

Bovine Porcine and Human Insulin. A present day comparative appraisal and policy discussions.

“As daunting as the over all costs of diabetes care the day to day challenge for individuals with diabetes and policy makers relates to choices in diabetes care. What benefits do various choices of insulin provide and at what cost. Whether these questions are asked at an individual or national level, knowing the answer is fundamental to cost effectiveness.”

A Panel discussion in Q/A formats.

From the desk of
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An INTRODUCTION

“As daunting as the over all costs of diabetes care the day to day challenge for individuals with diabetes and policy makers relates to choices in diabetes care. What benefits do various choices of insulin provide and at what cost. Whether these questions are asked at an individual or national level, knowing the answer is fundamental to cost effectiveness.”

India presents classic example,
In 1998,

Cost of Insulin therapy/year/person	\$ 350
Cost of non insulin therapy/year/person	\$ 70

17.5 mn diabetics in India,	
Total cost of diabetes in India	\$ 2.2 Bn.
Total healthcare budget for entire India	\$ 720 Mn.

Percapita expenditure for all healthcare	\$ 21
- Including water and sanitation.	

There is no doubt that Insulin is the *most studied Hormone* in the world & no other hormone has been studied so much & as many as 45 or more animals Insulin - also (from Rhinocerus - Elephant down to Rat & mouse) has been studied in detail - Many many peculiarities in animals & Insulin & the life style connections studied in animals.

For example, even Guinea Pig - *two* insulins are found - native insulin plus porcine & so on - do not know the reason.

Porcupine - quick erection of spines & more monomeric Insulins & so on & vertebrates & even non vertebrates' animal studies. Thus *animal Insulinology* - animal pancreatology & animal diabetes are all continuously studied in comparative Diabetology.

Clinical animal Insulins limited to Bovine & Porcine apart from Human insulin. Animal Insulin Bovine & porcine used for more than 80 years since Banting & Best 1922 & no other animal hormones we use in humans so much etc.

The long experience with natural insulin, bovine insulin has been extremely satisfying both for the patients as well as their physicians especially after the availability of monocomponent natural insulins. Since 1980, synthetic insulin manufactured adopting recombinant DNA technology and using E.Coli or Yeast for expression is being used with mandatory warning on hypoglycemic episodes expressed on the commercial products (BMJ 1991 Sep 14; 303 (680:622-6), Lancet 1992; 340(8814): 301-2).

Early study showed no difference with regard to three-dimensional structure of the bovine, porcine and synthetic insulin (J Pharm Sci 1998; 87:170-6).

The binding affinity of insulin to insulin receptors at the three major site of insulin action namely muscle, adipocyte and hepatocyte, as well as the post receptor events in terms of autophosphorylation of insulin receptor substrate have been found to be *similar* with *bovine, porcine* and *recombinantly produced synthetic insulins* (Diabetic Med 1997; 14: 1044 -50).

Onset of action synthetic insulin has been found to be faster by about 15 minutes due to its rapid absorption. This effect however has been found to have *nonbearing* on the overall glycemic control achieved, though offlate there have been

several reports of hypoglycemia unawareness following the use of synthetic insulin. Even in pregnancy no difference have been observed in terms of neonatal macrosomia and ponderal index between users of bovine and synthetically produced insulin. A careful review of literature showed no relationship between insulin antibodies produced and long-term complications of diabetes like retinopathy, neuropathy and nephropathy (Diabetes Care 1989;12:641-648).

Synthetic insulin was introduced primarily with the promise that *cost of insulin therapy would come down remarkably and insulin antibody formation may not occur with its use*. In reality however after two decades of its use it has been observed that synthetic insulin also cause formation of antibodies in substantial number of users (55%).

The major projected benefit of GE insulin viz-substantial reduction in cost has *never been realised*. We do not know why? Paradoxically despite 20 years of technology use of production the cost of synthetically produced insulin continues to mount threatening to price out of existence those who depend on it for treatment. Unlike in the west treatment cost of most Indian patients is not met by insurance and *patients have to fund* for themselves. There is also the problem of inadequate manpower for patient education.

Porcine & Human Insulin are in *one boat (SGPM)* - since only one amino acid sequence less. The small difference between human and porcine preparation seems to be of no clinical importance.(Diabetes ; Vol - 34 : Supple - 2 , 1985)

After 1975 Insulin is the fist hormone manufactured by Genetic Engineering.

