Intensive Insulin Treatment
Issues in Type 1 Diabetes

Jay S. Skyler, MD, MACP
Division of Endocrinology, Diabetes, and Metabolism
and Diabetes Research Institute
University of Miami Miller School of Medicine
Commercial Interests

- **Board of Directors Member** – Dexcom, Moerae Matrix, Paean Therapeutics, VasoPrep Surgical
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- **Stock or Option Holder** – Dexcom, Ideal Life, Moerae Matrix, Paean Therapeutics, Patton Medical Devices, Tandem Diabetes Care, VasoPrep Surgical
- **Research Support (to University of Miami)** – Halozyme, Mesoblast
• Intensive Management of Type 1 Diabetes: Moshé Phillip
• How Big (Hypoglycemia) Is an Issue in T1D: Hans DeVries
• Real Life Diabetes Management Issues Internist’s Perspective: Richard Bergenstal
• Real Life Diabetes Management Issues Pediatrician’s Perspective: Desmond Schatz
• Steps to a Perfect Close-Loop: Irl B. Hirsch
• DREAM Project: Moshé Phillip
• Future of AP at Home: Hans DeVries
• Role of CGM in Diabetes: Irl B. Hirsch
• Role of SMBG and CGM – REACT Study: Richard Bergenstal
• New Basal and Prandial Insulin: Robert Ratner
Evolution of Intensive Insulin Therapy
Radical New Method of Treating Diabetes

The Allen Plan, Which Upsets Old Traditions, Is Being Given a Thorough Test at the Rockefeller Institute—Five Salient Points of the System

RAdICAL and revolutionary in method is the treatment of diabetes under the so-called Allen Plan, which brought noted investigators and experimenters together in a symposium recently at the New York Academy of Medicine in this city. It is being thoroughly tested at the Rockefeller Institute for Medical Research.

Periodicals in which the treatment was described for the profession for the first time are at a premium and investigators from all parts of the country are in correspondence over the results obtained.

There have been students of diabetic conditions who have tried making patients starve to some extent, but never was the disease before combated by long initial fasts and the reduction of the weight of the body by a fifth. The commonly accepted treatment for diabetes consisted in keeping the patient with as much flesh on his bones as possible, in having him rest, and above all in keeping him aloof from alcohol. The new régime even diet and the faulty conversion of food into living cells—metabolism—may go on for years. The new dispensation says to the patient that he must correct those errors of diet, not by any casual effort, but through a course of self-discipline under the supervision of physicians and preferably in an institution where a daily routine of life is maintained.

When the stove goes wrong through having been improperly fed, the first thing the man who knows about stoves does is to get rid of the cinders, the slag, the ashes which choke—to take off the stress and strain. The basis of the new treatment of diabetes is reduction of the body to a minimum, so that the burden of transforming food into cells for its use will be reduced to the lowest possible equation.

This is essentially the Allen Plan, so-called because it was developed by Dr. Frederick M. Allen of the Rockefeller Institute. It is described by the author for the benefit of his profession in a recent number of The Journal ofMedi-

devote along the best paths of growth. Increase or vary those factors to a point which is abnormal and keep this change a constant factor and damage is bound to be done.

So it is in diabetes, where the blood is overcharged with dextrose: this surplus begins to have its effect on the walls of the vessels in which it is carried, on the organs in which it is produced and stored.

Hence it is that in diabetes, the unwelcome dextrose clogging the body appears in abnormal amounts in the cerebrospinal fluid, in fluids of the ventricles. It extends to brain and heart. The excess appears in the tears, in perspiration, and in the saliva. It reaches even the fluids of the eyeballs. Oculists, in fact, often get the first danger signal of diabetes in examining the eyes where there is shown a certain abnormal effect due to variations of the osmotic pressure of fluids.

The experiments at the Rockefeller Institute with animals have demonstrated that with fasting of two or three days the dextrose almost disappears from the tissues. To show the analogy which exists between human diabetes and the malady as artificially produced in guinea pigs and dogs, the hospital of the insti-

and vitality of the patient, for every unnecessary ounce makes more work for the organs of assimilation and especially increases the strain on the internal pancreatic function.

