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The story of insulin discovery

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ABSTRACT

Many researchers had tried to isolate insulin from animal pancreas, but Frederick Banting, a young surgeon, and Charles Best, a medical student, were the ones that succeeded. They both worked hard in very difficult conditions in the late 1921 and early 1922 until final success. They encountered problems with the impurities of their extract that was causing inflammations, but J. Collip, their late biochemist collaborator, worked many hours and was soon able to prepare cleaner insulin, free from impurities. This extract was administered successfully to L. Thomson, a ketotic young diabetic patient, on 23 January 1922. Following this, Eli Lilly & Co of USA started the commercial production of insulin, soon followed by the Danish factories Nordisc and NOVO as well as the British Wellcome.

Nicolae Paulescu who was professor of Physiology in Bucharest, was also quite close to the discovery of insulin but the researchers in Toronto were faster and more efficient. Banting and Macleod won the Nobel price, which Banting shared with Best and Macleod with J. Collip. The contribution of Paulescu in insulin discovery was recognized after his death.

1. Background to the discovery

In 1869, Paul Langerhans, a German medical student, described the pancreatic islets in his thesis. At that time, he knew nothing about their significance. In 1889, von Mering and Minkowski, who were conducting pancreatectomy experiments, showed that diabetes develops without the presence of pancreas [1]. In 1893, the French E. Hedon performed total pancreatectomy on a dog and transplanted a small part of the pancreas under its skin. The dog developed diabetes only after the graft was removed. With this experiment, the internal secretion of the pancreas was confirmed [2]. Following that, there was significant amount of research regarding the secretion of the pancreas. Many researchers tried to treat diabetes using pancreatic extracts. However, there were only a few publications because the results were disappointing. It is estimated that approximately 400 researchers dealt with this issue between 1890 and 1910 [3].

2. First successful attempts with many doubts

Among the many researchers of the pancreatic extracts, a prominent one is the German G.L. Zulzer. A young doctor in about 1900, he experimented with alcoholic extracts of internal pancreas secretions in rabbits and dogs. After some encouraging results, Zulzer injected to a diabetic patient in a very serious condition with the extract, in a private clinic in Berlin, and repeated the injection next day. The patient showed clear clinical improvement, but there was no more extract available.

Zulzer named his therapeutic substance “Acomatol” and managed to get funding for his studies from the Schering Company. But the subsequent applications in humans, apart from the elimination of diabetic symptoms, were associated with adverse reactions such as vomiting, fever and, in some cases, even convulsions [3]. I wonder if these were actually febrile convulsions or even severe hypoglycaemia, but there is no relevant information.

Zulzer published three articles on the results (in 1907–1908) and concluded that “it is possible to inject pancreatic extract to stop glucosuria and ketonuria in a diabetic patient without changing his diet”. Following these publi-

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cations, J. Forschbach, in Minkowski clinic at Breslau, tried to administer Zulzer's extract as well, however his conclusion was negative because of the toxic adverse reactions [4]. Consequently, Schering Company withdrew the funding for Zulzer's studies. In 1911, the company Hoffman-La Roche financially supported his research, and in 1912 Zulzer got the patent for the use of extraction granted. However, all animals that have received injections of the extract presented convulsions. He kept experimenting until 1914 when he joined the army because of the 1st world war [4]. Meanwhile, in 1911–1912, on the other side of the Atlantic, in Chicago E.L. Scott, a medical student thought that protease enzymes of the external secretion may be responsible for the failures of the extracts at that time. Therefore, he ligated the pancreatic duct in order to render the externally secreting cells atrophic, but he was not satisfied. Eventually, he tried the use of alcoholic extract and got encouraging results from testing this in four dogs [5]. However, his supervisor, Professor A. Carlson, modified the conclusions of Scott's experiments in a more conservative way and recommended further investigation. The Professor of Physiology in Toronto, J.R. Macleod, told Scott that it would be impossible to isolate internal secretion for a variety of reasons, such as:

1. The external secretion *in vitro* destructs the internal secretion.
2. There are probably no reserves of internal secretion to isolate.
3. The internal pancreatic secretion is in an inactive form and becomes activated probably in blood.

Scott was disappointed and turned to another research field [3].