So naturally since all the insulins are in use in diabetic patients a periodic comparative appraisal is done by clinical scientists & some policies made in different countries including INDIA.

How did this subject of "Relook into animal insulins" - come up in present era. We are now in post - post newer insulin ERA? Why do we have this debate? (A Prelude)

- ◆ We are now in the post - post newer Insulin Era & Insulin analogues era.
- ◆ The subjects of "Relook into animal Insulins" - have come up because of the following reasons - some like the subject some do not like the subject - pharma & medical personnel.
 - This subject has been scientifically come up - Not Because Pharma companies have reintroduced animal insulins - NO Not ATALL.
 - The relative scientific appraisal of Human Insulin & animal Insulin - well studied & still being studied.
 - At the moment the cost Benefit & Socioeconomic & Insulin Burden in India deserves special discussion.
 - All this does not mean to stop the scientific progress of Human Insulins & other hormonal products . This progress will go on & on.
 - Thus Insulinology as a special drug speciality (on par with Aspirinology - on par with statinology has all come to stay).
 - Animal comparative pancreatology, comparative Insulinology & animal Insulin has all come to stay (apart from commercial animal Insulins)
 - It may be particularly good that a few pharma companies have boldly reintroduced animal Insulins, ensuring highest purity. In the bargain, *Purity of Insulin has become supremo.*
 - More studies & more progress in animal insulins versus Human Insulin is wished all success

- Thus the debates in this area of insulinology are unavoidable and may open up extra thoughts.

QUESTION 1:

Bovine - Porcine & Human insulins are all mutual - natural analogues well accepted to human patients (actually the subject of insulin analogues was born out of this idea) and insulin receptor systems and well worked out for years - what are all the comments?

- ◆ Bovine / Porcine & Human insulins apart from the Insulin usage for over 80 years has now been well declared as "Mutual" / "Natural" - analogues , though it was known earlier.
- ◆ Now officially declared as Mutual Natural analogues after the advent of synthetic Genetic Engineering analogues since 1997 / 1998 onwards.
- ◆ The whole subject of analogues was born out of the idea of Bovine / Porcine & Human Insulin - all the three are able to sit on insulin receptors & give the performance.
- ◆ Incidentally the mutual natural analogues were very safe :(no mitogenicity) (no cardiogenesis) no other side effect unlike the present day analogues like "Glargine" , Long acting analogues & even pro insulin analogues etc with various contradictory harmful reports here and there.
- ◆ Incidentally the Genetic Engineering Insulin companies are also restless. Surprisingly restless in going on manufacturing analogues . so the question is often raised & discussed in panel discussions "*Do we need so many insulin analogues*" - "*Do we really need them in Insulin practice?* "

- ◆ Replace Human Insulin with Human Insulin in one slogan all though (at the same time now trying to combine analogues + Human Insulin (eg. Lispro + NPH) only to promote sales at increased cost . what is the rationale?? ; that puzzles many senior diabetologist's like me and others.
- ◆ Brent Hoadley's Insulin Patent Research and Findings:
Feb 28, 2001 – Hoadleygold, inc, Brent hoadley PhD.

In his book 1984, George Orwell wrote about “newspeak”. This is now the language used by the pharmaceuticals to create billions of dollars in profit from genetically engineering insulin-like molecules.

Pharmaceuticals will tell you the foreign protein insulin source is the pancreas of a pig or cow. When given names such as humalog, lantus or novorapid by giant corporations, a foreign protein becomes a wonder ‘analog’ of human insulin. The truth is all three of these substances are foreign proteins – in some cases not even an insulin molecule. All could be considered new growth hormones with very little being known about long term effects. Diabetics need to apply for long-term guinea pig status.

- ◆ Thus “*Insulin Restlessness*” in Pharma minds etc. Probably can not be helped.

QUESTION 2:

Porcine & Human insulin go together in the present day in one boat for various reasons . Humanised Porcine (Semi synthetic) is also used as human insulin .what are the ideas?

Human insulins have many theoretical advantages, but in reality its status can be best expressed by the following line from Hand Christian Anderson's Fairytale.

***THE EMPEROR'S NEW CLOTHES:
"HE HAS NOTHING ON"***

The small difference between purified human and porcine preparation seems to be of no clinical importance.

*Diabetes Vol 34
Suppl., 2 1985.*

If it is so let us look into the facts.