To sum up the salient points of the Allen Plan, it may be said that it rests for its efficacy on:

1. An initial fast.
2. Diet.
4. Its opposition to the feeding of fats.
5. The education of the patient.

Under the old régime a heavy weight was considered desirable and the taking of fats was recommended. The educating of the patient himself is most important, for he is impressed with the idea from the first that he is merely correcting errors of diet, changing the intake of fuel for his furnace, and that he may, therefore, not be suffering from an inherently progressive disease. It rests with him to learn what weakness of metabolism is, and to correct the tendency. Therefore
PANCREATIC EXTRACTS IN THE TREATMENT OF DIABETES MELLITUS

Preliminary Report by F. G. Banting and C. H. Best, Dept. of Physiology
J. B. Collip, Dept. of Path. Chemistry
W. R. Campbell and A. A. Fletcher, Dept. of Medicine, University of Toronto, and
Toronto General Hospital

Since the year 1889, when von Mering and Minkowski (1) produced severe and fatal diabetes by total removal of the pancreas in dogs, many investigators have endeavoured to obtain some beneficial effect in diabetes mellitus, either by feeding pancreas, or by administration of pancreatic extracts.

Minkowski, Sandmeyer (2), Pflüger (3) and others found that feeding pancreas was followed by negative or even harmful results. More recently, Murlin (4), Kleiner (5) and Paulesco (6) have tried the effects of aqueous extracts of the pancreas. Believing that extracts of the pancreas, as usually prepared, did not satisfactorily demonstrate the presence of an internal secretion acting on carbohydrate metabolism, because the active principle was destroyed by the digestive enzymes also present in such extracts, attempts were made to eliminate these enzymes. In the first experiments, this was done by taking advantage of the fact that the acinous tissue (from which the digestive enzymes are derived) but not the insular tissue of the pancreas degenerates in seven to ten weeks after ligation...
DIABETES SUFFERERS GIVEN MESSAGE OF HOPE

Discovery Made at University of Toronto Will Be Means of Prolonging Life Considerably—F. G. Banting and C. H. Best Pushed Experiments All Last Summer.

BANTING STAKES HIS ALL ON THE RESULT

A message of hope to sufferers from diabetes goes out authentically to-day from the medical research laboratories of the University of Toronto. The modesty of medical men and scientific investigators of the genuine brand attempts to minimize the results obtained. The harm of exaggeration and the injustice to both patients and research men in awakening false and premature hopes before the extracts can possibly be manufactured cannot be over-emphasized. But the fact remains that one of the most important dis...
THE DIABETIC LIFE
Its Control by Diet and Insulin
A CONCISE PRACTICAL MANUAL
FOR PRACTITIONERS AND PATIENTS

BY
R. D. LAWRENCE
M.A., M.D., F.R.C.P. (London)
Physician in charge Diabetic Department, King's College Hospital; late Chemical Pathologist and Lecturer in
Chemical Pathology, King's College Hospital

FIFTEENTH EDITION

With 19 Illustrations

LONDON
J. & A. CHURCHILL LTD.
104 GLOUCESTER PLACE, W.1
1955
“The temperament and usual habits of the patient should be considered in the type of treatment chosen and our object should be to interfere with these as little as is compatible with health… I know that full physiological control of severe diabetes – the most continuously normal blood sugar and the least hypoglycaemia – can be best obtained with 4–6 small injections of soluble insulin in the 24 hours…

Characteristics of Insulin Preparations

- Purity of Preparation
- Species of Origin
- Concentration
- Time Course of Action
  - Onset
  - Peak
  - Duration
Advances in Insulin Preparations

- Protamine insulinate - 1936
- Protamine zinc insulin - 1936
- Surfen insulin - 1938
- Globin insulin - 1939
- Phenylcarbomoyl insulin - 1944
- Isophane (NPH) insulin - 1946
- Lente insulins - 1951
Traditional Insulin Preparations

Short-acting
- Regular (Soluble)

Intermediate-acting
- NPH (Isophane)
- Lente (Insulin Zinc Suspension)

Long-acting
- Ultralente (Extended Insulin Zinc Suspension)
Protein Components in Insulin Preparations
Pre-1972

% of Total:

- Insulin: 92%
- Other: 8%
Purity of Insulin Preparations

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Proinsulin Content (ppm)</th>
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<tr>
<td>Conventional USP</td>
<td>10,000-40,000</td>
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<tr>
<td>“Single Peak”</td>
<td>300-3000</td>
</tr>
<tr>
<td>“Improved Single Peak”</td>
<td>&lt; 50</td>
</tr>
<tr>
<td>“Single Component”</td>
<td>&lt; 10</td>
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Components of Insulin Secretion

