SOME OBSERVATIONS ON THE EFFECT OF BLUEBERRY LEAF EXTRACT IN DIABETES MELLITUS

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REFERENCES to various so-called insulin substitutes have appeared in recent medical literature. The term 'insulin substitute' is perhaps an unhappy one. To those familiar with the beneficial effects of insulin in diabetes, the search for a substitute for this potent remedial agent may seem unwarranted. The efficacy of insulin in the treatment of diabetes mellitus is indisputable. Its mode of administration, however, bears disfavour. No method of administering insulin has yet been successful except by subcutaneous injection. Hypodermic medication, continued day after day, with unremitting care and precision is objectionable for very obvious reasons. Moreover, insulin is a powerful drug which, if misused in the hands of patients, possesses potentialities of dire consequence. Hence, hope ever exists that some substance may be prepared which when taken orally is capable of exhibiting the desirable properties of insulin, but is devoid of its disadvantages. Such an ideal therapeutic agent is not yet available.

The amount of insulin absorbed from the gastro-intestinal tract has generally been considered too insignificant to be of any real value in the treatment of diabetes. However, the observations of Murlin and Hawley[1] suggest that pancreatic hormone replacement by this route may not be an impossibility.

In the absence of an insulin-containing product which is efficient when taken by mouth, it may not be amiss to investigate certain non-pancreatic preparations from the standpoint of a possible salutary influence upon the carbohydrate tolerance of diabetic patients. Remedies of this class which have received attention recently are synthalin and blueberry leaf extract. Synthalin, although it appears to offer certain possibilities, is apt to give rise to unpleasant toxic by-effects. Blueberry leaf extract seems to be harmless, but its proper evaluation as a factor in the treatment of diabetes has not yet been decided. The following data have a bearing upon this latter consideration.

PREVIOUS OBSERVATIONS

Experimental evidence points to the existence in many or all plants of a substance which affects carbohydrate metabolism.[2,3,4] The leaves of the blueberry plant are said to contain this ingredient in relative abundance, in a form which permits of extraction.

The physiological action of an extract prepared from blueberry leaves was first investigated by Mark and Wagner.[5] This investigation was soon followed by observations relative to its effect in depancreatized dogs.[6] The variable results obtained by these workers were explained by the demonstration of two antagonistic principles in their preparations. The one tended to raise the blood sugar, the other to lower it. An attempt was made to separate and purify the latter substance, and the resulting product was given the name myrtillin.

On this continent, the problem has been investigated chiefly by F. M. Allen,[7] who believes "that myrtillin plays some accessory part in carbohydrate metabolism and that, if properly used, it will prove valuable as an accessory factor in diabetic treatment." This contention was the outcome of experimental observations in totally and partially depancreatized dogs and in clinical cases of diabetes. The lives of depancreatized dogs were prolonged by the use of myrtillin. Fluctuations in the blood sugar under similar conditions were apparently not so marked, and the amount of insulin required by the animals was probably less than when no blueberry leaf extract was used. Even the largest doses were without evident toxic effects.

Allen was able to report on eighty-one cases of diabetes treated with the drug. In sixty of these, conditions were such as to permit of comparative studies. Beneficial results, attributable apparently to blueberry leaf extract, were believed to have been obtained in thirty-six cases of this latter group, as evidenced by their ability to tolerate a higher daily consumption of carbohydrate, to decrease the amount of insulin, or

TABLE I.

SUMMARY OF CASES TREATED WITH BLUEBERRY LEAF EXTRACT

Case No.	Age (yrs.)	Sex	Known duration of the diabetic condition	Relative Severity of the Diabetes	Before Blueberry Leaf Extract		After Blueberry Leaf Extract	
					Insulin (Units per day)	Total Carbohydrate* (G. per day)	Insulin (Units per day)	Total Carbohydrate* (G. per day)
1	70	F	8 months	Moderately Severe	30	86	0	98
2	43	M	2 years	Mild	20	130	8	130
3	16	F	18 months	Severe	50	110	16	150
4	53	F	5 years	Mild	0	93	0	93
5	61	M	4 years	Moderately Severe	38	99	15	114
6	49	M	1 year	Moderately Severe	40	113	45	113
7	29	M	8 months	Mild	0	108	0	128
8	77	F	3 months	Mild	0	80	0	130
9	30	M	9 years	Severe	75	99	80	97
10	12	M	5 years	Severe	52	81	55	73
11	60	M	1 year	Moderately Severe	20	94	40	94
12	40	F	? (Less than 2 years)	Mild	30	116	0	140
13	12	F	1 year	Moderately Severe	60	94	40	107
14	66	F	4 years	Severe	45	90	70	84
15	23	M	2 years	Moderately Severe	65	125	65	125
16	67	F	1 year (?)	Moderately Severe	20	98	0	98

