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SALICYLATE OF SODIUM IN THE TREATMENT OF DIABETES.[1]

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THE treatment of diabetes mellitus by salicylate of sodium is by no means novel. Dr. Ringer has quoted two cases of Ebstein[2] and Müller's, which were cured by this drug after many others had been tried unsuccessfully. "Salicylates," wrote Dr. Ralfe in 1884,[3] "in the malarial forms of diabetes may be found useful. Thus Wortekewicz (*Vratch*, No. 43) relates a case of diabetes, apparently of malarial origin, treated with salicylate of sodium in large doses. The drug was given on three different occasions, and each time a marked decrease in the amount of sugar was noticed; on the last occasion there was even a temporary disappearance. The salicylates are useful in relieving the neuralgic pains, especially affecting the sciatic nerves, which are so often present in diabetic subjects." Later on, in 1886, he writes again,[4] that in his experience, salicylates are especially indicated in all cases of diabetes of constitutional origin, particularly in those in which an excess of uric acid can

[1] Read at the Annual Meeting of the Midland Branch of the British Medical Association at Derby, June 18, 1891.

[2] Ebstein's patients (*Lond. Med. Record*, July 15, 1876) were both elderly men, one aged 58, the other 53. After carbolic acid, diet, and Carlsbad water treatment had failed in the first case (one of severe glycosuria with some sciatica), salicylate of sodium completely abolished the sugar in his urine in less than a fortnight. Three months afterwards he was on a mixed diet, gaining in weight, and his water was free from sugar. He was then, as a precaution, taking 15½ grs. of salicylate daily. The second case for ten years had suffered from glycosuria; he was a great deal improved by salicylate, but not cured.

[3] *Year-Book of Treatment*, 1884.

[4] *Ibid.*, 1886.

be demonstrated, but they are of little use in the neurogenic. Also in 1886 Dr. Sinclair Holden published a valuable report of cases, chiefly in elderly and rheumatic persons, where the salicylates had done great good, while the effect of diet had been but little marked. In the same year Dr. Latham mentioned salicylic acid with praise in his well-known Croonian lectures. Sir William Roberts and Dr. Broadbent have both testified to the virtues of salicylates in diabetes, as has Dr. Jacobi to their good effects when the disease attacks young children. To Dr. Haig, whose admirable work on uric acid is now getting the attention it deserves, I personally owe the directing of my attention to this subject.

Speaking generally, there are two great classes of diabetics. In the *first*, are those on whom the disease falls while they are quite young, with symptoms of great intensity: as a rule, to which at present there are very few exceptions, this form is quickly fatal. The *second* class includes those who are attacked when they are elderly, and of gouty tendencies. In these it may not be very active, they may even become fat while they are suffering from it, they have not much glycosuria or polyuria, and they often do not die from the diabetes itself. Now a justification, if one were needed, for bringing forward the case about to be narrated, is that most of the praises lavished upon the good effects of salicylate of sodium in diabetes belong properly to its action in the second class of cases, while the patient in question was a good example, caught early, of the first—the younger and more fatal form. The last case given by Dr. Haig,[1] that of Jane B., is also one of the neurogenic form, but nearly all other recorded cases belong to the second of the two divisions.

The notes of the case are as follows:—

G. C., aged 17, an engineer's apprentice, first consulted me on April 18, 1891.

His *family history* was not at all good on his mother's side, as she was an epileptic, had had chorea twice, and died of some tuberculous disease probably; one out of two of her sisters died of phthisis, as did her mother. One of his own brothers died of

[1] "The Use of Salicylate of Soda in Diabetes Mellitus." *St. Bartholomew's Hospital Reports*, vol. xxv. pp. 7–26.

phthisis, another was markedly phthisical, and a sister had died of Bright's disease; another sister is a somnambulist. On the father's side the history was good.

Personal History.—He had been a fairly healthy lad till about six weeks before he came to me, when he began to suffer greatly from thirst, which was but little abated by drinking. He also began to pass a great quantity of urine and very frequently, which gave him disturbed nights. His appetite was almost voracious, but he had a feeling of never being satisfied, and he was rapidly getting thinner. He was extremely weak, tiring with any slight exertion. He had a nasty taste in his mouth, which was always very dry, and his lips bled occasionally.

He had become very costive, and passed, when his bowels were open, dark chocolate-coloured motions. His eyesight had been troubling him the last week before I saw him, and he complained of headache, generally coming on towards mid-day and lasting till six or seven o'clock in the evening.

