available,[13] but more time is needed before we can be convinced of its reliability. In the absence of such a test, an answer may be derived from (a) a series of families selected because both parents are diabetic (it is important that no attention be paid to the condition of the children at the time of selection of the families) and followed until all the children have passed age sixty or have died; (b) a series of families selected because one of the parents is diabetic (here again no attention must be paid to the condition of the children at the time of the selection of the families) and followed until all the children have passed sixty years of age or have died.

There is doubt concerning the sex ratio among those who became diabetic after the age of forty,[2, 9, 11] and concerning the relationship between parity and the frequency of onset of diabetes among women past the age of forty. While neither of these is directly a genetic question, both have bearing on the nature of the data collected for genetic studies, and both have bearing on the mode of expression of the gene(s) believed to cause susceptibility to the disease. A satisfactory answer to these questions could be obtained by following until death a group of men and a group of women of known parity, and known by examination not to have been diabetic at age forty.

The data needed to answer the several questions raised in the above paragraphs are not easily collected by any single center. A cooperative project, with several centers gathering the desired data, could supply information leading to an understanding of these problems. Such knowledge may shed light on some of the environmental factors which precipitate diabetes in those who are genetically liable to the disease. Physicians may then be in a position to prevent (or to reduce the likelihood of) the occurrence of diabetes in those genetically liable to the disease and thus be a major step closer in their conquest of diabetes mellitus.

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# Leonid V. Sobolev
## 1876-1919

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Leonid Vasiljevich Sobolev was born in 1876 in Trubchevsk, near Orel, Russia. He attended primary school at Karachev and secondary school at Novgorod-Severski. In 1893 he entered the Imperial Medical Military Academy at St. Petersburg, with which he remained connected throughout his career. Independent research which he did on diverticulosis of the colon while still a student in the Department of Histology and Pathological Anatomy, then under the direction of Prof. K. N. Vinogradov, was awarded the Iljonskay prize. In 1898 he was graduated with honors and was appointed Adjunct Assistant in the Pathology Department. He at first com-

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bined this with clinical work under Prof. Sirotinin, but gave it up for lack of time.

In August, 1899, he began to investigate the internal secretion of the islands of Langerhans. When he was only twenty-four Sobolev received his doctoral degree for work so outstanding that it must be considered in the same class as the brilliant investigations of von Mering and Minkowski in 1889, on which Sobolev built, and those of Banting and Best in 1921, for whom Sobolev's work was a starting point.

It is a matter of great regret that in our accelerated era the publications of such distinguished scientists are rarely read. Sobolev's most important papers were originally published in German as well as Russian, but even in Russia recognition came quite late and the full scope of his work is not yet completely grasped.* Elsewhere it is little known and rarely cited. It seems well worthwhile to examine its merits in detail here.

The experimental part of Sobolev's thesis material was worked up in the physiology laboratory directed by Prof. I. P. Pavlov; the morphological investigations were carried out in the Department of Pathology under Professor Vinogradov. Its title was "Contribution to the Morphology of the Pancreas following Ligation of its Duct, in Diabetes and in Some Other Circumstances, an Experimental and Pathological-Anatomical Investigation."

It was not at all a matter of chance that Pavlov was extremely interested in these investigations and even took an active part in the experimental work. Was it not Pavlov[1] who, while a student at the Imperial Military Academy of St. Petersburg, spent the summer of 1877 working in the laboratory of the renowned physiologist, Professor Heidenhain in Breslau, where he ligated the pancreatic duct in rabbits in order to study the morphological changes in the gland caused by the retained secretion?

As far as I can determine from the literature, Pavlov[2] was the first to use the microscope to make such examinations. He also observed atrophy of the parenchyma microscopically and was struck by the great number of lymphatic follicles in the interlobular and interacinic connective tissue. It is very probable that Pavlov interpreted as lymphatic follicles what he did not know were the islands of Langerhans. (Kühne and Lea[3] in 1882 had interpreted the islands as lymphatic structures.)

