing that the E.S.R. is not increased by anaemia, and therefore that the observed E.S.R. has the same significance in anaemia as in normal blood states.

Existing Correction Methods

Some recommend estimation of the E.S.R. in anaemia only after the packed cell volume (P.C.V.) has been adjusted to normal by manipulation of the blood sample (Hubbard and Geiger, 1928; Chung, 1935; Gibson, 1938), others after removal of enough plasma to raise the red cell count to 5 millions per c.mm. (Walton, 1933; Schuster, 1938). Charts have been devised to correct for various haemo-

globin levels (Gram, 1929) or haematocrit readings (Ernst and Rourke, 1930). The latter method was adopted by Wintrobe and Landsberg (1935), who constructed a chart based on numerous readings on normal blood samples made "anaemic" by dilution with their own plasma. Certain impossible situations in this chart were pointed out by Hynes and Whitby (1938), whose modification is based on the same data. Other methods include simple subtraction based on the haemoglobin level (Gregg, 1939) and a proportional correction depending on the P.C.V. (Della Vida, 1947).

Contrary views have been expressed, but they have been weakened by inadequate evidence (Bouton, 1938; Vogt, 1941) or change of opinion (Gregg, 1937, 1939). Britton (1936) concluded that an increased E.S.R. in anaemia indicated a search for some accompanying disorder, but not only did he allow an upper limit of 15 mm. an hour (Westergren) for women, accounting for this high figure by their lower average red cell count, but he also lent support to a correction chart (Whitby and Britton, 1946). A number of cases of anaemia with normal E.S.R.s were reported by Sugarman (1939), but he gave few details and made no comment on correction. Without referring to clinical results, and believing that the red cells played an entirely passive part in sedimentation, Cutler *et al.* (1938) opposed correction.

This opposition has been too indecisive, and the field is now firmly held by the supporters of correction. The present position remains as described in the exhaustive review of blood sedimentation by Ham and Curtis (1938), who concluded: "It has been clearly established that decrease in erythrocyte concentration causes acceleration of the sedimentation rate."

Fallacies of Correction

Anaemia is not a simple entity. Alterations occur in the red cells affecting their number, mass, size, shape, uniformity, and haemoglobin content, and these alterations vary with the cause of the anaemia, as do changes in the plasma proteins. It follows that a single correction factor will not be suitable for all forms of anaemia, and that consideration of one aspect of the anaemia will lead to other aspects being ignored or distorted. Thus adjustment of the haemoglobin to 100% in an anaemic sample may well increase the red cell count to 10 millions per c.mm. and the P.C.V. to 60%, while manipulating the red cell count of the same specimen to 5 millions per c.mm. may leave the haemoglobin at 40% and the P.C.V. at 30%; similarly, adjusting the P.C.V. to normal will not produce normality in other respects.

These methods of "correcting" the blood sample before estimating the E.S.R. also ignore other changes in the red cells. Cutler *et al.* (1938) maintained that the red cells played an entirely passive part in sedimentation. It seems certain that this view is incorrect. Ham and Curtis (1938), by suspending washed red cells of varying size in the same plasma, showed that large cells sediment faster than small cells. The experiments of Bunting (1939) with cases of sickle-cell anaemia are convincing. He found that their E.S.R. was greatly increased after reducing the sickling by bubbling oxygen through the blood, whereas when about 50% sickling was produced by using carbon dioxide, rouleaux formation and sedimentation were almost abolished.

Plasma protein changes affecting the absolute and relative amounts of albumin/globulin fractions and fibrinogen vary with the cause of the anaemia, but they are not considered in any correction method.