Present Condition.—He was of slight build, much emaciated, with rather a hectic flush on his cheeks. His tongue was dark red, dry, and glazed; his lips were dry and cracked. His breath smelt slightly of apples. His hands and skin generally were very dry and rough.

Pulse 76, hard and full (showing high tension). Respirations 18. Chest sounds normal. Heart normal. Temperature normal.

Urine was very pale, greenish yellow in tint, limpid, also smelling of apples, very acid, of specific gravity 1040, free from albumen, but giving a great deal of sugar by both Moore's and Pavy's tests. He was then passing about seven pints in the twenty-four hours. He was directed to take a little walking exercise every day, being careful never to overtire himself. This he increased gradually. He was at once put on a mixture of ten grs. of salicylate of sodium, five drops of tincture of nux vomica, and an ounce of infusion of gentian, to be taken every four hours. He was also cut off absolutely from sugar, pastry, bread (save well-baked toast) and biscuits, and of course from potatoes and starchy vegetables. To sweeten his tea and coffee I suggested he should get some glycerine, as we know from physiologists that the presence of glycerine in the hepatic cell

hinders the conversion of glycogen into sugar.[1] He *did* get it but to little purpose, as he found he had purchased a specimen labelled "pure glycerine, warranted tasteless"; so he turned to saccharin with advantage. For the dryness of his mouth I prescribed glycerine of borax as a mouth-wash, which made him very comfortable. Without repeating the table given later on, his progress may be summed up as follows:—In the *first* week his water became gradually reduced in quantity, from seven to five and a quarter pints in the twenty-four hours, while its specific gravity varied from 1050-1040, the amount of sugar remaining about the same, or decreasing a very little. His medicine was only given *sextis horis* at the end of the first week. He suffered a good deal with headache, which was relieved by the salicylate and by citrate of caffeine. By the middle of the second week we had got him well set on strict diet, gluten bread, almond cakes, &c., with no starch or sugar in any form. His water was greatly improved, only three pints being passed in the twenty-four hours, of specific gravity 1024, and containing by Dr. Oliver's test a little over five grains of sugar to the ounce. His thirst was lessening, headache had vanished, and his sense of satisfaction with both meat and drink was increasing. By the end of April, *i.e.* by about the twelfth day of treatment, he was passing about *two pints* of urine, of specific gravity 1014, with a mere trace of sugar, less than one gr. to the ounce by Oliver's test (it was still quite enough to show the reaction with Pavy's fluid). In six more days there was no sugar at all in his water. On April 10 the note is as follows:—"For four days has been without the medicine; has had rather more desire to micturate; he has passed about half-a-pint more water daily, and has suffered from a slight return of the headache. His pulse has changed its character entirely, being now 74, soft and easily compressible." On May 18 had again been off the salicylate mixture for three days, with the result that he passed just twice as much water daily as he had done before. He complained also a little of pains in his back when without the medicine. Since May 19 his water has never been over $2\frac{3}{4}$ pints; it has never contained any trace of sugar, and the last analysis

[1] Foster's *Physiology*, 5th ed. p. 734.

of it, on June 24, was—"acid, sp. gr. 1025 : no albumen or sugar."

It has given marked salicylate reaction all through the treatment till June 12. As he complained of dimness of sight, I examined his eyes several times, but they seemed perfectly natural, so his trouble (which soon passed away) was probably a temporary amblyopia. I also examined his blood, which under the microscope appeared perfectly normal. He was, as has been said, constipated, but there was no evidence of any fatty matter in the stools, which were dark brown in colour. The salicylate caused him to perspire very freely, and in a few weeks' time his skin entirely lost the harsh and dry character which it had at the outset. He has gained quite a stone in weight during June, though he has not gained so much since the weather has been warm. He is now looking quite fat and rosy, and can take a great amount of exercise without fatigue. At the time of writing (July 9) he is still very well, but having had some lumbar and hypochondriac pain, he is taking the medicine again for relief of that. His weight has not altered this last month.

CASE OF G. C. (DIABETES MELLITUS).