In the same year, G.R. Murlin and B. Kramer published comments related to a reduction of glucosuria in dogs following administration of pancreatic extract. Their conclusions, however, were very hesitant [6].

In 1915, I. Kleiner, another American, published his findings on the use of pancreatic extract. After the war, in 1919, he came back to the scene with enthusiasm about the therapeutic value of the pancreatic extract. Blood glucose measurements provided proof of efficacy. Minor febrile reactions, likely due to protein impurities, could in future be addressed through better methods of chemical purification [7]. However, Kleiner did not continue his research, probably due to lack of funding. When later asked about the reasons for not continuing, he succinctly replied "This is a long story" [3].

N. Paulescu (Fig. 1), a Professor of Physiology in the Medical School in Bucharest, started experimenting with pancreatic extracts in 1916. French language journals published his conclusions that "the extract of the pancreas will be the method of treatment of obese and ketotic diabetics". Paulescu's publications appeared in 1921, but the journal was francophone and he himself was a Romanian so he did not receive much of attention. The main publication (he published under the French equivalent of his name: Paulesco) was in the Archives Internationales de Physiologie of Liege and Paris on the 31st of August, 1921 [8].

I wonder whether the devaluation of Paulescu's investigations was due to his subsequent involvement in politics with the party of "Romanian Christian Nationalists", which had strong anti-Semitic and anti-Masonic character. The results

Fig. 1 – N. Paulescu.

of Paulescu's investigations were better compared to other researchers that worked before him on pancreatic extracts [9].

However, in order to perform his experiments, Paulescu needed 20 ml of blood in order to obtain a glucose measurement, while on the other side of the Atlantic, a method had been already discovered, in which only 0.2 ml of blood was sufficient. Indeed, Paulescu's experiments were not characterized by a full clinical application in humans. There is no doubt that Paulescu actually did discover insulin, but his success was annulled as he did not continue his experiments; however, it remains historically recognized [9]. Paulescu died in 1931 and was buried in a cemetery for prominent Romanians. His contribution to the discovery of insulin was recognized at the celebration of 50 years of implementing insulin therapy.

3. Research in Toronto

Frederic Banting, born in 1891, completed his studies in the Medical School of Toronto with cutbacks due to the First World War (Fig. 2) [10]. After working in a hospital in England, Banting was sent as a captain to the military front. He was shot by a projectile and he was awarded with the Military Cross. He returned to Toronto in March, 1919 and served in a military hospital for a while. He became a member of the Royal College of Physicians of London and the Royal College of Surgeons. He then decided to open a private practice in the city of London, 180 km away from Toronto.

Although his clinic was well situated in town, Banting, an unknown new doctor, had not examined a single patient in the first 28 days. At that time, the patients were few and the benefit modest. Shortly afterwards, Banting took a part-time job in London Western University, as an assistant professor of Surgery and Human Anatomy under professor Miller.

On October 30, 1920, Banting, in preparation for a lecture on the metabolism of carbohydrates, read an article published by M. Barron on the lithiasis of pancreas leading to atrophy and loss of exocrine function. At 2 a.m. he came up the idea that if the exocrine part of the pancreatic could be-

Fig. 2 – F. Banting. Photo courtesy of the Canadian Diabetes Association.

come atrophic experimentally, one might receive the internal secretion of the pancreas without impurities.

The next day he reported the idea to Professor Miller, who recommended to him to discuss the subject with Professor Macleod in Ontario, who was considered a specialist on the metabolism of carbohydrates. On November the 7th, he had a discussion with Professor Macleod (Fig. 3) who, after many misgivings, agreed to adopt the proposed research, because, as he said, "even negative results would have great significance in physiology".

The first experiment was performed by Banting on 17 May 1921. Professor Macleod gave him two students as assistants to help him during summer. The first was Charles Best, (Fig. 4) who, among other things, would take measurements of sugar in the urine and blood of animals. 22-year-old Best was the son of a family doctor and had just passed the exams in physiology [3]. The room where their experiments took place, a small old operation theater for experiments, was not in use for many years. Macleod was not optimistic about the outcome of experiments. The first experiment involved a dog and Macleod participated himself [3].

The operation lasted 80 minutes but the dog died due to an overdose of anaesthetic. Banting and Best continued a series of experimental surgeries. They had to learn from their

Fig. 3 – J.R. Macleod. Photo courtesy of the Canadian Diabetes Association.

