held the field for four years without any of those failures in the Medical Service by which so many campaigns have been marred. The cause of this continual success was various. The service had been created in time of peace by Bergin, Neilson, Fiset and Jones; in time of war by Jones and Foster. The officers under command were skilled professionally, trained in medical schools of old excellence, imbued with a sense of loyalty and discipline. Above all the service had been incorporated into the British Army; it was made partaker of all the traditions accompanying that privilege; it had the equipment and organization of that army to rely upon. Coming into such an inheritance, all that was required was intelligence, initiative and industry. The Canadian Medical Service proved, on the wide field of war, that it possessed those virtues."

RESISTANCE TO INSULIN*

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RESISTANCE to insulin may be considered to be present when extraordinarily large amounts of insulin are required to control the hyperglycæmia and ketonæmia in a patient ill with diabetes mellitus. Patients temporarily requiring very large doses of insulin, as in coma, and severe infection, should not be classed as resistant. The term is purely relative since in all cases hyperglycæmia and ketonæmia can be reduced if sufficiently large doses of insulin are administered.

From the experiments of Hedon and Macleod on depancreatized dogs, Root[1] has estimated that a completely depancreatized man would require between 200 and 300 units of insulin daily. He has assumed that any diabetic who requires more than the above amount is resistant to insulin.

The condition, although not common, has been observed a number of times with varying degrees of severity.

Lawrence[2] reported on a 19 year old boy who while taking 200 units of insulin daily excreted 55 grams of glucose daily; on one occasion he was given 400 units without effect on the glycosuria. Glassberg, Somogyi and Taussig[3] reported a diabetic who took 317 units of insulin daily, and who required 1,100 units during one day when acidosis supervened. This patient later improved spontaneously and behaved like an ordinary diabetic. Root[1] recorded the case of a physician, age 52, who had cirrhosis of the liver and hæmachromatosis, and who in spite of receiving 100 units of insulin daily was in acidosis and excreted 40 to 90 grams of glucose. His dosage was increased to 840 units daily. Despite this he went into coma and died even though 1,680 units of insulin was injected. Allan and Constam[4] observed a man with hæmachromatosis for two months who took 500 units of insulin daily. Wegener's[5] patient required 300 units of insulin daily. Wood and Fitzhugh[6] used 175 units on their case without affecting the glycosuria. Engel's[7] patient was given 1,365 units of insulin daily just before death. The patient did not die of acidosis. Karr, Scull and Petty's[8] case received between 470 to 620 units daily. Various types of insulin were used without success in an attempt to overcome the extreme insulin resistance. They sensitized rabbits with the patient's serum and administered 5 c.c. of sensitized rabbit's serum to the patient. In one week the daily dosage of insulin was reduced to 150 units and was discontinued in one month. Labbe and Boulin[9] reported a case who was given 3,850 units of insulin in 13 days. Rudy[10] reported a mild diabetic with urticaria and temporary insulin resistance requiring 515 units daily. This was discontinued after eleven days. Edgar Wayburn[11] recorded a case in which diabetes mellitus and pulmonary tuberculosis coexisted. The highest amount of insulin given her was 415 units in one day. This patient eventually went into coma and died. Clay and Lawrence's[12] case received 160 units of insulin every four hours but died a cardiac death. Altshuler and Gould[13] reported a case of diabetes mellitus in whom autopsy revealed a suprasellar cystic hæmatoma compressing the anterior and posterior lobes of the pituitary gland. This individual had glycosuria and acetonuria despite the administration of 100 units of insulin daily. Larger amounts were not tried. Marble[14] reported a case of extreme insulin resistance of long duration. He stated that this was the only case of its kind he had encountered amongst the 11,500 cases of diabetes mellitus he had treated in his clinic. This patient required between 240 and 675 units daily. When more than the latter amount was given hypoglycæmic reactions ensued. Weiner's[15] patient was first controlled by 50 units of zinc protamine insulin, but several months later needed 2,200 units daily. The patient recovered spontaneously so that 440 units was sufficient to control the glycosuria.