- ◆ The amino acid sequence in Human / Porcine / Bovine & connects chains - briefed as

	Bovine	Porcine	Human
A8	Ala	TR	TR
A10	Val	Iso	Iso
A30	Ala	Ala	TR

58 amino acids are identical . *None of the changes are at sites crucial to the binding or action of insulins . Hence no significant difference between species of insulin in receptor binding and action of insulin . Theoretically changes in amino acid could affect the solubility and diffusion properties of insulin molecules* (Clinics in Endocrinology and Metabolism – vol II, No 2. P.D. Home, K.G. M. M. Alberti)

- ◆ Human Zinc Insulin crystals attract more water than beef and pork. But studies of absorption, action of Insulin have not revoked any clear cut differences between porcine & Human Insulins.
- ◆ Porcine insulin is capable of many modifications. purification, Highly purified and “*monocomponent insulin*” and enzyme modification of aminoacid to make semi synthetic human insulin - *is all possible with porcine insulin* .
 - Porcine Insulin goes in same boat as Human Insulin & even in animals with two insulins (Guinea pig - native insulin + porcine insulin are the double gene effects) - to be noted Probably *porcine insulin goes along with any animal and also for Humans.*
- ◆ All types of Diabetes react in same way with porcine & Human Insulins . Thus there are no major clinical differences.
- ◆ Suppression of C peptide was equal. Similar effects of insulin on C peptide and blood glucose and pyruvate .
- ◆ Insulin has wide spread metabolic effects on carbohydrate, protein and lipid metabolism. By measuring intermediary metabolites Bioequivalence of the insulins in terms of response of blood glycerol and lactate levels .
- ◆ On the other hand, 3 hydroxyl pyruvate was maximally suppressed maximally at lowest dose and the alanine levels

were unchanged at the highest dose. So these measurement give no discrimination between the insulins.

- ◆ Human and porcine insulins were found to be identical interns of glucose requirement and adjustment.

There is universal agreement on the equivalence of insulins and comparisons of the extent and time courses of the changes in blood glucose , serum C peptide , glycerol , Alanine and hydroxy butyrate showed no difference of any kind .

- ◆ Comparative studies of insulins in diabetic patients :
 - No differences were found in either glucose requirement or free insulin after SC in profiles of equal purity .
 - No differences in peripheral glucose uptake and identical metabolic clearance rate .
 - Solubility differences between pork and human insulin will not affect the characteristics of intermediate acting insulin

Comparison of Human Insulin and Pork Insulin

Much Ado About One Amino Acid?

Sir George Alberti. Clinics in endocrinology and Metabolism 1982; 11(2): 453-483.	There is as yet little evidence to suggest that there are major (or even minor) clinical differences between Human Insulin, whether semi-synthetic or biosynthetic, and Monocomponent Porcine Insulin.
Much Ado About One Amino Acid. Markussen J, Diabetologia (1983) 25; 457- 459.	When porcine Monocomponent preparations are used local or systemic insulin allergy, lipodystrophy or immunological insulin resistance occurs very rarely.
Much Ado About One Amino Acid. Sonnenberg and M Berger, Diabetologia (1983) 25; 457-459.	The present vogue for human insulin is not matched by comparable benefits in clinical practice. The commercial versus scientific aspects of human insulin are reflected by the tide of commercially sponsored symposia, unreviewed papers and reports in books are supplements to well-known journals compared with relatively small number of original papers on human insulin which have passed a peer review system.
Larkins Et al. NEJM 1986 Vol. 16 206-210.	The structures of human and porcine insulin differ by only one amino acid, and that this amino acid, which lies in position 30 of the B-chain, does not appear to be directly

	involved in the antigenic activity of the hormone.
Larkins Et al. NEJM 1986 Vol. 16 206-210. Double blind trials in newly treated diabetic subjects.	Human insulin was shown to be indistinguishable from porcine insulin of comparable purity with respect to plasma glucose and glycosylated hemoglobin levels and insulin does requirements. Human insulin was no less antigenic than porcine insulin; significant IgG-associated insulin binding activity was detected in six of the ten patients in the human insulin treated group and four of the ten patients in the porcine insulin treated group.
By Acta Pediatr Scand Suppl 270 Vol. 12.	Porcine Monocomponent insulin has therefore recently become the insulin of choice in the long-term treatment of newly diagnosed diabetic children.