Fig. 4 – C. Best. Photo courtesy of the Canadian Diabetes Association.

mistakes and become more "intelligent" by better learning the subject of their research. The first four dogs died. The fifth dog survived after the transplant operation. The researchers continued, without interruption, with the surgery of pancreatic duct ligation. One dog succeeded the other.

Banting and Best did great work that summer. They cleaned the blood from themselves and the area of experimental surgery. They took the role of husbandry, cleaners, nurses, doctors, researchers. They were determined to succeed. At some point, when they started to have problems with the provision of dogs from the University, they found the solution in market dogs from the streets of Toronto. Charles Best later described Banting dragging a dog to the laboratory tied to his tie. The situation was rather tragic. At the same time, the director of the Board was in Scotland for his holidays. The first results of their experiments were controversial, however, they were highly determined. At one stage, Best took a break to have short-term holidays.

Then Banting did everything on his own, and discovered that the solutions of the chemicals used for the measurements were not in proper condition, the glassware was dirty, and Best's measurements were unreliable. Best came back refreshed from his holidays, only to find a dismal Banting, determined to reprimand him regarding the quality of his laboratory work. At this point, Best could have left offended, but he did not. He washed all the glasses and prepared new solutions. And since then, they became an inseparable team. In addition, Best decided to continue filling in for the other student for the rest of the summer and finally continued to be the companion of Banting for a long time.

In early July, Banting and Best operated on seven dogs with pancreatic ligated duct. The ligation of the duct was not successful in five out of the seven dogs. They had already operated in 19 dogs. Twelve of them died because of postoperative complications [3].

On the 30th of July, Banting removed the pancreas from a dog that had the pancreatic duct ligated for 53 days. He put the pancreas in an ice bath with sodium Ringer solution. He placed the material in low temperature in sodium

chloride. He cut small pieces of the cold pancreas. The material was worked with sand in the mortar. He passed the material through filter cloth and paper to remove the solids. He then warmed the filtrate at 37°C. In the morning of the 30th of July, Banting injected a dog intravenously with 4 cc of this fluid. He observed a significant drop in blood sugar. He then gave sugar to the dog through a nasogastric catheter. The dog's blood sugar rose, despite injections of pancreatic extract, but was not increased as high as in the other dogs that were not injected with this extract. It was Saturday, 6:15 p.m., when Banting and Best decided to go to sleep. The next morning, the dog was in a coma but died without a very high blood sugar, which was something promising. On Monday the 1st of August, a new extract preparation was ready for use. They injected a very ill dog with 8 cc of the extract. The dog's blood sugar fell and the animal stood on his feet and walked. Banding gave another injection of extract. But the dog fell back into a coma and died at 3:30 p.m. Banting and Best did not have the courage to perform autopsies of these two dogs but were very impressed by the recovery from the coma. Meanwhile, there were no other dogs available. Best urged Banning to do pancreatectomy once without the duct ligation [3]. On August the 3rd, the intervention was performed and proved to be very successful. The dog survived with the help of several injections of the extract. The name Isletin was given to the extract. The effect of liver's and spleen's extract was tested but with no results. Only Isletin decreased the blood sugar. The morale of the two researchers was very high now. The Banting wrote a letter to Professor Macleod in which he presented fifteen queries. One of these was the application of the extract in humans. He asked for better facilities in the experimental surgery, as well as assistance with more staff. He also wrote nice comments for Best [3].

On September the 6th, Banting received a letter from Macleod, mentioning that he considered their findings "certainly very encouraging and definitely positive". He also wrote that "with these experiments we have to convince ourselves of the value of the extract for the treatment of diabetes, but also to convince as well the scientific community." He asked for more successful experiments. He also asked them to take into account the dilution factor of blood from the administration of liquids.

Banting and Best continued with more experiments, operating and sacrificing more dogs. Sometimes they had bad luck. Inflammations, bleedings, and deaths were frequent events. They tried granting Isletin rectally, which did not work. They discovered that mixing trypsin with extract destroys the inner secretion. On September 17th, Isletin was given subcutaneously for the first time, however, the result was not so good [3].