PATHOLOGY

The post mortem findings throw no light on the etiology of extreme insulin resistance. One feature common to all these cases is some alteration in the histology of the liver. The case reported by Root[1] showed hæmachromatosis in practically all the organs; being especially marked in the pancreas, liver and adrenals. In addition the liver showed periportal cirrhosis and the pancreas was almost completely replaced by fat and fibrous tissue. Clay and Lawrence's[12] patient presented congestion and slight fatty degeneration of the liver. All the endocrine glands were normal. The pancreas had a normal amount and normal appearing islets of

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Langerhans. Wayburn's[11] case had pulmonary tuberculosis. The pancreas microscopically showed slight fatty infiltration with normal appearing islets of Langerhans and acini. The liver also prseented fatty infiltration. There was no glycogen in the liver and pancreas. Altshuler and Gould's[13] patient had a suprasellar cystic hæmatoma. The liver had irregular areas of fatty infiltration, but the pancreas and adrenals were normal.

CASE REPORT

A Jewess, aged 61, first came under observation on April 23, 1936; complaining of pruritus vulvæ of six weeks' duration. She had no other significant complaints. Her past history was uneventful except for the treatment of metrorrhagia in 1933 with radium. She had eleven children and no miscarriages. Physical examination—essentially normal findings, blood pressure, 150/90, weight, 126 lbs. The urinalysis showed a four plus glycosuria and no acetone. The fasting blood sugar was 139 mg.

Sugar tolerance test on April 30, 1936, gave the following results:

	Blood sugar mg. per cent	*Glycosuria*
Fasting	160	0
½ hour	224	2 plus
1 hour	272	4 plus
2 hours	345	4 plus
3 hours	284	4 plus

She was placed on a restricted diet which was gradually increased to yield 1,750 calories daily and which contained—protein 60 g., fat 45 g., carbohydrate 265 g. On this regimen glycosuria disappeared and the fasting blood sugars ranged between 127 and 155 mg. She was thus adequately controlled until January 19, 1939, when glycosuria recurred despite strict adherence to her diet and despite the absence of any discoverable infection. She was given zinc protamine insulin, the dosage by June, 1939, being 40 units daily. She attended the clinic infrequently and it was known that glycosuria persisted.

On September 26, 1939, one of us (L.I.F.) was called to her home. The story was that at 5 a.m. on the previous day she began to vomit dirty dark brown material. The examination revealed an exhausted looking woman who was fully conscious. Her eyeballs were normal and the blood pressure was 180/90. The urine was loaded with sugar but contained no acetone. Hospitalization was advised but was refused. She resumed her usual diet of 1,750 calories and her insulin dosage was increased to 50 units zinc protamine insulin. This was progressively increased until on October 3rd, she received 112 units zinc protamine insulin and 38 units of plain insulin. On this day at 5 p.m. her blood sugar was 450 mg. A fasting blood sugar on October 23rd, after having received 160 units of zinc protamine and 200 units of plain insulin the day previously, was 299 mg. On October 26th, acetonuria appeared and hospitalization was insisted on. At this time she was taking 512 units of insulin daily.

On October 29th, three days after admission to hospital, she developed an acute pharyngitis which was accompanied by a temperature of 99.2. By this time the insulin dosage was 960 units daily. Sulfanilamide therapy was instituted and the pharyngitis cleared up; but the fever and acetonuria persisted. On November 4th, she again began to vomit dirty dark brown material. The blood sugar was 399 mg. per cent and the CO_2 combining power was 24 vol. per cent. She was given 1,000 c.c. of 10 per cent glucose saline intravenously with 500 units of plain insulin subcutaneously. Subsequent to this 1,700 units of plain insulin were given in one day in divided doses. The vomiting and acetonuria disappeared and she developed insulin shock which was characterized by profuse perspiration. Blood sugar was 31 mg. per cent. Glucose by mouth and intravenously, brought relief. On November 5th, marked pyuria was discovered for the first time which practically cleared up after two days except for two to three pus cells per high power field, but the low grade fever continued. Intravenous pyelogram revealed bilateral hydronephrosis. Subsequently she received 3,000 units of plain insulin daily in divided doses which was sufficient to prevent acidosis, but glycosuria persisted. On November 30th, a palpable spleen was discovered. The liver had been felt to be three finger-breadths below the costal margin since her entry into the hospital. Because of these findings the diagnosis of hæmachromatosis was suggested. This could not be substantiated since there was no pigmentation of the skin. A biopsy was not done.

