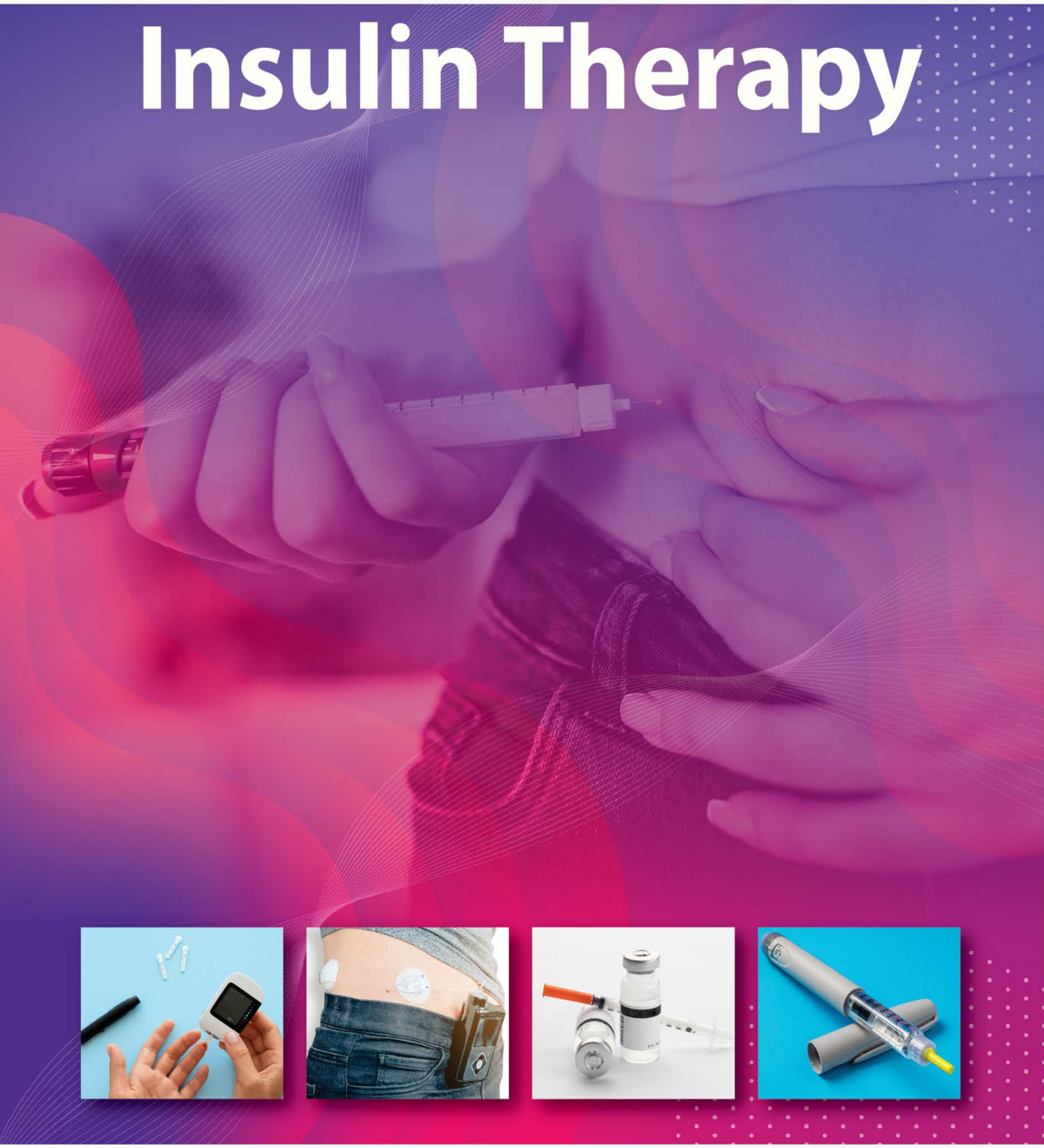
Practical Insulin Therapy



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Contents

CHAPTER 3

Evolution of Insulin Therapy

INTRODUCTION

"Insulin" which Master Leonard Thompson received on January 19, 1921 was a murky light brown liquid with significant sedimentation and had to be heated before subcutaneous injection to increase its solubility. It was 1:1 mixture of beef pancreas extract and alcohol. In the case papers at Toronto General Hospital, in Canada, where it was administered to a human being for the first time ever, it was mentioned as "Dr McLeod's serum." It was officially christened a few months later as insulin. There was a significant drop in blood glucose after the first injection but ketosis persisted and Master Thompson developed an injection site abscess. Obviously, it was too impure to continue. Collip, the fourth member of the team that discovered insulin, and a biochemist with a special interest in protein purification, who was working day and night on the purification of pancreatic extract and improving its purity continuously as an ongoing process even before it was administered to master Thompson on January 19, 1921 increased alcohol content of extract and improved it further. Master Thompson received his second dose of insulin on January 23, 2023. This time, the improvement in blood glucose was far greater and there were no side effects. Since then, there has been continuous ongoing improvement in evolutionary manner as regards purification, structure, pharmacokinetic capabilities, suitability for individual needs, reduction in side effects, modes of administration, etc. Insulin analogs which we use today in day-to-day clinical practice with precise administration devices are poles apart from murky light brown precipitate which was injected in Master Thompson's subcutaneous tissue with a crude metallic syringe and a blunt needle resulting in unbearable pain, 100 years ago. Let us review this fascinating, ever-evolving journey of 100 years.

PURITY OF INSULIN

Though the second dose of insulin received by Master Thompson was better, it still had many impurities which included several other proteins from

pancreatic extract. Purification of insulin was a continuous process till the introduction of genetically engineered human insulin in the market.