When Macleod returned to Toronto on September 21st, Banting and Best had completed new experiments. The dog they had operated on, on August the 11th, lived for twenty days with injections of Isletin and died due to lack of extract but the challenge was almost established. More detailed study and purification of the extract, in order to avoid causing aseptic inflammation in the injection sites, was needed. Additionally, they tested different ideas in animals.

In all great discoveries there is always a little, albeit important history. Human moments, emotions, conflicts, compromises. Something like this was part of the adventure of the discovery of insulin. Banting met Macleod and asked him to help to improve their work conditions: a husbandry to take care of the dogs, the floor of experimental surgery to be repaired and of course a salary for him. Professor Macleod had a lot of objections. There were no funds for repairs; also they were going to be transferred to a new building. Their research was nothing exceptional as compared with other projects of the University. How could he possibly request from the board of the Medical School all the things Banting demanded?

Banting then threatened that if in 24 hours Mcleod did not provide the facilitations he asked for, he would leave and work for another University. For Best, that was a huge surprise. Nobody had spoken in such a way to this professor. The debate between the two men was very intense and obviously Banting was filled with anger.

Outside Macleod's office Banting told Best "I'll show that little son of a bitch that he is not the University of Toronto" [3].

The improvements began two days after the Banting-Macleod quarrel. A more spacious room was found for the dogs to be kept in; a part-time husbandry was granted; the floor of the surgery was repaired. From October the 1st, Banting was appointed as a special lecturer of Pharmacology with a salary of $250 per month. Moreover, a retrospective bonus of $150 was granted to Banting and $170 to Best. Banting was relieved, but in early October he asked Macleod to strengthen their team with the biochemicist James B. Collip who was aware of the experiments and expressed interest in participating. Macleod at this stage denied this request [3].

On November 14th, Banting presented their findings at a scientific gathering of doctors and students. Macleod made a long eloquent introduction for the subject of their research. He often used "we" and did not leave much room for Banting to become distinguished. His nervousness and the lack of experience made Banting lose the battle of impressions. From this event, however, it was concluded that they should try a long-survival experiment on a diabetic dog [3].

At 2 a.m. on November 16th, 1921, Banting thought of using fetal pancreas of cows to receive the extract. He did this on the next day and the cows' pancreatic extract proved to be very active in the dogs. He then tested a new porous porcelain filter (Berkefeld filter), which removes bacteria, and the extract is sterilized without boiling, because boiling was shown to destroy the inner secretion. From such an extract, Banting subcutaneously injected 1.5 cc to himself and saw that it did not cause a reaction. The experiments continued while the first publication was prepared and sent to the *Journal of Laboratory and Clinical Medicine* to be published in the February issue of 1922 [11]. The authors were two: F.G. Banting and C. Best. Macleod declined to participate with his name in the publication. In the paper, it was stated that similar research were performed by N. Paulescu, which, however, mentioned that "indicate that intravenous injections in peripheral veins produce no results and experiments show that the second injection does not take this result as the first." At that point the team in Toronto was questioned why they did

Fig. 5 – J.B. Collip. Photo courtesy of the Canadian Diabetes Association.

not take care to correctly translate Paulescu's publications from the French language, since he did not write anything negative on the substance discovered by him. On December the 2nd, an injected extract killed a dog after 90 min. On December the 6th, the two researchers decided to use alcohol in the receipt of the extract. They performed tests also in the pancreas that they took off from the dog. The extract was effective [3].

In mid-December 1921, J.B. Collip (Fig. 5) joined the research team. Twenty-nine years old at the time, he had a PhD since 1916 and was a Professor of biochemistry since 1920. He had published many papers on internal secretions and immediately began working with pancreatic extracts in rabbits. He found that the extract was active in the rabbit as well. He proposed to measure the activity of the extract from its effect on healthy rabbits.

Alongside Collip, Banting and Best did their own tests and observations. They unsuccessfully injected extract per os in a diabetic classmate of Banting. They had many failures when attempting to produce the active extracts. At the same time, Collip found an improved manufacturing process to produce an extract with very good activity. He also found that the extract was able to suspend ketogenesis and replenished the liver with glycogen [3].