*Total Carbohydrate Content of Diet = 100% C. + 58% P. + 10%F.

TABLE II.

CASE 16—MODERATELY SEVERE DIABETES IN AN ELDERLY PERSON, TREATED WITH INSULIN AND BLUEBERRY LEAF EXTRACT

Date	Diet				Urine			Blood Sugar (Mg. %)	Insulin (Units per day)
	Carb.	Prot.	Fat	Calories	Sugar	Acid aceto-acetic	Acetone		
1928									
4-7	?	?	?	?	++++	neg.	neg.	267	0
4-10	20	20	40	520	neg.	neg.	+	150	0
4-17	45	55	120	1480	neg.	neg.	trace	161	20
4-23	50	60	130	1610	+	neg.	neg.	186	25
4-30	50	60	130	1610	neg.	neg.	neg.	143	35
5-7	50	60	130	1610	+	neg.	++	182	38
5-10	50	60	130	1610	neg.	neg.	neg.	...	45
5-12	50	60	130	1610	neg.	neg.	neg.	90	35
5-14	50	60	130	1610	neg.	neg.	neg.	122	30
5-21	50	60	130	1610	neg.	neg.	neg.	116	20
5-26	50	60	130	1610	++	neg.	neg.	174	10
5-26	*Blueberry Leaf Extract Started.*								
5-28	50	60	130	1610	trace	neg.	neg.	...	20
5-31	50	60	130	1610	neg.	neg.	neg.	119	20
6-4	50	60	130	1610	Ft. trace	neg.	neg.	103	10
6-7	50	60	130	1610	neg.	neg.	neg.	...	6
6-9	50	60	130	1610	trace	neg.	neg.	108	3
6-14	50	60	130	1610	neg.	neg.	neg.	111	3
6-18	50	60	130	1610	neg.	neg.	neg.	119	0
6-22	50	60	130	1610	neg.	neg.	neg.	96	0
6-26	50	60	130	1610	neg.	neg.	neg.	...	0

both. In general, the best results were obtained in the milder cases and in middle-aged or elderly patients. Myrtillin never caused hypoglycæmia, but rather tended to prevent hypoglycæmic reactions due to insulin. The beneficial effects, when obtained, were indefinite in duration, and seemed to be prolonged, after stoppage of the remedy, for from one to several weeks. This phenomenon was explained on the assumption of storage within the body. The mode of action of myrtillin in bringing about improvement in carbohydrate tolerance is unknown. It has been suggested that the active principle may be of the nature of a vitamine. In this regard, it is noteworthy that Mills[4] has recently obtained encouraging results in the treatment of diabetes with a vitamine-rich extract of various plants administered by mouth. His preparation, however, was without effect in depancreatized dogs, but it increased glycogen storage in the livers of rabbits kept on a constant diet.

FURTHER DATA

There are recorded here the results of the administration of blueberry leaf extract to sixteen patients with diabetes mellitus of varying grades of severity and varying lengths of duration. The extract was supplied in the form of tablets, 0.3 grm. each, one tablet being given one hour before meals. The results are summarized in Table I. The blood sugar estimations were carried out by the Folin-Wu method, upon blood samples obtained during the morning fasting state, unless otherwise designated. Apparently beneficial effects were obtained in nine cases(56 per cent). As noted above, Allen claimed beneficial effects in 60 per cent of a larger series of cases.

In Table I, the insulin dosage before the exhibition of blueberry leaf extract refers to the amount of insulin received by these patients immediately before blueberry leaf extract was started, not the maximum requirements of the

TABLE III.