In the initial experiments, dog pancreatic extract was used. Subsequently, bovine pancreatic extract was the starting material for purification. In 1923, Illy Lilley was the first company to mass-market insulin for the first time under the Iletin brand. In 1926, the first progress toward insulin purification occurred through the availability of insulin crystals. The conventional bovine insulin was purified by the process involving a series of isoelectric precipitations and recrystallizations. However, in spite of the method of purification, conventional insulin contained some impurities in the form of proinsulin, glucagon, pancreatic poly peptides, somatostatin, vasoactive intestinal polypeptides, etc., in very small amounts.

In the seventies, highly purified bovine insulin, soon followed by monocomponent bovine insulin was introduced. Improved purity led to reduced chances of significant anti-insulin antibodies and reduced chances of therapy-related insulin resistance.

STRUCTURE OF INSULIN

The structural difference between bovine, porcine, and human insulin is enumerated in **Table 1**.

The insulin molecule consists of two polypeptide chains. The shorter "A" chain contains 21 amino acids while the longer "B" chain contains 30 amino acids. Bovine insulin differs from human insulin by three amino acids (two in the "A" chain at the 8 and 10th positions and one in the "B" chain at the 30th position). Porcine and human insulin have an identical "A" chain while it differs by only one amino acid (at 30th position in the "B" chain). The following table shows species of insulin and the corresponding amino acids at the 8th and 10th positions in the "A" chain and the 30th position in the "B" chain (at all other positions in both chains, the amino acids are identical) **(Table 1)**.

The aforementioned structural differences between bovine and porcine insulin with human insulin were responsible for systemic allergic reactions that were occasionally seen in clinical practice. Since porcine insulin differs from human insulin by only one amino acid, the prevalence of allergy to porcine insulin is less than that to bovine insulin.

TABLE 1: Structural differences between bovine, porcine, and human insulin.

	"A" chain		"B" chain
Type of insulin	8th position	10th position	30th position
Bovine	Alanine	Valine	Alanine
Porcine	Threonine	Isoleucine	Alanine
Human	Threonine	Isoleucine	Threonine

The commercially available human insulin is immunologically identical to insulin produced in the human islets of Langerhans, hence allergic reactions to human insulin are extremely rare and are obviously due to the presence of additives and preservatives.

Besides the above-mentioned differences, human insulin has a neutral pH while conventional animal crystalline insulin has an acidic pH. Neutral pH makes them more stable and more compatible with the tissues.