On December the 20th, Banting, very nervous, presented their research at a meeting of the American Association of Physiology at Yale University in New Haven. Professor Macleod responded fluently to questions from participants. Most questions were related to the toxicity of the extract and what differences Banting and Best research had from the previous research carried out by Zulzer, Scott, Kleiner, and Paulescu. The main answer was "the long survival of two diabetic dogs". One of those, named Marjorie, survived for 70 days with injections of the extract. Banting, however, was disappointed by his poor presentation. Macleod stole the impressions with his academic experience. Banting then began to see Macleod with suspicion, because although he had no involvement in the experiments, and was on his holidays abroad, was now talking about these experiments using "us" [3]. The conference was attended by the representative of the research department of the pharmaceutical company Eli Lilly Co, which would later play an important role in the industrialization of insulin.

After this historic report, the members of the team worked in the department of Macleod, somewhat isolated from one another, but by agreeing to discuss the findings all together. Another student, Clark Noble was added to the group. In early January the phenomenon of hypoglycemia in rabbits and the therapeutic value of glucose administration were observed by Collip. Such knowledge was also acquired independently by Noble. Banting was rushed to give the extract in humans.

The first patient was a 14-year-old boy named Leonard Thomson, who had reached the brink of the grave. He weighted a mere 27 kg, his urine was full of acetone and sugar, his breath was ketotic and waited for the inevitable end. On January 11, 1922, the first injection was administered. The outcome was moderately satisfactory. The sugar fell from 440 to 320 mg, but the patient presented signs of inflammation at the injection sites. They administered two doses of the extract, however, due to the inflammation the temporary suspension of injections was decided [3].

Working hard, long hours, Collip quickly produced a cleaner extract which was administered on the 23rd of January. The results were by far better [8,9]. The path to the wide application of insulin therapy had opened. Ultimately, Collip succeeded in a few weeks what Zulzer had failed to achieve for years [10].

Collip wanted to get his own patent on the method of cleaning the pancreatic extract. On the 25th of January, 1922, and after many debates, Banting, Best, Collip and Macleod signed an agreement for cooperation that prevented them from doing separate individual actions towards ensuring patent [3].

Meanwhile, the progress of Leonard Thomson with injections of pure extract was most impressive [11]. In February 1922, the injections of the miraculous extract were administered to six patients [11].

At the same time, Banting, Best and Macleod wrote several articles regarding the internal secretion of the pancreas. In late February, an article was published in the *Canadian Medical Association Journal* entitled "Pancreatic extracts in the treatment of diabetes" with Banting, Best, Collip, Cambell and Fletcher as authors [12]. In this publication, they reported the involvement of Collip in the procedure of cleaning the extract and the participation of Fletcher's patient L. Thomson. The newspapers showed interest and *The Star* published a comprehensive interview with Banting [13].

At the same time (25th of February 1922) Paulescu successfully administered his extract to humans. On the 3rd of March, he gave his extract to a second patient. He asked and took patent on the method of manufacturing through the secretion he called "pancrein" [3,8]. However, the speed and quality of work in Canada and later in the USA left behind Paulescu's work and patent. In April, the Canadian researchers decided on the name of Insulin for the pancreatic extract, a name that had been proposed by a Belgian doctor for the internal secretion of the pancreas, a few years prior to its isolation [14].

Macleod did a scientific presentation in the American

Association of Physicians on the 3rd of May, 1922. There was expansive admiration and appreciative comments [14]. This was the beginning of a new era. Juvenile diabetes mellitus would be a short and fatal disease no more.

On the 21st of August, 1922, Banting was appointed as head of hospitalization for diabetic patients of the General Hospital of Toronto, a paradox for a surgeon, but in this case it was the right decision [3].

In February 1923, there was enough pancreatic extract available in the USA as the pharmaceutical company Eli Lilly began the mass production of insulin followed by the Medical Research Council in London (the rights acquired later by the company Wellcome). In Denmark, the non-profit Nordisk was founded in 1923 and the company Novo in 1925.

4. The glory and the rewards

As the glory of the discovery of insulin was growing, so did the problems among the protagonists. Banting and Best had cool feelings with Collip. Banting always had obsessions with Macleod because during the crucial summer of experiments he went on holiday and later shared or even took the glory [13]. Reading a single view of one of them one can find many things right. But it seems that when the glory is too much, it can cause dizziness.