- Meal Related
- Basal
Components of Insulin Secretion

- Meal related
- Basal
Physiologic Serum Insulin Secretion Profile

Plasma Insulin (µU/mL) vs. Time

- Breakfast
- Lunch
- Dinner

4:00 8:00 12:00 16:00 20:00 24:00 4:00 8:00
Classical “Split-Mixed” Treatment Program

Breakfast  Lunch  Dinner

REG  NPH  REG  NPH

Classical Treatment Program

Plasma Insulin

4:00  8:00  12:00  16:00  20:00  24:00  4:00  8:00

Time
THE DAWN PHENOMENON

AS THE SUN RISES, SO DOES THE BLOOD GLUCOSE
“Split-Mixed” Program With Bedtime Intermediate Insulin

Plasma Insulin

Breakfast Lunch Dinner

REG NPH REG NPH

8:00 12:00 16:00 20:00 24:00

REG NPH

4:00 8:00 12:00 16:00 20:00 24:00 4:00 8:00

Time
Typical Treatment Program
circa 1970

- Single Daily Injection - NPH or Lente
  (Mixed Beef-Pork - U40 or U80) – 24-25 g
Normal non-diabetic blood insulin profile

Management with intermediate-acting insulin in the morning
Typical Treatment Program circa 1970

- Single Daily Injection - NPH or Lente (Mixed Beef-Pork - U40 or U80) – 24-25 g
- Meal Plan - 3 meals, 3 snacks - 40% carbohydrate, 40% fat, 20% protein - never skip meals, always eat on time
ENERGY SOURCE (FOOD) → INSULIN → ENERGY UTILIZATION (ACTIVITY)
<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
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<tr>
<td></td>
<td>trim</td>
<td>Milk</td>
<td>Vegetable</td>
<td>Fruit</td>
<td>Bread</td>
<td>Meat</td>
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<tr>
<td><strong>Breakfast</strong></td>
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<td></td>
<td></td>
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<tr>
<td><strong>Time</strong></td>
<td>7:30</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td><strong>Snack</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Time</strong></td>
<td>10:00</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Lunch or Dinner</strong></td>
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<td></td>
<td>0-1</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td><strong>Time</strong></td>
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<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td><strong>Snack</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Time</strong></td>
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<td>1</td>
<td></td>
<td>1</td>
<td>1</td>
<td></td>
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<tr>
<td><strong>Dinner or Supper</strong></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
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<tr>
<td><strong>Time</strong></td>
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<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td><strong>Bedtime Snack</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td><strong>Time</strong></td>
<td>10:00</td>
<td>2</td>
<td></td>
<td></td>
<td>1</td>
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</tbody>
</table>
Typical Treatment Program circa 1970

- Single Daily Injection - NPH or Lente (Mixed Beef-Pork - U40 or U80) – 24-25 g
- Meal Plan - 3 meals, 3 snacks - 40% carbohydrate, 40% fat, 20% protein - never skip meals, always eat on time
- Urine Glucose Testing (first void or “double void”?) (Clinitest tablets with dropper)
Urine Glucose Testing Approaches

Red cuprous oxide
Classical “Split-Mixed” Treatment Program

Plasma Insulin

Time

4:00 8:00 12:00 16:00 20:00 24:00 4:00 8:00

Breakfast Lunch Dinner

REG REG REG

NPH NPH NPH
Instructing Patients in Making Alterations in Insulin Dosage
Typical Treatment Program circa 1976

- Split-Mixed Insulin Schedule (Mixed Beef-Pork or Pure Pork-U100)
- Meal plan - 3 meals, 3 snacks - 40-60% carbohydrate, 30% fat, 10-20% protein
- Urine glucose testing (first void or “double void”?) (Clinitest tablets or Glucose oxidase test strips)
Could messy urine be avoided?
Pancreatic transplantation in human diabetes: long-term results

Diabetic truncal mononeuropathy: a new clinical syndrome

Urine glucose testing for patients with impaired vision

Home blood glucose monitoring and jet insulin injection

Diabetes and a clinical review

Policy statement: urine testing materials
The First Article on SMBG

Jet Injection of Insulin During Self-Monitoring of Blood Glucose

T. S. Danowski and J. H. Sunder

Insulin-dependent diabetes mellitus has been treated with four jet injections of insulin (regular insulin before each meal and intermediate insulin at bedtime) during self-monitoring of blood glucose levels. The blood glucose levels generally remain within 60 and 150 mg/dl. Diabetes Care 1: 27–33, January–February, 1978.