CASE 2.—MILD DIABETES IN AN ADULT TREATED WITH INSULIN AND BLUEBERRY LEAF EXTRACT

Date	*Diet*				*Urine*			*Blood Sugar (Mg. %)*	*Insulin (Units per day)*	*Remarks*
	Carb.	*Prot.*	*Fat*	*Calories*	*Sugar*	*Acid aceto-acetic*	*Acetone*			
1926										
6–21	?	?	?	?	++++	+	+	330	0	
10–18	159	84	135	2187	neg.	neg.	neg.	...	0	
1927										
3–8	60	70	180	2140	+++	neg.	neg.	...	0	
5–28	60	70	180	2140	++	neg.	trace	...	10	
8–29	50	70	160	1920	neg.	neg.	neg.	...	20	
10–12	80	60	150	1910	Ft. trace	neg.	neg.	...	20	
12–5	85	50	160	1980	neg.	neg.	neg.	111	20	
12–13	85	50	160	1980	neg.	neg.	neg.	114	20	
12–21	*Blueberry Leaf Extract Started.*									
12–31	85	50	160	1980	neg.	neg.	neg.	...	16	
1928										
1–4	85	50	160	1980	neg.	neg.	neg.	119	13	
1–7	85	50	160	1980	neg.	neg.	neg.	...	5	
1–12	85	50	160	1980	+	neg.	neg.	130	5	
1–16	85	50	160	1980	+++	neg.	neg.	136	16	Pt. has "cold."
1–23	85	50	160	1980	neg.	neg.	neg.	119	27	Pt. has "cold."
2–8	85	50	160	1980	neg.	neg.	neg.	...	36	Pt. has "cold."
2–15	75	50	160	1940	neg.	neg.	neg.	...	40	Pt. has "cold."
2–21	75	50	160	1940	neg.	neg.	neg.	133	23	
2–27	75	50	160	1940	neg.	neg.	neg.	122	15	
3–3	75	50	160	1940	neg.	neg.	neg.	...	10	
3–15	85	50	160	1980	++	neg.	neg.	142	5	
3–20	*Blueberry Leaf Extract Stopped.*									
3–27	85	50	160	1980	neg.	neg.	neg.	133	8	
4–2	85	50	160	1980	neg.	neg.	trace	166	8	
4–8	85	50	160	1980	++++	neg.	trace	183	8	

individuals previous to this time. The insulin dosage after blueberry leaf extract indicates the minimum amount of insulin needed after the use of the tablets. For example, the case record epitomized in Table II shows that an attempt was made to reduce the daily requirement of insulin to a minimum while maintaining the urine aglycosuric and the fasting blood sugar normal, first without blueberry leaf extract, and afterwards with blueberry leaf extract. This patient, on admission to hospital, presented the manifestations of moderately severe diabetes. The diet and insulin were as indicated. The insulin was gradually reduced, from a maximum of forty-five units per day on a constant diet to twenty units without glycosuria and without elevation of the fasting blood sugar. But when the insulin was further reduced to ten units per day, glycosuria appeared and the blood sugar rose above the normal. The patient was again given twenty units of insulin a day, and blueberry leaf extract was started. After about one week, reduction of the insulin was once more attempted. The insulin could now be eliminated entirely, the urine still keeping sugar-free and the blood sugar normal.

Considerable variations in effect were encountered in different patients and in the same patient at different times. Such discrepancies were referable, perhaps, to variations in potency of several lots of tablets or to vagaries in absorption. The effects of the remedy were lost in the presence of even a slight infection (Table III.) Ketosis was not readily corrected by the drug (Table IV). As regards the inhibiting effect of blueberry leaf extract upon hypoglycæmic reactions, it may be said that blood sugar concentrations as low as 0.047 per cent have been observed during the period of its administration, without the usual manifestations of insulin shock.

TABLE IV.

CASE 3.—SEVERE DIABETES IN A YOUNG PERSON TREATED WITH INSULIN AND BLUEBERRY LEAF EXTRACT.