She continued on the same dosage of insulin but with poor control, until December 2nd, when she developed a temperature of 104°. There was a red indurated area over the right thigh; the site of an insulin injection. Concomitant with this acetonuria and vomiting reappeared. To combat this it was necessary to administer 5,780 units of plain insulin with orange juice in 24 hours. The acetonuria and glycosuria disappeared and the temperature fell to 99°. No insulin shock occurred. The area of induration gradually subsided without surgical intervention. The low grade pyrexia ceased on December 8th. Following this episode it was necessary to give her between three and four thousand units of plain insulin daily. She was completely aglycosuric between December 18th and December 26th, when she was receiving 3,600 units of insulin daily. A.C. and p.c. blood sugars on December 21st were 81.5 and 167 mg. per cent respectively. There were the occasions when it was necessary to discontinue the insulin for 12 to 24 hours in order to prevent the onset of insulin shock, but the glycosuria and acetonuria reappeared in a matter of hours and insulin injections had to be resumed. The pendulum swung very readily and rapidly from one extreme to the other.

On December 28th, following the suggestion of Dr. J. B. Collip, of McGill University, we gave her, by mouth, the "medullotrophic principle obtained from primary alcoholic extracts of the pituitary gland"[16]; the dosage being 2 c.c. three times a day before meals. Concomitant with this the insulin dosage was reduced to 500 units daily, but acidosis recurred and persisted despite the increase of the insulin to 2,000 units daily. Finally after using this extract for one week it was discontinued, since it had not reduced the amount of insulin necessary to control our patient's diabetes mellitus. Dr. Collip[17] employed this extract on ordinary cases of diabetes mellitus and he reported a few cases in whom it caused some reduction in the glycosuria; in others it was ineffectual.

On January 3, 1940, x-ray irradiation of the pituitary gland was started. We felt we had given the patient ample time to recover spontaneously from her insulin resistance, as has occurred in some of the cases recorded in the literature. We also had a standard by which to compare the effectiveness of this therapy; for her insulin dosage at this time was between three and four thousand units daily.

Dr. C. Liebman, chief radiologist of our hospital, conducted this therapy. Based on reported experience he considered it desirable to give the treatment in diminishing dosage. The factors and technique employed were as follows: 175 K.V.P., 10 M.A., F.S.D., 50 cm. Field—6 x 8 cm. Filters, Cu. 0.5 mm. plus Al. 1.0 mm. Time 5 min.

This gave 136 r units (measured in air without back scatter) per field per treatment. The central ray was directed to the pituitary gland through 3 fields—frontal, right temporal and left temporal. Ten treatments were given to each field, a total of 1,360 r units per field and

4,080 r units total for the three fields. For the first eleven treatments two fields were irradiated on one day and one field the following day. After this one field daily was treated at a time. The sixteenth to the twentieth treatments inclusive were given every two days and the last four treatments were spaced three days apart. The entire irradiation covered the period from January 3rd to February 13th, inclusive.