Besides problems related to structural differences, demand–supply mismatch of raw material (bovine/porcine pancreas) was a major bottleneck leading to inadequate supply of finished insulin in the market. This also led to cost escalation. In advanced countries, porcine insulin was introduced soon after bovine insulin, while it was introduced in the Indian market around 1980 and it was costlier than bovine insulin. Thus, though it reduced immunological issues to some extent, availability problems persisted. All these issues were automatically eliminated when human insulin was introduced in the market. Human insulin was initially manufactured by a semisynthetic process for a short period. The manufacturing was subsequently upgraded to biosynthetic method using genetic engineering technology, [recombinant deoxyribonucleic acid (DNA) technology]. In this process, a plasmid is isolated from a bacterium (*Escherichia coli*) or a fungus (*Saccharomyces*) and cut open. Insulin-producing gene from β-cells in the pancreas is then inserted in the plasmid and both are recombined together by DNA ligase enzyme and inserted into suitable host (*E. coli* or *Saccharomyces*) which starts synthesizing insulin. A chain and B chain are produced separately by an identical process and then both the chains are joined together to form the complete insulin molecule having 51 amino acids. Thus, the introduction of genetically engineered human insulin, which has exactly the same structure as that of native human insulin secreted by β-cells in the pancreas, has eliminated several issues, such as immunogenicity, raw material shortage, lipodystrophy at the injection site, and availability at one go and has made animal insulin redundant. This was a major milestone in the continuous evolution of insulin development. Human insulin was commercially introduced in 1982.

LONGER-ACTING INSULIN

Insulin introduced in clinical practice initially was a short-acting insulin and thus, besides its purity problems, major additional drawbacks were the need for multiple daily injections to cover all major meals and the inability to maintain adequate hepatic insulinization throughout the night without producing hypoglycemia. Soon after the introduction of insulin in clinical practice, work on the development of longer-acting insulin was started. Different proteins such as protamine and globulin were combined with insulin in a suspension to prolong its duration of action. The developmental work in this direction ultimately led to the introduction of isophane insulin in 1946 on the market. The addition of a protein (protamine), along with

zinc and phenol in suspension form leads to slower absorption from the subcutaneous tissue and thus prolongation of duration of action. After subcutaneous injection, it starts acting in 90 minutes, has a peak of around 6–10 hours and duration of action of 10–16 hours. Since its action is not long enough to maintain therapeutically effective blood levels for 24 hours; it is classified as intermediate-acting insulin. In 1952, lente insulin with a similar pharmacokinetic profile was introduced in clinical practice and withdrawn subsequently as it could not match the stability of neutral protamine Hagedorn (NPH) insulin.

PREMIXED INSULIN

After the introduction of NPH insulin, thrice-a-day short-acting insulin along with once or twice-a-day NPH insulin became the gold standard basal-bolus therapy in all type 1 diabetes mellitus (T1DM) and many type 2 diabetes mellitus (T2DM) patients with poor β-cell reserve or with complications driven by severe insulin resistance. Some patients, particularly elderly patients, were not comfortable with self-mixing of short-acting and intermediate-acting insulin and, at the same time, not ready to accept multiple injections daily. The development and introduction of fixed-dose, premixed combinations of short- and intermediate-acting insulin was the industry's response. At present 30:70 and 50:50 combinations (short-acting:intermediate-acting) are freely available. Premixed insulin provides convenience at the cost of precision. In the hands of a learned and experienced clinician, it is a pragmatic option in carefully selected patients. More information on the pros and cons of premixed insulin is given in the appropriate chapter.

INHALED INSULIN

Inhaled ultrashort-acting human insulin was developed for prandial blood glucose control especially for those T1DM and T2DM patients who are averse to taking multiple insulin injections, they can combine inhaled insulin at each meal with one injection of long-acting insulin, and T2DM patients with predominant postprandial hyperglycemia in spite of taking multiple OADs and desiring to improve glycemic control without restoring to insulin injections. Use of a large pulmonary alveolar surface is gainfully utilized for rapid absorption of powdered human insulin packaged in a cartridge and inhaled through a small inhaler. Launched in the USA in 2015, it serves the needs of patients who are hell-bent on avoiding insulin or avoiding more than one injection per 24 hours. Its pharmacokinetic profile is similar to that of ultrarapid-acting injectable insulin.