It has been both proposed and denied that precise control of blood glucose in diabetes mellitus will prevent or defer the onset and progression of microangiopathy, with its possibly devastating effects on vision and kidney function. However, with currently available treatment modalities, a commitment to control undue hyperglycemia and avoid hypoglycemia in insulin-dependent diabetes may not be attainable even with meticulous attention.

This preliminary report suggests that self-monitoring of blood glucose levels and four daily injections of insulin i.e. at bedtime and before each meal, are not unduly burdensome and usually improve the control of glycemia in juvenile- or young-adult-onset type of diabetes. The insulin was administered by jet injection rather than with syringe usual amounts of insulin injected by needle by syringe. During this month also, glucose was measured in venous blood by the nurses and laboratory personnel in the course of two days before and after each meal and at 9 p.m., 12 midnight, and 3 a.m.

They were next taught to inject insulin with the Syrijet jet injection device (figure 1). The insulin schedule was then altered to include a bedtime dose of intermediate insulin and three before-meal injections of regular insulin. Blood glucose was measured each morning before breakfast and at one other time, i.e. after breakfast one day, before lunch another day, after lunch, before supper, after supper, and at bedtime. The cycle was then repeated. Also, at intervals, the patients monitored their blood glucose before and after each of the three meals of one day. They
Home Blood Glucose Monitoring
As an Aid
in Diabetes Management
Karl Sussman – Patients WOULD NOT do it

Philip Felig – Patients COULD NOT do it

Leonard Madison – Patients SHOULD NOT do it
Read my lips!
Most blood lancets have the patient-calming charm of a broken razor blade.
Week beginning Monday: ________________ (Date)

### INSULIN INJECTIONS

<table>
<thead>
<tr>
<th>TYPE</th>
<th>NUMBER of UNITS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Action</td>
<td>MORN</td>
</tr>
</tbody>
</table>

- SHORT
- LONGER

### TIME of INJECTION

**MON**

- SHORT
- LONGER

**TUES**

- SHORT
- LONGER

**WED**

- SHORT
- LONGER

### MONITORING: BLOOD and URINE

<table>
<thead>
<tr>
<th>TEST</th>
<th>BREAKFAST</th>
<th>LUNCH</th>
<th>DINNER</th>
<th>BED TIME</th>
<th>OVER NIGHT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
<td>Before</td>
<td>After</td>
<td>Before</td>
</tr>
</tbody>
</table>

- **BG** = Blood Glucose
- **US/UK** = Urine Sugar
- **UK** = Urine Ketones

**SUPPLEMENTAL INSULIN**

<table>
<thead>
<tr>
<th>TIME</th>
<th>TYPE</th>
<th>UNITS</th>
</tr>
</thead>
</table>

**NOTES:**
Algorithms for Adjustment of Insulin Dosage by Patients Who Monitor Blood Glucose
Classical “Split-Mixed” Treatment Program
“Split-Mixed” Program With Bedtime Intermediate Insulin
Basal/Bolus Insulin Absorption Pattern:
Standard Insulin Preparations

Breakfast  
Lunch  
Dinner  

Plasma Insulin

Time  
4:00  8:00  12:00  16:00  20:00  24:00  4:00  8:00  
REG  REG  REG  NPH

REG  REG  REG  
4:00  8:00  12:00  16:00  20:00  24:00  4:00  8:00
Basal/Bolus Insulin Absorption Pattern: Standard Insulin Preparations

Breakfast | Lunch | Dinner

Plasma Insulin

REG

NPH
Intensive Insulin Therapy
System of Intensive Therapy of Type 1 Diabetes

1. Multiple Component Insulin Program
2. Careful Balance of Food Intake, Activity, & Insulin Dosage
3. Daily Self-monitoring of Blood Glucose
4. Planned Patient Alterations of Food Intake and of Insulin Dosage & Timing
5. Defined Target Blood Glucose Levels (Individualized)
6. Frequent Contact Between Patient and Staff
7. Patient Education & Motivation
8. Psychological Support
9. Assessment (A1c)
HbA1c

- Integrated Measure of Glycemic Control
- Correlates with Mean Blood Glucose
- Patient Independent Assessment Tool
- Facilitates Control
- Predicts Complications
- Reflects Tissue Changes
GLYCOXYLATED HEMOGLOBIN

Official Hemoglobin Of The 1984 Olympics
DCCT: Absolute Risk of Sustained Retinopathy Progression by Mean A1c