Date.	Character of Urine, Treatment, &c.	Amount in Pints.
April 18—19.	℞ Sod. salicyl. ℥ij Tinct. Nuc. V. ℥j	7
,, 19—20.	Inf. gent. ad ℥xij ℥j 4*tis horis*	6
,, 20—21.	Ur. ac. 1050 ; sugar plentiful	7
,, 21—22.		6½
,, 22—23.	Ur. ac. 1044 ; sugar	6
,, 23—24.	Medicine 6*tis horis*	6
,, 24—25.		5¼
,, 25—26.	On strict diet ; urine ac. 1024 ; sugar, 5 gr. to ℥j (Oliver)	2½
,, 26—27.		3¼
,, 27—28.	Ur. ac. 1026 ; less than 5 gr. to ℥j (Oliver)	3
,, 28—29.		3¼
,, 29—30.	Urine ac. 1014 ; less than 1 gr. to ℥j by Oliver's tests	4
,, 30—May 1.		2
May 1— 2.		1¾
,, 2— 3.	Urine ac. 1026 ; less than 1 gr. of sugar to the ℥j (Oliver)	2½
,, 3— 4.		2
,, 4— 5.		2

CASE OF C. G. (DIABETES MELLITUS)—*continued.*

Date.	Character of Urine, Treatment, &c.	Amount in Pints.
May 5— 6.	Urine ac. 1030 ; no trace of sugar by Oliver's, Pavy's or Moore's tests	2½
,, 6— 7.	. . . . .	1⅓
,, 7— 8.	. . . . .	2
,, 8— 9.	. . . . .	2¼
,, 9—10.	Urine ac. 1016 ; no sugar	2½
,, 11—12.	. . . . .	2
,, 12—13.	. . . . .	1½
,, 13—14.	. . . . .	1½
,, 14—15.	. . . . .	1¾
,, 15—16.	. . . . .	1½
,, 16—17.	Urine ac. 1012 ; no alb. or sugar. Phosphates.	3
,, 17—18.	No medicine	3¼
,, 18—19.	. . . . .	3
,, 19—20.	. . . . .	2¾
,, 20—21.	. . . . .	2½
,, 21—22.	Urine ac. 1030 ; no alb. or sugar	2
,, 22—23.	. . . . .	2½
,, 23—24.	. . . . .	2½
,, 24—25.	. . . . .	2
,, 25—26.	Urine ac. 1025, turbid with lithates ; no alb. or sugar	2

For the next week the urine averaged 2½ pints, being on—

June 5, ac. 1030, with no sugar or albumen. Now he was only taking the salicylate once a day.

June 12. For the following week the urine varied between 2½ and 2¼ pints in the 24 hours. It was acid, sp. gr. 1024, with no sugar or alb. No salicylate reaction for the first time since he was on the treatment.

July 9. Average daily 2½ pints, normal in every way.

We thus see that when G. C. was on a mixed diet at the very beginning of treatment, salicylate of sodium made a difference of nearly two pints *per diem* in the amount of water passed.

Again, when he was on strict diet, the temporary cessation of the medicine on two occasions caused him each time to pass nearly double as much water as he did before or since, and gave him much uneasiness and more desire to micturate. I believe that it is greatly due to the salicylate that the urine became free from sugar and kept so ; however, as the effect of strict diet is so marvellous in some cases, I will not press that point. His headaches, which were frequent and distressing at first, gradually disappeared, owing partly no doubt to the salicylate, partly to the effervescing citrate of caffeine, which had an excellent aperient effect, and would serve, on that score as

well as from the caffeine it contains, as a useful preventive of diabetic coma. The high pulse-tension soon under the medicine became full and soft. He has had no bad effects from the drug, his depression of spirits has gone weeks ago, his appetite is excellent, and his digestion also, although he has been taking 10 grains every six hours in the day for nearly two months. The case is not brought forward as cured; that cannot be truly stated till he has been on a mixed diet, and without his medicine again for some considerable time, and has given no evidence of glycosuria. Even then he will be, as Sir Thomas Watson said many diabetic patients are, "kept in a predicament of dangerous safety, *i.e.* on the brink of a precipice."

But it seems worth while to record the action of salicylate of sodium in a bad case of glycosuria; the more of such individual records we have, the sooner will our knowledge "grow from more to more," and thereby some fresh light may be thrown on this far too fatal malady.