It is therefore quite understandable that Pavlov performed the first ligations of the pancreatic duct for Sobolev's experiments. In 1899, while doing routine microscopic examinations, Sobolev was fascinated by the islands of Langerhans which, according to him, could only be structures for internal secretion. He based this opinion on the absence of ducts and the very intimate relation with the tortuous capillaries. He stated the hypothesis[11] that it is the islands which, as anatomically and functionally independent structures, control carbohydrate metabolism, and tried to prove this by experimental and morphological research. It was known to Sobolev that von Mering and Minkowski[4,5] (1889 and 1890) had proved experimentally that total pancreatectomy in dogs resulted in a fatal diabetes, and that no diabetes was found when, after ligation of the Wirsungian duct, the pancreas had atrophied to a small string of connective tissue. It was thus clear that something persisted, and that something, in Sobolev's opinion, could only be the islands. Sobolev established that after ligation of the pancreatic duct in rabbits, dogs and cats there was no glucosuria and that the islands persisted. (Schulze[6] independently arrived at the same conclusion after tying off the pancreatic duct in guinea pigs.) Sobolev successfully grafted, in two dogs, the vertical part of the pancreas subcutaneously. A month after the operation, the fistulate duct of the graft closed and secretion stopped. After fifty and 130 days, respectively, the transplant was removed and on microscopical examination showed severe atrophy of the parenchyma, while the islands remained intact. Once more the resistance of the islands had been demonstrated.

Sobolev also studied the functional states of the island cells. He observed more than the normal number of granules in the protoplasm of the island cells after fasting. But in animals fed preponderantly on carbohydrates and receiving glucose intravenously, only a few granules were observed. This was even more evident in a dog with two thirds of the pancreas removed; here the island cells had atrophied. Sobolev concluded that the cells produce a granular substance which disappears when the organism must utilize a lot of carbohydrate.

Sobolev had noticed in guinea pigs as well as in rabbits two distinct types of granule-containing island cells. The majority of cells did possess fine granules in their protoplasm, but in addition, and usually located peripherally, bigger cells with coarser granules were observed. Sobolev did not pursue this observation. It required pathologic-anatomic investigations to furnish him with a clinical proof of his experimental conclusion that the islands are to be considered the morphological substratum of an internal secretion which controls carbohydrate metabolism.

*In 1950 Sobolev's thesis was reprinted in Moscow with an introduction by Prof. Rossiiski, from which I have borrowed some biographical data.

Sobolev expected intact islands in sclerotic and atrophic pancreases belonging to persons who had not suffered from diabetes, and indeed they appeared to persist and proved to be more resistant than the parenchyma. In pancreases belonging to persons who had died of diabetes, Sobolev expected qualitative or quantitative changes in the islands. In thirteen out of fifteen cases, quantitative changes were found; in four cases not one island was present, and in nine cases fewer than the normal number were seen. Moreover, atrophied and vacuolated island cells were observed in two cases. Thus atrophy and hydropic degeneration of island cells were described and drawn by Sobolev at the same time as, but independently of, Weichselbaum and Stangl.[7,8] Sobolev concluded that in diabetes the islands are less resistant, sometimes disappearing via atrophy. In fact, according to Sobolev diabetes could be considered as the result of a lowered resistance of the islands through an hereditary tendency, in view of the rather frequent familial occurrences.

Sobolev concluded his report of his investigations by indicating how the internal secretion of the islands could be isolated in order to use it in the treatment of diabetes:

"By ligating the pancreatic duct," he wrote, "we now have a means of isolating the islands anatomically and of studying their chemical properties freed from the digestive ferments. This anatomical isolation will permit the testing, in a rational way, of an organotherapy for diabetes."

Convinced of the difficulty of obtaining enough glands with isolated islands, he even advised the use of newborn animals (calves) in which the islands are well developed in comparison with the acinar tissue which, moreover, is functioning on a very low level.

"We are justified in the hope that in the near future the question will be decided whether or not this method of approach will succeed in relieving the ills of the diabetic patient."

Obviously Sobolev had no opportunity to isolate the internal secretion himself, for in none of his papers does a hint in this direction appear. It remained for Banting and Best[9] to isolate insulin in 1921 in the same way that Sobolev had indicated. A paper covering part of the results of his investigations was read by Sobolev in January, 1900, at a meeting of the Association of Russian Physicians at St. Petersburg and was published in the same year in Russia and in Germany[10] as a preliminary communication. His complete thesis (177 pages) was published in the spring of 1901 in Russian, and a condensed version of thirty-three pages appeared in German.[11] The extensive list of references shows that Sobolev had read practically all the papers of importance which had appeared up to 1900 in English, French, German, Italian and Russian.