INSULIN ANALOGS

After genetically engineered human insulin, the introduction of insulin analogs was a major milestone in the evolution of insulin. Insulin analogs are

altered forms of human insulin. Through genetic engineering of the underlying DNA, the amino acid sequence of insulin can be changed to suitably alter the absorption, distribution, metabolism, and excretion characteristics of human insulin without reducing their glycemic efficacy and also ensuring that their mitogenicity is not increased. In rapid-acting analogs, the altered structure is responsible for their faster absorption in circulation and quicker elimination. The first pharmacokinetic alteration can lead to better postprandial blood glucose control, while the later pharmacokinetic alteration can lead to lesser chances of late postprandial hypoglycemia. Precise alteration in amino acid structure, the resultant change in pharmacokinetic profile, and its clinical advantages over human insulin are discussed in Chapter 7. Lispro was the first insulin analog to be introduced in clinical practice by Eli Lilly Company in 1996 and was followed by Novo Nordisk's aspart insulin (1998). Both are examples of rapid-acting insulin. Sanofi's glulisine is the third rapid-acting insulin analog.

Just as there was a need for rapidly acting insulin for better postprandial glycemic control and lesser postprandial hypoglycemia, there was an even greater need for a long-acting insulin providing therapeutic plasma insulin levels for 24 hours and thus effectively providing basal insulin to suppress nighttime hepatic glucose production and at the same time reducing episodes of hypoglycemia, particularly severe and nocturnal hypoglycemia. Scientists working in research and development departments of major insulin-producing European countries successfully developed long-acting and ultra-long-acting insulin analogs and introduced glargine (2000), detemir (2005), degludec (2013), and glargine 300 (2015) in clinical practice. The desired pharmacokinetics were achieved by working on the amino acid sequence as well as by adding side chains to the amino acid structure for longer combination with subcutaneous tissue, and additionally as in the case of glargine, by changing the pH of insulin preparation.

Another major development or step forward in insulin therapy was the introduction of a coformulation of a rapid-acting insulin analog, aspart, with ultra-long-acting analog, degludec in the 30/70 format in 2013. Earlier premixed combinations with rapid-acting analogs were available (aspart with NPH and lispro with NPH). These formulations overcame the drawbacks of short-acting insulin but their longer-acting counterpart did not have 24-hour action; hence, these formulations were not suitable for once-a-day therapy in the majority and were associated with a higher prevalence of hypoglycemia, coformulation of aspart with degludec has very effectively overcome this drawback. Another advantage of this coformulation is that both the components are in solution and retain their individual identity on electrophoresis and also their individual pharmacokinetic properties. Furthermore, there is no need for shaking the formulation before each injection as it is not in suspension form.

Subsequent to the availability of long-acting and ultra-long-acting insulin analogs, ultrarapid-acting versions of aspart (Fiasp) (2018) and lispro

(ultrarapid lispro) (2020) were introduced. These analogs get absorbed even quicker as compared to rapid-acting insulin analogs and offer better control of 1-hour postprandial blood glucose levels. In Fiasp niacinamide is added to aspart for further increase in speed of absorption, while in ultrarapid-acting lispro, treprostinil and citrate are added as expedients to facilitate faster absorption. Ultrarapid-acting insulin analog is a small step forward over rapid-acting insulin analogs in the ever-evolving insulin therapy scenario. All the aforementioned insulin analogs except ultrarapid-acting lispro are easily available in India.