Date	*Diet*				*Urine*			*Blood Sugar (Mg. %)*	*Insulin (Units per day)*	*Remarks*
	Carb.	*Prot.*	*Fat*	*Calories*	*Sugar*	*Acid aceto-acetic*	*Acetone*			
1927										
9–21	?	?	?	?	++++	+++	+++	316	0	Weight, 92 lbs.
9–29	70	35	120	1500	neg.	neg.	neg.	124	60	
10–2	70	40	140	1700	++	neg.	neg.	...	85	
10–10	70	40	170	1970	neg.	neg.	neg.	200	70	
1928										
1–13	70	50	160	1920	neg.	neg.	++++	166	50	
1–13	*Blueberry Leaf Extract Started.*									
1–20	70	50	150	1830	+++	trace	++	172	40	Weight, 110 lbs.
1–27	70	50	150	1830	++	neg.	neg.	168	40	
2–10	70	50	150	1830	neg.	neg.	neg.	128	40	
2–17	70	50	150	1830	neg.	+	+++	94	30	
3–2	80	50	150	1870	neg.	+	+++	132	20	
3–9	80	50	140	1780	neg.	trace	++	105	20	
3–16	90	55	130	1750	neg.	+	+++	103	18	
3–23	100	45	140	1840	neg.	neg.	neg.	129	16	
3–23	*Blueberry Leaf Extract Stopped.*									
3–30	100	55	140	1880	++	neg.	neg.	140	16	
4–6	100	55	140	1880	+++	neg.	trace	164	16	
4–6	*Blueberry Leaf Extract Re-started.*									
4–13	100	55	140	1880	++	neg.	+	95	16	
4–20	100	55	140	1880	neg.	++	+++	149	18	3:30 p.m.
5–4	95	55	130	1770	Ft. trace	neg.	+	69	20	
5–11	95	55	130	1770	neg.	neg.	neg.	103	18	
5–18	*Blueberry Leaf Extract Stopped.*									
5–25	95	55	130	1770	neg.	neg.	neg.	82	20	
6–1	95	55	130	1770	trace	neg.	neg.	85	20	
6–8	95	55	130	1770	+	neg.	neg.	108	25	Weight, 117 lbs.
6–15	95	55	130	1770	++	+	+++	71	30	3:00 p.m.

But reactions have not been absent. The effects could not be appreciably augmented by giving double the usual dose.

DISCUSSION

The above results, based upon purely clinical observations, would seem to support Allen's view that blueberry leaf extract has a stabilizing influence upon the carbohydrate tolerance of certain cases of diabetes. That it cannot take the place of insulin need not be gainsaid. But, if it can be shown to permit the dosage or frequency of administration of insulin to be decreased, or cause insulin to be eliminated entirely in certain cases, or allow for added carbohydrate intake without increasing insulin, its use is justified. Judgment regarding the value of a therapeutic agent of this sort is truly difficult and one must weigh the evidence carefully before arriving at conclusions. The fallacy of basing opinions upon a small number of observations is also realized. As everyone familiar with the malady knows, the course of diabetes is variable. There exist all grades of severity between the case which can be readily controlled by minor dietary restrictions and that which cannot be balanced even with large doses of insulin. That carbohydrate tolerance does improve as a result of, or in spite of, insulin is common experience. An example is shown in Table V, in which the daily amount of insulin was reduced from fifty-five units to zero in the course of about eight weeks Had any treatment been employed other than that which was used in this case, one might have been led to quite erroneous deductions.

Tangible evidence in favour of the regeneration of pancreatic islet tissue as a result of insulin has been furnished by Boyd and Robinson.[8] It is also true that the daily insulin requirements of many patients remain unaltered or even need to be increased. Such cases have been reported by Newburgh[9] Harrison[10] and Brace.[11] Efficient diabetic therapy is a composite process to which many factors contribute. Whereas insulin acts as a specific under certain conditions, the mainstay of diabetic treatment still lies in the realm of dietary regulation. The importance of undernutrition has been emphasized by Rabinowitch.[12] Other factors which are known to influence carbohydrate metabolism in the diabetic, such as muscular exercise, infections, an altered basal metabolism, and time, should be given their proper due in any individual case.

Therefore, one may justly ask the following questions: Was the association of blueberry leaf extract administration and improvement in carbohydrate tolerance in the cases above mentioned merely a matter of chance? Could the recuperation of the metabolic functions be accounted for by one or several of the factors to which reference has just been made? Were these patients, at the time the blueberry leaf

TABLE V.