Differential effects of human and animal insulin on the responses to Hypoglycemia in elderly patients with NIDDM. Graydon s. Meneilly et al. Diabetes Care Vol. 16, 1991. Diabetes, 1995, 44,272-277.	It is likely that animal insulin cross the blood-brain barrier more readily than human insulins, since they are more lipophilic. It has shown in animals that insulin stimulates glucose uptake the hypothalamus and that direct stimulation of hypothalamic insulin receptors evokes behaviors consistent and hypoglycemia. If hormonal responses are mediated mainly by the glucose levels in the central nervous system and the symptom responses are mediated, at least in part by or direct effect of insulin on neurons, this could be an explanation for the differential effect of the two insulins. Animal insulin provided a greater awareness of a hypoglycemia beginning than human insulin.
Biologic activity of BHI v/s HPI. Diabetes Care Vol. 4, 1994.	The amount of insulin given by the GCIIS to maintain plasma glucose levels within a normal range was virtually identical for BHI and pork insulins.
Diabetes, Vol. 44., March 1995, PP.257-260.	As clinicians we must respond to the experiences of the people using it, especially perhaps because the anticipated theoretical advantages of human insulin have not really materialized. Human insulin is not markedly less immunogenic than highly purified porcine equivalents and, it has not become cheaper.
What are the advantages of human insulin? Prof. S Amiel. WWW.diabetes.org/publications/insiderorg/html/expertes.htm	In retrospect, the advantages are less clear today than when it was first introduced. Initially, it seemed logical that human insulin would be better for human patients in the event, human insulin is not significantly less immunogenic than neither purified pork insulin, nor it is less expensive to buy.
Human insulin gone wrong? Diabetes Medicine 1991 Philip Home Newcastle upon Tyne	Lessons from the current debacle are then many, but if freedom of information, justice and medicine are to prosper in a world where the consumer is increasingly king, then professionals will have to learn a degree of self-regulation that may clash with more entrepreneurial instincts.

<p>Biosynthetic Human insulin : Progress and Prospects. Jay S. Skyler et al. Diabetes Care, Vol. 4, No. 2, March-April 1981.</p>	<p>The plasma glucose lowering action of BHI is similar to that of purified pork insulin (PPI). A potential problem with BHI is contamination with protein antigens from E.coli in which the A and B chains of BHI are produced. It can not be excluded completely.</p>
<p>A Prager and G. Schernthaner. Diabetologia - Springer Verlag 1983.</p>	<p>The healthy control subject showed no statistical significant difference between the binding of human and porcine insulin at any insulin concentrations. Absolute receptor number and average did not differ significantly between human and porcine insulin either. We conclude that the binding behaviors of semisynthetic human insulin and porcine is comparatively identical. Patients treated from the onset of their disease with SSH insulin did not differ from those treated with porcine insulin with regard to their insulin receptor status.</p>
<p>Diabetes Medicine 1995. Glycaemic control.</p>	<p>No significant differences in the control achieved during each treatment and also observed within or between groups and glycated globin concentrations did not change significantly through out the study.</p>

The production of human insulin is a major scientific achievement . There is little evidence to suggest that there are major (or even minor) clinical differences between human insulins whether semisynthetic or biosynthetic and pork Insulin. Presently therefore the use of human insulin must rest largely on economical grounds. (Clinics in Endocrinology and Metabolism – vol II, No 2. P.D. Home, K.G.M.M. Alberti).

- “If it is so, why can’t we use porcine monocomponent insulin which is available in India at RS 65 to 85 economical than human insulins” in general diabetic population (Sam Moses).

QUESTION 3:

What are the advantages of Bovine insulins? Should bovine insulin be retained in clinical practice?

◆ In 1998,

Cost of Insulin therapy/year/person \$ 350

Cost of non insulin therapy/year/person \$ 70

17.5 mn diabetics in India,

Total cost of diabetes in India \$ 2.2 Bn.

Total healthcare budget for entire India \$ 720 Mn.

Percapita expenditure for all healthcare \$ 21

- including water and sanitation.

Nearly 400 Mn Indians live in absolute poverty.

When you need cost effective solutions in diabetes care, considering the above scenario, certainly the availability of bovine insulin at Rs.65/vial will protect the fundamental right to health and right to life of the Indian Diabetic.

◆ Insulin has been available for therapeutic purposes for over 80 years since Banting & Best 1922. The earliest Therapeutic preparation were obtained from Beef Pancreas - first animal insulin in clinical practice.

◆ Clinicians are "consumer advisors" to market.