CONCENTRATED INSULIN

Another direction in which insulin has evolved over the years is the development of concentrated insulin. In patients with severe insulin resistance, injection of large doses of insulin is associated with some disadvantages, such as large volume of injections, which can cause pain or discomfort, and the need for frequent refill prescriptions for insulin vials or pens, which can cause logistic problems. Following insulin products were developed to take care of these problems: (1) U-500 and U-200 short-acting insulin, (2) U-200 degludec, and (3) U-200 lispro. Out of these, U-200 short-acting insulin and U-200 lispro insulin are available in India. All the aforementioned variants have the same pharmacokinetics as those of corresponding U-100 insulin. Formulations with higher concentrations with special manufacturing technology to alter the pharmacokinetics are also available **(Fig. 1)** (glargine 300). In this example, the main purpose of development was to prolong the duration of action.

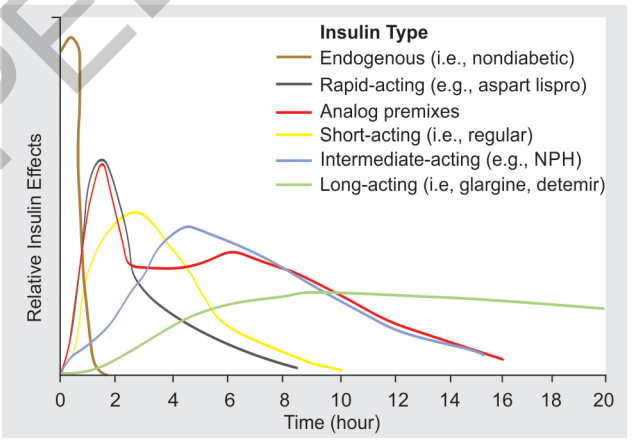


FIG. 1: Pharmacokinetic profiles of human insulin and insulin analogs.

Source: Freeman JS. Insulin analog therapy: improving the match with physiologic insulin secretion. J Am Osteopath Assoc. 2009;109(1):26-36. Quoted by White JR Insulin analogs: what are the clinical implications of structural differences? US Pharm. 2010;35(5)(Diabetes Suppl):3-7.