The Nobel Prize was awarded to Banting and Macleod on October 26th, 1923. Banting got frustrated because he shared the price with Macleod, whose contribution he considered superficial. Banting immediately announced that he shared the prize and the accompanying money with his co-worker, C. Best. Immediately, Macleod announced that he shared the prize with Collip [3]. The Medical school of Toronto decided upon a reward for Banting, establishing for him a research institute and private office in the School for research, but with no teaching obligations.

Banting also received an award by the Parliament of Canada that granted $7,500 a year in order for him to remain focused on his research [3]. The University of Edinburgh also gave the "Cameron award" to Macleod who was born in Scotland. Professor Paulescu, who claimed that he was the first who discovered insulin, complained but to no effect.

5. The following years for the protagonists

In the coming years, Professor Macleod strengthened the research on insulin and proved to be a very capable manager. He left Canada in 1928 as elected professor of physiology at the University of Edinburgh. In 1933, he died at the age of 59 years suffering from severe arthritis.

Banting continued to be a restless investigator. He tried many ideas as a researcher and made several observations on insulin therapy [3]. During the last night of his life, he was in Montreal talking with Collip. The old disputes were forgotten [13]. He was killed in an airplane accident on February 20, 1941, on a military mission [3].

Charles Best succeeded Macleod as Professor of physiology in Toronto. In his lab heparin was later discovered. He died in 1975.

J. Collip worked hard to isolate hormones. His investigations on the parathyroid hormone, ovarian hormones, ACTH and the gonadotrophins are innovative. He became chairman of the Medical School of Ontario and died at the age of 72 in 1965.

The question on who discovered insulin is answered by history. The first report of Banting and Best on the administration of insulin to humans had these two investigators as authors. Professor Macleod at some point admitted that he was playing the role of an impresario [3]. However, it appears that he played this role well. He played a significant role in the speed by which insulin was industrially produced and became known as a new therapeutic method [9].

However, some facts can show us that major discoveries are not sudden and heaven-sent. Von Mering and Minkowski discovered that if the pancreas was removed, diabetes ensues. Zulzer first administered pancreatic extract to a man. The toxic effects prevented his investigation from reaching clinical application. Scott and Kleiner had positive findings, but did not have the courage to continue. Professor Paulescu did well and many believe that he was the first who discovered insulin, because his publication appeared five months prior to those of Banting and Best. Paulescu's publication had higher scientific characteristics compared with the publications of the inexperienced Banting and Best and were up from April and August of 1921 [15] but the Romanian researcher did not have the industrial methods and was unable to compete with the Canadians in speed. Thus, during the time that Paulescu was trying to obtain larger quantities of "pancrein" the Canadians had time and improved the manufacturing process of insulin from the pancreas of cows, a method soon industrialized by company Eli Lilly, USA. Moreover, Paulescu did not publish results for pancrein administration to humans, unlike Banting and Best who eventually managed to clean up and administer insulin to a human, with Collip's valuable contribution.

Banting and Best were not fully aware of older studies, and had not read Paulescu's publications [8] carefully. Their actions were characterized by haste and impatience. However, Banting and Best understood that this was a race and they wanted to be the winners. This belief produced a new idea almost every day, which was immediately implemented, and that is why they succeeded. But many researchers had contributed to the discovery of insulin, as already mentioned. The contribution of Paulescu was recognized after his death. A part of the Nobel Prize perhaps rightfully belonged to him, but the Nobel prizes once given are not subject to objections.[1]

[1] Shortly before his death in 1931, N. Paulescu wrote the following: "Formerly I believed and maintained that a scientist can work in perfect safety, convinced as I was that the date of his publications protected him against any injustice. Unfortunately, I am obliged to admit now that I was utterly mistaken in this regard. I am not dominated by pride and I struggle against this odious vice. Indeed, on publishing my discovery I never for one moment thought of publicity, which could have affected my modesty that I consider one of the first qualities of a scientist. But I certainly cannot accept another, more odious defect, that of the theft of someone else's scientific property".

Finally, we must not forget that the first successful administration of insulin in humans has mainly achieved by a young surgeon and a medical student who worked in difficult conditions with determination, selflessness and belief in success. They deserve the largest share of glory. Their absolute devotion to a high target such as the discovery of insulin should be followed by every researcher.

Conflict of interest

The author has no conflicts of interest to report.

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