After receiving his degree, Sobolev applied for a travel fellowship. At the discussion of his candidacy for this grant, Pavlov stated that he was impressed by Sobolev's ability: "an eminent scientist, penetrating deeply into his problem." Sobolev was abroad for two years which he spent in part in Paris at the Pasteur Institute[12] (1902), and in part in Germany at several places including Marburg[13] (1903). In 1903 he returned to St. Petersburg where in 1904 he was appointed prosector and lecturer in the Department of Pathology.

In the same year he published another important paper.[13] He had attended, in the autumn of 1903, a demonstration course given by Professor Benda in Berlin. Benda demonstrated, among other things, the organs of a fifty-five-year-old woman who had died of diabetes and pulmonary tuberculosis. Sobolev received a piece of the caput, corpus and cauda pancreatis and in the section of the corpus observed an island of 1½ mm. diameter. This island he for various reasons considered rather as a compensatory hypertrophic and hyperplastic island than as an adenoma. Almost all the other islands were atrophic and a few showed hyaline degeneration. All changes were recorded in a set of drawings. The papers published by Opie[14,15] in 1901, the first to describe hyaline (now amyloid[16,17,18]) changes in the islands in diabetes, and by Nicholls,[19] who in 1902 described the first island cell adenoma, were both unknown to him. Sobolev was the first to report a macroscopically visible, circumscribed hypertrophic and hyperplastic island in the autopsy of a diabetic, and even now it remains most difficult to identify the borderline between hyperplasia and adenoma in those small structures.

In 1910 Sobolev[12] communicated lack of success in finding a substance which would cause diabetes by destruction of the islands. He conducted an extensive microscopical investigation of carcinoma and sarcoma of the pancreas, in which diseases the islands appeared to be the most resistant parts, surviving uninvolved even after tumor tissue surrounds them. This explained the absence of glucosuria. Thus once again microscopical examination revealed that whenever the pancreas is diseased but diabetes is absent, the islands remain relatively free from involvement. In those cases in which the Wirsungian duct was occluded by carcinoma a regeneration of island tissue from the smaller ducts was observed in the tail of the pancreas. Sobolev also con-

sidered the possibility of the existence of an island cell carcinoma; this would be a rarity, and could not originate from prenatally formed islands but from island cells which were later derived from duct epithelium.

In 1912, Sobolev[20] returned to his favorite subject for the last time. On morphological grounds he thought that regeneration of islands from smaller branches of the main duct, as it is to be seen in diabetes, leads to insufficiently differentiated and thus functionally inferior island tissue. Sobolev explained thus the presence of oversized islands in diabetes. These are unable, because of their inferiority, to replace diseased island tissue.

Ill health forced Sobolev to resign in 1912 and in 1919 he died, only forty-three years old, in the clinic for mental diseases in St. Petersburg. He was a gifted teacher who was interested in his students and a remarkable scientist who had a strong feeling for the technical side of his profession. He published in all, on various subjects, about forty papers, twelve of them in German. During his entire working life he gave a large share of his time to the study of the islands of Langerhans. His investigations were in many respects pioneering, and his accomplishments great by any standard.

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# ABSTRACTS

*Allwood, M. J.; Ginsburg, Jean; and Paton, A.* (Sherington Sch. of Physiol., St. Thomas's Hosp. Medical Sch., London S.E. 1, England): THE EFFECT OF INSULIN HYPOGLYCAEMIA ON BLOOD FLOW IN INTACT AND SYMPATHECTOMIZED EXTREMITIES IN MAN. J. Physiol. *139*:97-107, Nov. 14, 1957.

Blood flow was measured in the limbs of seventeen intact and fifteen sympathectomized human subjects during insulin hypoglycemia, using venous occlusion plethysmography. In 'skin' segments—hand and foot—there was a variable response to hypoglycemia in intact limbs. A vasoconstriction occurred in sympathectomized limbs. In 'muscular' segments—fore-arm and calf—there was an increase in flow during hypoglycemia in both intact and sympathectomized limbs. The onset of flow changes following intravenous insulin was retarded by the infusion of a glucose-saline solution. Flow changes were absent in three subjects who failed to develop clinical evidence of hypoglycemia.

The variable response in the skin of the intact limb is believed to result from the constrictor response to circulating adrenalin being opposed by a dilatation mediated by the sympathetic nerve supply. It is suggested that the increased vasoconstrictor response seen in the sympathectomized