CASE J.P., MALE, AGE 27.—INSULIN REDUCED FROM 55 UNITS PER DAY TO ZERO WITHOUT BLUEBERRY LEAF EXTRACT.

Date	Diet				Urine			Blood Sugar (Mg. %)	Insulin (Units per day)	Remarks
	Carb.	Prot.	Fat	Calories	Sugar	Acid aceto-acetic	Acetone			
1927										
8–16	?	?	?	?	++++	neg.	+++	333	0	Admission to Hospital, Weight, 137 lbs.
8–19	20	30	60	740	+++	neg.	+	168	45	
8–23	25	50	75	975	trace	neg.	+	158	45	
8–27	30	60	90	1170	neg.	neg.	neg.	...	55	
9–7	60	70	125	1645	neg.	neg.	neg.	181	45	
9–17	70	70	150	1910	+	neg.	neg.	150	45	
9–24	90	70	160	2080	neg.	neg.	neg.	120	50	
9–29	90	70	160	2080	neg.	neg.	neg.	...	35	
10–3	90	70	160	2080	neg.	neg.	neg.	128	15	
10–10	90	70	160	2080	neg.	neg.	neg.	114	5	
10–29	90	70	160	2080	neg.	neg.	neg.	95	0	
11–15	90	70	160	2080	neg.	neg.	neg.	...	0	
1928										
1–28	75	60	170	2070	neg.	neg.	neg.	...	0	Weight, 151 lbs.
2–8	75	60	170	2070	neg.	neg.	neg.	114	0	
3–2	75	60	170	2070	neg.	neg.	neg.	...	0	

was started, receiving more insulin than their required minimum? These are, of course, all possibilities. The only reply to such speculations is that in several instances unsuccessful attempts at insulin reduction or dietary increment had been made before blueberry leaf extract was given; also, there were indications in certain cases of a decline in carbohydrate tolerance when the extract was withdrawn.

If a preparation, such as that under consideration, possessing possible insulin-like properties, is to be available for general use, some means of standardization is necessary. To date, a satisfactory method for this purpose does not seem to have been evolved; hence, a uniformly potent product can not be assured.

SUMMARY AND CONCLUSIONS

A limited experience with the use of blueberry leaf extract in the treatment of diabetes mellitus permits the following generalizations, in which the claims of Allen have been at least partially verified:

1. Blueberry leaf extract appears to exert a beneficial effect in certain cases of diabetes. Its action is not consistent.

2. Its utility is most apparent in middle-aged or elderly patients, and in mild cases of the disease.

3. Owing to its relatively slow and feeble action, the drug is of no avail in the emergencies or complications attendant upon diabetes.

4. Blueberry leaf extract can not be regarded as a substitute for insulin, generally, but it may become an adjunct in the treatment of diabetes.

5. Blueberry leaf extract is without evident deleterious effects. It does not give rise to serious hypoglycæmia.

6. Withdrawal of the drug may be accompanied by a partial relapse in carbohydrate tolerance after a variable length of time.

7. Finally, blueberry leaf extract has, at best, a limited application in the treatment of diabetes, and exaggerated confidence in any therapeutic agent is to be deprecated.

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An Address

ON

ASTHMA*

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ASTHMA is a constitutional disease with an hereditary tendency. That it is constitutional is shown by the manner in which it may recur after an absence of several decades. The hereditary factor is also well established. It is as fitting to speak of an asthmatic constitution as it is to speak of a melancholic disposition. If one regards the asthmatic as one who is capable of having asthma it is hardly an exaggeration to say "Once an asthmatic, always an asthmatic."

Since Sir John Floyer published his classical treatise in 1698, spasm of the muscles of the smaller bronchi has been taken as the cause. Kessler recently did experiments to substantiate this, but other investigators state that the cause is not so certain and that probably œdema of the epithelial cells lining the bronchi produces the narrowing. I have tried to demonstrate spasm by means of lipiodol injections into the lung but have not been successful. There was no apparent difference in the width of the shadow during an attack compared with its width during the freedom from asthma experienced after injection of adrenalin. Cocainization of the throat for

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