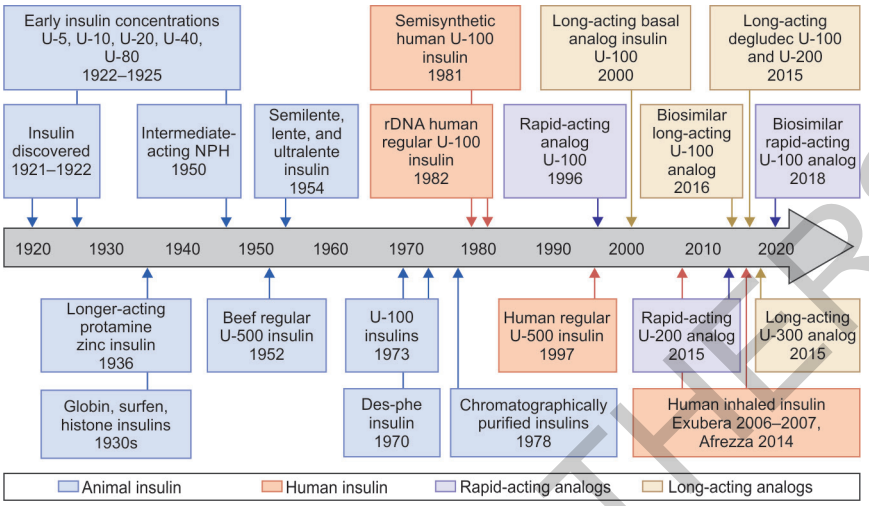
BIOSIMILAR INSULIN

The ultimate aim of the medical profession is to achieve optimal glycemic control in as many patients as possible. We now have adequate medicines to do this, provided patients are compliant with our prescription. Alas, in reality, noncompliance with prescriptions is rampant, and one of the main reasons is the cost of therapy, particularly modern insulin analog therapy in a country like India, where the majority of the patients buy medicines out of pocket. Biosimilar insulin is a biological product that is highly similar to a reference biological product of a pioneer company that invented it, notwithstanding minor differences in clinically inactive components. There are no clinically meaningful differences between the biosimilar product and the reference product in terms of the safety, purity, and potency of the product. In short biosimilar insulin is more or less an exact copy of approved and thus commonly prescribed insulin from an inventor company, manufactured by a competitor company using its own technology and marketed at a considerably lower cost to the user. Thus, availability of high-quality insulin products at lower cost leads to more compliance with the prescription and thus, better glycemic control. In short biosimilar insulin is similar to a generic drug. Why it is called *biosimilar* and not generic and several other questions are answered in a chapter on biosimilar insulin. Thus, the manufacturing of several biosimilar insulin products, their acceptance by the licensing authorities, and their availability at lower and affordable costs was a major step forward in the evolution of insulin therapy. We should be proud to know that Biocon, a Bengaluru-based biotechnology company has developed biosimilar glargine that is not only available in India but also available in countries including Japan and USA; where it is licensed as interchangeable biosimilar insulin meaning thereby that even if a patient carries prescription for the branded innovator glargine to the chemist's shop, the later has legal rights to replace it with Biocon's glargine without consulting the prescribing doctor. This is a classic example of the success of the "*Atmanirbhar Bharat*" (self-reliance) and "Made in India for the world" policies of the Government of India.

Flowchart 1 gives the timeline for the insulin development.

FUTURE OF INSULIN

Revolution comes in one stroke, introduction of insulin in clinical practice in 1922, revolutionized treatment of diabetes, subsequent continuous and ongoing improvements, in big and or small steps at a time is an ongoing evolution which will ever continue. Now let us take a view of some future insulin products in the pipeline.



FLOWCHART 1: Timeline of insulin development with approximate historical dates.
(NPH: neutral protamine Hagedorn; rDNA: recombinant deoxyribonucleic acid; U: units)
Source: Hirsch IB, Juneja R, Beals JM, Antalis CJ, Wright EE. The Evolution of Insulin and How it Informs Therapy and Treatment Choices. Endocr Rev. 2020;41(5):733-55.

NOVEL INSULIN MOLECULES IN THE PIPELINE

Once Weekly Long-acting Insulin (Icodec)

Icodec is a long-acting insulin for once-a-week administration. It is in an advanced stage of development and has already completed phase 3 studies. In 26 week comparative study of 526 T2DM patients, the glycemic efficacy as judged by reduction in glycated hemoglobin (HbA1c) and time spent in range during continuous glucose monitoring (CGM) was equal to the patients in the comparative group on once or twice a day long-acting insulin analogs (glargine and glargine 300; degludec). The incidence of hypoglycemia was negligible and equal in both groups.

In a similar comparative study done on T1DM patients, glycemic efficacy was similar but the incidence of hypoglycemia was higher in icodec group, probably because of greater day-to-day variability of insulin requirement in T1DM patients.

Availability of once-a-week long-acting insulin is expected to significantly improve acceptance and ease of insulin initiation and long-term compliance.

Glucose-responsive Insulin

This novel concept is in the early stage of development. Glucose-responsive insulin has two separate sites for host receptors, one each for insulin and mannose. Depending upon prevailing blood glucose concentration, insulin is shunted from one to another receptor site for attachment. When blood glucose falls beyond a threshold, more insulin gets attached to mannose

receptors, thus less is available for insulin receptors. In this way, hypoglycemia is avoided.

Insulin Analog 327—Liver Specific Insulin

This insulin analog is also in an early developmental stage. It has an albumin-binding side chain, which considerably reduces its binding to insulin receptors while passing through systemic circulation and helps it selectively concentrate in the liver. Thus, it restores the hepatosystemic insulin gradient and reduces episodes of hypoglycemia.

ORAL INSULIN

Insulin molecule being a protein is split up into its constituent amino acids by the enzymes in the upper gastrointestinal (GI) tract before its absorption in the circulation, thus it is totally ineffective when administered by oral route. However, considering the patient's resistance to accepting injectable insulin, several groups are attempting to develop a system of an envelope or a coating that would prevent the digestion of insulin in the upper GI tract and facilitate its absorption in an intact form. An Indian group working for Biocon, a biotechnology and pharmaceutical concern based in Bengaluru, is at the forefront of the development of oral insulin. They have used polymer technology and their oral insulin (IN 105) is in a phase 3 clinical trial. Some groups are working on nanoparticle technology. Both rapid and long-acting oral insulin preparations are being developed. Research has been ongoing for years, but it still has a long way to come to the market.