During the first two days of the irradiation therapy insulin was discontinued. Acidosis rapidly supervened; the fasting blood sugar on January 5th being 462 mg. per cent. At this time, Ellis'[18] method of employing insulin was adopted. This was done for two reasons; first, to be able to anticipate insulin shock, and second, to help improve her sugar tolerance. Twenty-five units of plain insulin with 200 c.c. of orange juice were given every hour for two days, but on this regimen she became progressively worse and on January 6th she again began to vomit dirty dark brown material. She also became stuporous and her face was flushed. To counteract this she was given 1,500 c.c. 5 per cent glucose saline with 1,000 units of plain insulin, in one single dose, intravenously. These measures removed the clinical signs of threatening coma but the acetonuria persisted. Following this episode, 50 units of insulin every hour was given with the diet, consisting of 1,000 c.c. of milk, and 100 grams of oatmeal divided into six equal parts. This regimen was adhered to from January 8th until January 13th. Her original diet of 1,750 calories was again resumed; the insulin dosage fluctuating between 300 and 960 units daily. During all this time she continuously excreted sugar and acetone, and she had lost 15 lbs. in weight. On February 14th, one day after the last irradiation treatment had been given, the acetonuria disappeared.

The patient continued to improve and was discharged from the hospital on March 18th, with instructions to take 880 units of insulin daily since this amount had kept her free from acetonuria, and allowed only a slight glycosuria.

At home her improvement was even more striking. One month after leaving the hospital her insulin dosage was 500 units daily. Nine months later 80 to 120 units was required. May 12, 1941, approximately 16 months after irradiation, her fasting blood sugar was 108 mg. on a dosage of zinc protamine insulin—40 units daily.

She has gained in weight and strength and at present weighs 130 pounds. She looks well and has resumed her usual household duties. The liver and spleen are no longer palpable but the hypertension has persisted. The pyuria has not recurred.

LABORATORY DATA

1. October 28, 1939.—X-ray of skull and sella turcica: no abnormalities noted.
2. November 7, 1939.—Urine sediment smear: no acid fast bacilli found.
3. November 22, 1939.—Blood Wassermann: negative.
4. November 23, 1939.—Intravenous pyelogram: bilateral hydronephrosis.
5. November 27, 1939.—Urine culture: *B. coli* found.
6. November 28, 1939.—Electrocardiograph: ventricular myocardial disease.
7. November 27, 1939.—Blood chemistry studies: non-protein nitrogen 25.1 mg. per cent; cholesterol 232.
8. November 29, 1939.—Hæmogram: red blood cells, 4,000,000; white blood cells, 2,700; hæmoglobin, 70 per cent.
9. November 29, 1939.—Icteric index: 6.7.
10. December 6, 1939.—X-ray of chest: no parenchymatous disease seen.
11. December 6, 1939.—Basal metabolic rate: plus 6 per cent.
12. December 6, 1939.—Blood culture: no growth.
13. December 27, 1939.—Reducing substance in urine: pentose 0; galactose 0; lactose 0. The sugar was completely fermentable.

SPECIAL INVESTIGATIONS

Studies were made to determine (1) whether the blood and serum of the patient contained an insulin antagonist; (2) whether the patient's blood contained an insulin destroying substance; (3) whether the patient excreted insulin in the urine.

These studies were attended by entirely negative findings.

ETIOLOGY OF INSULIN RESISTANCE

Our investigations threw no light on the etiology of insulin resistance in our patient. This is in accord with the experience of those who have investigated other cases.

The type and source of the insulin employed does not affect the insulin resistance, Marble[14] and Kerr, Skull and Petty.[8] Insulin made from the pancreas of various animals, such as beef, pork, etc., produced no alteration in the amounts of insulin necessary to control glycosuria. The use of zinc protamine and crystalline insulins likewise showed no advantages.

An insulin antagonist was not demonstrated in the blood, nor was it possible to demonstrate the presence of insulin in the urine of the patient. The experiment performed by Weiner[15] who postulated a "contra-insulin hormone", was repeated by us, and we too failed to demonstrate the existence of such a substance. Riddle[19] and Cope and Mark's[20] work on the rôle of the pituitary gland in diabetes mellitus was used as the basis for the experiments performed by Professor J. B. Collip and Dr. N. H. Neufeld, who also failed to demonstrate an insulin antagonist in the blood of our patient.