- ◆ Bovine Insulin more "Polymeric" situation for long time (action of insulin polymer → dimer → monomer) & hence *Bovine is able to constitute True ultra lente effects*. No peak ; peakless insulin - (Human ultra Lente two peaks, not real ultra Lente).
- ◆ Bovine insulins are difficult to be chromatographically purified. But fortunately we are getting highly purified bovine insulin < 2ppm in India for RS 65 - 400 units IU .
- ◆ Bovine Insulin - Less of weight gain compared to human synthetic insulins due to what effect? Experience based medicine can answer this.
- ◆ Bovine Insulin antibodies and antigenicity? A theoretical discussion: Antigenicity is largely related to purity and site of action. Antigenicity is no longer a problem in causing iatrogenic complication of diabetes. Purity abolishes and overtakes Insulin resistance. Complexing with ZN, lente type insulin will exacerbate this Antigenicity. This will apply to all species of Insulins. Antigenicity and long term clinical effects are similar to any species of insulin. (Clinics in Endocrinology and Metabolism Vol. II, No 2. P.D. Home, K. G. M. M. Alberti).
- ◆ Bovine Insulins acceptable for religious perspective. Muslims not for pork, who could not afford human insulins can go for bovine insulins. Thus their right to life and right to health are well protected by keeping in mind their religious sentiments.
- ◆ Antibodies developed in response to bovine insulin have no functional significance:
 - have low affinity constant
 - negligible insulin neutralising power
 - no clinical insulin resistance
 - daily insulin dose within physiological range.

*Diabetes research and clinical Practice 49 (2000) 7 -15

- ◆ There is no relationship between Antibodies produced by insulin and long term complications like retinopathy, neuropathy and nephropathy.
- ◆ Low cost bovine insulin is as effective as human insulin
 - JAMA INDIA - Physician Update, April 2001 Vol. 4, NO 4.

QUESTION 4:

Is "Species" of insulin important or "Purity" is more important in clinical practice? Discussion.

- ◆ Usually Three fold Triangular question is asked
 - Purity -
 - Species of Insulin &
 - Duration of action (Three fold) J. Skyler formula

- ◆ The amino acid sequence in Human / Porcine / Bovine & connect chains - briefed as

	Bovine	Porcine	Human
A8	Ala	TR	TR
A10	Val	Iso	Iso
A30	Ala	Ala	TR

58 aminoacids are identical. None of the changes are at sites crucial to the binding or action of insulins. Hence no significant difference between species of insulin in receptor binding and action of insulin. Theoretically changes in amino acid could affect the solubility and diffusion properties of insulin molecules (Clinics in Endocrinology and Metabolism Vol. II, No 2. P.D. Home, K. G. M. M. Alberti).

- ◆ Receptor studies proved that there was complete identity between Porcine and Human insulins employing equal potency with bovine insulin as well. The parameters measured include receptor number, affinity, association and dissociation kinetics, down regulation negative, comparative and internalisation.

Why impure Insulins?

“If insulin was a new product marketed for first time this year there is no doubt that production insulin free from significant hormonal contaminants would be an obligatory requirement and there is no known benefit in injecting the contaminants. We now have porcine monocomponent insulin, i.e. only insulin and no contaminants.”

- ◆ Antigenicity is largely related to purity and site of action . Antigenicity is no longer a problem in causing iatrogenic complication of diabetes. Purity abolishes and overcomes Insulin resistance. Complexing with ZN, lente type insulin will exacerbate this Antigenicity. This will apply to all species of Insulins. Antigenicity and long term clinical effects are similar to any species of insulin. (Clinics in Endocrinology and Metabolism Vol. II, No 2. P.D. Home, K. G. M. M. Alberti).
- ◆ There seems to be no reason to believe that human insulin preparation made by biotechnological or chemical techniques will be any less contaminated by such derivatives (desamido insulin, arginyl insulin, insulin ethylesters), and indeed the yield figures would seem to indicate problems of contamination with previously unencountered insulin like compounds in the biosynthetic process. These may well be more difficult to separate from the insulin than the contaminants found in pancreatic extracts.
- ◆ *Purity avoids* antibodies & local insulin problems.
- ◆ Purification process involves almost 14 steps and various methods of purification includes Gel filtration & Chromatographic purification. Single chromatography aims at removal of A and B components of crystalline insulin. Thus offering C or Singlepeak insulins which will have Pro-insulin contamination of ≤ 3000 PPM. Insulin impurities not the insulin itself was responsible for the immunogenicity of recrystallised insulin in-patients (Schlichtkrull etal 1970).