MISCELLANEOUS NONINJECTABLE INSULIN PREPARATIONS

Looking at the large potential for insulin administration through the noninjecting route due to severe aversion to lifelong injection of insulin, several groups are working to find out the solution. Subcutaneous patches, orally ingested unfolding microneedle devices, and indigestible micro-applicator devices that adhere to the GI wall and deliver the calibrated dose of insulin, are some of the ongoing projects.

SUMMARY

Since its introduction in clinical practice exactly a century ago, there has been continuous ongoing improvement in insulin molecule. In the initial decades, purity of insulin was the focus of attention. This was followed by the introduction of longer-acting insulin. In the eighties, genetically engineered human insulin was introduced into clinical practice, while around the turn of the century, introduction of rapid-acting analogs followed by long-acting analogs was a major milestone in the ever evolving history of the insulin molecule. Simultaneously, there has been continuous and ongoing

development as regards insulin delivery devices. Once a week insulin is expected to enter the therapeutic armamentarium in second half of this year. The availability of biosimilar versions of different insulin formulations is also a very encouraging development as more patients will be able to afford it and diabetes therapy will become more inclusive. While transferring the patent for large scale insulin manufacture almost free of cost to Toronto University, Dr Banting made a statement, "*Insulin does not belong to me, it belongs to everybody*". He would have been extremely pleased to know the progress on biosimilar insulin.

Practical Insulin Therapy

Salient Features

- Written in a simple and lucid language
- Provides predigested scientific information
- Illustrated with many tables, flowcharts, and figures
- It is an essential in clinic and bedside tool for all primary and secondary care physicians who treat patients with diabetes

Pradeep G Talwalkar is a practicing diabetologist for four decades. Currently, he is a Senior Consultant Diabetologist and teacher in Diabetology at SL Raheja Hospital, All India Institute of Diabetes in Mumbai, Maharashtra. His other attachments affiliations include visiting consultant at Shushrusha Hospital and Dhanwantari Hospital, Mumbai. Earlier, he held the position of Honorary Professor of Medicine at Grant Medical College, Mumbai. He has been a postgraduate teacher for a decade in Internal Medicine and currently in Diabetology for the last three decades. He is a much sought-after speaker at various conferences, symposia, and CMEs, and he has lectured extensively in various parts across the country. He has authored more than 50 papers in various national and international journals and has also written and edited books on diabetes for family physicians and internists and for lay people in Marathi, Gujarati, and English.

He is very active on the patient education front. He uses various media, such as live interactive programs, print, radio, television, and web conferences, to spread the knowledge about diabetes to patients, as well as to those who care for them.

He was an Assistant Editor of API Textbook of Medicine, 6th edition, a popular textbook with a wide readership in our country. In the course of attending various international conferences on diabetes and visiting centers of excellence in the field of diabetes, he has extensively traveled across the world. He has actively participated in many International Diabetes Federation Conferences, since the 1988 conference in Sydney, Australia.

Other publications by Pradeep G Talwalkar include:

- Handbook of Management of Non-insulin Dependent Diabetes Mellitus
- How to Live a Good Quality Life in spite of Diabetes
- Metformin: The Gold Standard (Monograph)
- Madhumeha ani Sukhi ani Samrudhha Jivan (in Marathi)
- Madhumeha ane Sukhi-Samrudhha Jivan (in Gujarati)
- Living Easy with Diabetes: The Ultimate Handbook
- Madhumeha Mutheet Tar Mashumehi Khusheet (in Marathi)
- Reverse Diabetes
- Diabesity Thopavanyasathi (in Marathi)
- Practical Diabetes Mellitus, 7th edition

He has been the Executive Editor of Current Concepts in Diabetes and Current Concepts in Hypertension.

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