Rate of progression of retinopathy (per 100 patient-years)

DCCT: Absolute Risk of Severe Hypoglycemia by Mean A1c

DCCT: 1986 to 1993

Rate of severe Hypoglycemia (per 100 patient-years) vs. Glycosylated Hemoglobin (%)

DCCT. N Engl J Med 1993;329:977-86
Flexible Insulin Therapy
Principles of Flexible Therapy

- Patient lifestyle determines treatment program
- Meal pattern totally flexible—including number of meals, timing of meals, content of meals, variations from day to day
- Unrestricted activity pattern—totally flexible, including sporadic exercise
- Unrestrained creativity in treatment options
- Insulin program should be tailored to patient lifestyle on ongoing basis
Ideal Basal/Bolus Insulin Absorption Pattern

Breakfast  Lunch  Dinner

8:00  12:00  16:00  20:00  24:00

Plasma Insulin
Advances in Insulin Preparations

- Protamine insulinate - 1936
- Protamine zinc insulin - 1936
- Surfén insulin - 1938
- Globin insulin - 1939
- Phenylcarbomoyl insulin - 1944
- Isophane (NPH) insulin - 1946
- Lente insulins – 1951
- Rapid Acting Insulin Analogs – 1995
- Basal Insulin Analogs – 2000
Rapid-acting Insulin Analogs Provide Ideal Prandial Insulin Profile

Breakfast
Aspart or Lispro or Glulisine
Lunch
Aspart or Lispro or Glulisine
Dinner
Aspart or Lispro or Glulisine

Plasma Insulin

Time
4:00  8:00  12:00  16:00  20:00  24:00  4:00  8:00
Four Questions Before Each Meal

1. What is my blood glucose level now?
2. Do I plan to eat a larger or smaller meal than usual?
3. Will I be more or less active than usual?
4. What has happened previously in these circumstances?
Ideal Basal/Bolus Insulin Absorption Pattern
Long-acting Insulin Analogs Provide Ideal Basal Insulin Profile

Plasma Insulin

Breakfast  Lunch  Dinner

Glargine or Detemir
Basal/Bolus Treatment Program With Rapid-acting and Long-acting Analogs

Glargine or Detemir

Plasma Insulin

Breakfast
Aspart or Lispro or Glulisine

Lunch
Aspart or Lispro or Glulisine

Dinner
Aspart or Lispro or Glulisine

4:00 8:00 12:00 16:00 20:00 24:00 Time
Basal/Bolus Treatment Program With Rapid-acting and Long-acting Analogs

![Graph showing plasma insulin levels at breakfast, lunch, and dinner times.](image-url)
Basal/Bolus Treatment Program With Rapid-acting and Long-acting Analogs

Plasma Insulin

Breakfast  Lunch  Snack  Dinner

Time
Variable Basal Rate Continuous Subcutaneous Insulin Infusion (CSII) Program

Plasma Insulin

Breakfast  Lunch  Dinner

Bolus  Bolus  Bolus

Basal Infusion

Time
Change in A1c from Baseline to 26 Weeks in \( \geq 7.0\% \) HbA1c Cohort

- **CGM** vs **Control**
  - **\( \geq 25 \) yr olds**: \( P < 0.001 \)
  - **15-24 yr olds**: \( P = 0.52 \)
  - **8-14 yr olds**: \( P = 0.29 \)

Change in A1C by Sensor Use

Age ≥25: n = 6, n = 43
Age 15-24: n = 10, n = 29, n = 17
Age 8-14: n = 7, n = 21, n = 28

- <4.0 days/week sensor use
- 4.0-<6.0 days/week sensor use
- ≥6.0 days/week sensor use

P = 0.02
P = 0.002
P < 0.001

DCCT: Absolute Risk of Severe Hypoglycemia by Mean A1c

DCCT: 1986 to 1993
Two Eras of Diabetes Management

Rate of severe Hypoglycemia (per 100 patient-years)

Glycosylated Hemoglobin (%)

DCCT: 1986 to 1993

JDRF CGM Study

Control Group 2006-2007

DCCT. N Engl J Med 1993;329:977-86
Impact of Continuous Glucose Monitoring on Rate of Severe Hypoglycemia Compared to DCCT

Glycosylated Hemoglobin (%)

Rate of severe Hypoglycemia (per 100 patient-years)

Intensive Insulin Therapy
We’ve Come A Long Way