Levine, Hechter, Grossman and Soskin,[21] on the basis of the observation that *in vitro*, insulin is inactivated by sulphydryl compounds, studied the glutathione content of the livers of normal and hypophysectomized animals and of animals with decreased sensitivity to insulin produced by injections of an anterior pituitary extract. They were able to show that the livers of the pituitary injected animals contained somewhat more glutathione than the normal and considerably more than the very insulin sensitive hypophysectomized animals. Hyperactivity of the pituitary may in this way account, at least in part, for insulin resistance.

The very opposite suggestion is advanced by Himsworth[22] who suggested that there is a deficiency of "an insulin activating substance" or factor in the body of patients with extreme re-

sistance to insulin. If this were so no amount of insulin would then be effective. However, it has been demonstrated that insulin resistance is only relative since if enough is given characteristic effects are observed.

Bruger and Friedman[23] have shown that rabbits excrete insulin, provided large enough quantities are injected. The possibility that our patient was excreting insulin in the urine was considered. Examination of the urine for insulin as previously described failed to show its presence.

TREATMENT

The management of a case of severe insulin resistance is beset by many difficulties. The wide fluctuations in daily requirement of insulin, demands constant vigilance if coma and insulin shock are to be avoided. The large and frequent injections place a severe strain on the co-operation of a patient, even one tenacious of life. The cost of the large amounts of insulin required may use up the entire family income.

Under the circumstances, any therapeutic measure, even though based on the slimmest theoretical grounds must be tried. In our case a reasonable time was allowed for spontaneous remission and when this seemed unlikely to occur, consideration was given to the possibility that reduction of secretory activity of the pituitary by x-ray irradiation of the area of the brain in which this organ lies might offer some relief.

Such a method of treatment has been reported by others. Pieri and Sarradon,[24] Merle[25] and Cannavo[26] obtained satisfactory responses. Marble[14] on the other hand failed to benefit his patient. This procedure was carried out in our patient with the gratifying results already recorded.

It would be idle to speculate on the mechanism by which improvement was produced. Reduction in secretory or other modifications in the activity of the pituitary may have been the factor. On the other hand the radiations passed through the thalamic, hypothalamic and other regions of the brain. To what extent did this contribute to the results? And finally, the remission may have been entirely coincidental.

SUMMARY

1. A case of resistance to insulin has been described for whom 3,000 to 4,000 units of insulin daily were required to prevent hyperglycæmia, acidosis and coma.

2. Several experiments were performed in an attempt to demonstrate the cause of the refractoriness to insulin. None of these gave evidence of the presence of an anti-insulin or insulin destroying substance in the patient's serum, nor was evidence obtained to suggest that the patient excreted insulin in her urine.

3. The technique of irradiation directed to the pituitary gland and the very satisfactory response to this treatment in the case reported are described.

The authors wish to acknowledge gratefully, the co-operation received from Dr. M. A. Simon, Director of Laboratories, in connection with laboratory work.

Since this manuscript was prepared a paper on "Insulin resistance. Critical survey of the literature with the report of a case", Walter P. Martin, *J. Clin. Endocrinol.*, 1941, **1**: 387, has come to our attention. This paper contains a complete bibliography of the subject.

A full bibliography can be found in the reprints of this article.

CANADA BEGINS TO GROW CRANBERRIES.—Canada's first cranberry plantation at Lemieux, Nicolet County, Quebec, is expected to yield its first crop in 1943, according to an article by John Robitaille in the December issue of the *C-I-L Oval*. Representing an investment of some $100,000, the undertaking was begun in the spring of 1938 by Edgar Larocque. Canada now imports about $500,000 worth of cranberries annually from the United States, but by 1950 it is expected that a large percentage of Canada's present consumption will be produced domestically. The first requirement for the cultivation of cranberries is water and Mr. Larocque has built channels from nearby Lake Soulard and can flood his land in two hours should the need arise. Flooding kills insect pests but does not hurt the cranberries. Parasitic plants are destroyed with a spray of fuel oil and salt brine and weeds are kept down by a generous sprinkling of sand over the dark loam in which the plants are rooted.—C.I.L., December, 1941.