Just a few words to finish with as to the action of salicylate of sodium in this disease. Dr. Latham considered there were two kinds of diabetes differing in the immediate source of the sugar, one the *neurogenic*, where the function of the liver is so altered as to interfere with the metabolism of glucose; and the second, the *rheumatic*, where there is some interference with the function of muscle, which allows glucose to pass into the circulation from that tissue. Then in this second class, according to the amount of oxidation, lactic acid or glucose will appear in excess in the blood. When salicylic acid is given, it arrests the formation of both lactic acid and glucose. Dr. Latham expressly mentions salicylic *acid*, though I notice Dr. Holden, in treating his cases of diabetes already referred to, prefers giving practically a solution of salicylate of sodium; and according to Ebstein, quoted by Senator,[1] salicylic acid is of no use whatever in this disease, but he may not have used it in the right kind of case. So far then as muscular, malarial, or rheumatic diabetes is concerned, this explanation may hold good. But Dr. Haig goes further, and suggests as the reason for the good action of salicylates in the *neurogenic* form—that due to vascular eccentricities of the liver—that there is an

[1] Ziemssen's *Cyclopædia of Medicine*, vol. xvi. p. 1003.

excess of uric acid in the blood, causing irritation of the vascular system of the liver and so abnormal transformation of glycogen into glucose. Now salicylate of sodium causing a great excretion of uric acid (the salicylic acid, according to Dr. Latham, prevents its formation, but perhaps the salt will not do that) relieves this. Most probably this is the explanation of the good work of salicylate of sodium in my case, though I exceedingly regret I did not test for uric acid throughout the progress of the disease. But there is one point brought out strongly by the records of diabetic necropsies, which shows that the liver in many cases even of the neurogenic type is not the only, perhaps not even the principal organ at fault. And this point is the large proportion of cases wherein some affection of the pancreas has been found. Fles and Silver have recorded cases of atrophy of the pancreas in diabetics with fatty stools. Friedreich [1] gives a number of instances (in treating of diseases of the pancreas) of the same thing, with varieties of course in the morbid anatomy of the gland. Lancereaux describes two cases and mentions ten others, wherein the symptoms of diabetes were extreme, and where atrophy of the pancreas was found. He remarks that the emaciation and the voracity are symptoms of which the existence has been noted in animals whose pancreas has been destroyed by physiologists.[2] Depierre [3] has also devoted much attention to this—the pancreatic form of diabetes. Lately Dr. Saundby has em phasised this in his Bradshawe lecture,[4] and he states "so far as my own observations go, I am disposed to agree with Lancereaux, as I have found the pancreas shrunken in all my cases of typical wasting diabetes." He also quotes a case of Dr. Bull's, of New York, of a patient who died of diabetes after extirpation of the pancreas. My partner, Dr. J. T. Collier, has published a case of glycosuria with extreme wasting, dyspepsia, and polyuria, where *post mortem* there was found cancer of the head of the pancreas.[5] Senator says that from what has been already recorded, we may justifiably assume that quite half of all the

[1] Ziemssen's *Cyclopædia*, vol. viii. p. 575.

[2] *London Medical Record*, v. p. 513.

[3] *Ibid.* April 15, 1881. [4] *British Medical Journal*, August 23, 1890.

[5] Curiously enough, the stools in this case were of a greenish-brown, showing that they contained comparatively unaltered bile.

cases of diabetes have some disease of the pancreas. The symptoms which have generally been ascribed to pancreatic disease have been partially mentioned. They are excessive wasting, with great voracity, fatty stools, and the passage of undigested portions of meat. Cases where fat has been passed in the urine, and several where an excess of fat has appeared in the blood, have been recorded. In one case of diabetes of which I saw a specimen of the blood, it looked like raspberry-cream. Professor Sanders and Mr. Hamilton have drawn attention to the number of recorded cases of lipæmia in diabetes, and have put forward the suggestion that one form of diabetic coma is due to fat-embolism.[1] Hertz,[2] again, gives the case of a servant girl, aged 17, who suffered from glycosuria for a year, and died from diabetic coma. There was a peculiar brown colour of the blood, which on standing gave, instead of serum, a yellowish-white milky fluid, which consisted of an emulsion of the finest fat-drops. Drs. Fraser and Logan[3] also report a case of a patient, aged 35, who died comatose, and whose blood contained a quantity of fat. Dr. Dreschfeld also, in his lecture on diabetic coma, mentions lipæmia, lipuria, and disease of the pancreas. The functions of this gland are usually described as threefold, its juice splits up fats and probably emulsifies them simultaneously, it digests proteids with the formation of peptones, and it converts starch into glucose. The symptoms just mentioned are most likely due to interference with its power of digesting proteids, and of dealing with fats. And the lipæmia and lipuria are possibly only instances of its failure in the second function. Are these then all its functions? Probably not; for Dr. T. J. Walker, in a most interesting paper,[4] has given good reasons for thinking that clay-coloured stools without other evidence of liver-trouble may be due to disease of the pancreas; and he has added two cases (one of glycosuria), with necropsies, wherein there had been fatty and clay-coloured stools, and where obstruction of the pancreatic duct was found, the absence of the action of pancreatic juice

[1] *Edin. Med. Journal*, July 1879.
[2] *Deutsche med. Woch.* 1881, No. 27.
[3] *Edin. Med. Journal*, September 1882.
[4] *Med. Chirurg. Transact.* lxxii. p. 259.

on the bile causing the abnormal colour. This may help to a more careful scrutiny of all diabetic cases and other wasting complaints, to see whether the pancreas may not be responsible in part or altogether.

But there is yet another function of pancreatic juice beyond these already given, if we can believe the record of the following experiments, and they are from quite independent sources. "Drs. Von Mering and O. Minkowski (*Birm. Med. Review*, March 1890) report a number of experiments from their laboratory at Strassburg, showing that extirpation of the pancreas results in true diabetes mellitus with the usual symptoms. A dog whose pancreas had been removed, secreted, after forty-eight hours' fasting, from 5 to 6 per cent. of sugar. Another dog, similarly treated, secreted, under an exclusively meat diet, two pints of urine daily with 6 to 8 per cent. of sugar. Glycogen at the same time disappeared altogether. In a dog which had been rendered diabetic for four weeks, and which was killed while on full flesh diet, neither liver nor muscle contained glycogen." Again, M. Lépine (*Lyon Méd.*, p. 619, 1889; p. 83, 1890) explains the fact of diabetes occurring in cases where atrophy of the pancreas has been found after death, by the hypothesis that a sugar ferment is formed in that organ, and is carried to the liver by the portal vein, to assist in the transformation of glucose. To demonstrate this, two dogs of equal size were both kept fasting several hours. One had the pancreas completely removed some time before, and being kept unfed for sixty hours was bled to death. The other was not operated upon, but was kept fasting for the same period, and then also killed by bleeding. The blood taken from the dog without a pancreas was then found to contain three times the percentage of sugar contained in that from the dog which had been left with his pancreas. Moreover, after the blood had been left under the same conditions for fifteen hours, the blood of the dog deprived of its pancreas had lost only 6 per cent. of its sugar, while the other dog's blood had lost 33 per cent. This much greater loss would seem conclusive of the continued action of the ferment absorbed from the pancreas in transforming the glucose in the blood.[1] There seems to lie the explanation of the varied affections of the pancreas in

[1] *Year-Book of Treatment*, 1890.

diabetes. In some, no doubt, a lesion attacking or involving the cœliac plexus may be responsible for the state of the pancreas and the state of the liver giving rise to diabetes. But so many of the reports give evidence of obstructed ducts, of atrophy and degeneration of the gland itself, that these experiments seem to clear up the pathological difficulty. There is one rather weak link at present in the chain of argument; namely that this glycogenic ferment has not yet been isolated.[1] It probably is poured out into the portal vein (if it went into the duct, it would be neutralised by the glucose-forming ferment already present there), and carried thereby to the liver. As long as there is a normal supply there it keeps carbohydrate material in hand as glycogen. When, either from too great blood supply to the liver (which will expose the glycogen to the action of the glucose-forming ferment in the blood) or from failure of the pancreatic secretion, the sugar formed by digestion passes into the blood; and, moreover, as there is no restraining influence, the glycogen already formed in the liver is converted into sugar, and diabetes mellitus is the result. Then it becomes a very interesting question as to whether many of the more acute cases, occurring in youthful patients, may not be really due to pancreatic disease; the severity and the issue will depend on the cause of that pancreatic disease. This suggests at once the treatment, which has been carried out with some success, of giving these patients liquor pancreaticus, calves' sweetbreads, &c. Finally, if salicylate of sodium does any good in these cases, I would suggest that it stimulates the pancreatic gland, just as it certainly does good to nursing mothers by stimulating the mammary gland. Again, as it makes the bile more watery and less likely to form gall-stones, so with much probability it does with the pancreatic juice.

[1] The various experiments made by the writer in this direction have not been successful; perhaps for the reason given immediately as to its being sent into the portal vein.