- ◆ Highly purified insulin available in India is the chromatographically purified insulin which contain < 10 PPM and other hormonal contaminants do present. Antibodies cross-reacting with insulin are induced by proinsulin, insulin derivatives (desamido insulin, arginyl insulin, insulin ethylesters) and complexes insulin.
- ◆ Monocomponent insulin means “*Insulin alone and nothing else*” (no contaminants). It requires several radio immuno assays to declare that each contaminant such as glucagon, somatostatin, pancreatic polypeptide, VIP etc. are below the level of detection.

QUESTION 5:

Bovine insulin v/s insulin antibodies and their clinical problems what are all the ideas?

- ◆ Essentially all patients who receive Insulin for long periods develop antibodies to Insulin - (Even antibodies to endogenous Insulin is known) (IAA) - even if completely Purified insulin is available - some Antigenicity will exist.
- ◆ Antigenicity is the fundamental problem and property of polypeptide hormone.
- ◆ It may be true that patients with large Insulin requirements have antibodies - overall correlation of Insulin requirement to antibodies is not constant (Kurtz & Nabarro).
- ◆ Clinical insulin antibodies, theoretically have some "advantages" and "disadvantages"
- ◆ Advantages - Insulin reservoir effect - smoother insulin effects - reduces Brittleness.

◆ Disadvantages - insulin + antibody complexes.

- It is disputed whether insulin antibodies exert a stabilizing effect on glycemic control, assuming that dissociating antibody complexes would help mimic basal insulin secretion, or whether they cause hyperlabile state of glycemic control. Van Haeften et al (Timon W. Van Haeften Diabetes Care 1989; 12 (9)) have described a slower rise in free insulin levels after injections of short-acting insulin preparation in insulin antibody positive as compared with insulin antibody negative patients. Although some reports can doubt on the clinical relevance of this observation, this delay in insulin availability may contribute to post-prandial hyperglycemia, conversely high levels of insulin antibodies can also cause an increase in the half life of plasma free insulin with resultant prolongation of post-prandial and night time hyperinsulinaemia and consequent hypoglycemia. However very high levels of insulin antibodies can certainly produce post-prandial hyperglycemia and night time hypoglycemia. Whether human insulin analogues are useful candidates for short-acting insulin treatment under this particular condition still needs wide clinical confirmation. (Medicine update 2002 Page no:289).

◆ Few Syndromes associated with insulin antibodies recognised- (circulatory insulin Reservoir syndrome) – is interesting. (Congenital Temporary Diabetes of newborn) etc are known.

◆ Now Insulin Antibodies are measurable - Also at AIIMS, Kochu pillai et al, worked over Bovine Insulin & antibodies. Antibodies developed in response to bovine insulin have no functional significance:

- have low affinity constant (2 magnitude less than the native ligand)
- negligible insulin neutralising power
- no clinical insulin resistance
- daily insulin dose within physiological range.

*Diabetes research and clinical Practice 49 (2000) 7 -15

There is no relationship between Antibodies produced by insulin and long term complications like retinopathy, neuropathy and nephropathy.

Low cost bovine insulin is as effective as human insulin
- JAMA INDIA - Physician Update, April 2001 Vol. 4, NO 4.

QUESTION 6:

Are there any special advantages of porcine insulins in clinical practice? Should porcine insulins be still retained in clinical usage? Comments about humanised porcine insulin; Its anatomical and clinical references and differences?

- ◆ Porcine Insulin & Human Insulin are in *one Boat* for over 30 years & hence most popularized.
- ◆ Among animal Insulins porcine Monocomponent Insulin is supreme & has stood the Test of time - In India it is still available at half the price of Human Synthetic.
- ◆ The Big advantage is that Porcine is capable of extreme purification & porcine monocomponent is same as Human Insulin.
- ◆ As already stated Humanised Porcine Insulin is semi
- ◆ synthetic & many companies are using Human Insulin labelled as such and call it Human.
- ◆ Chemical recombination of the chains loses the advantage of the natural folding of molecule that occurs with porcine insulin production and hence the curvature of insulin Peptide is maintained with its advantages.
- ◆ Sometimes the question is raised. Are there any differences between Humanised Porcine (semi synthetic human insulin) or Human Insulin produced by Genetic Engineering.

S.No	Semisynthetic Insulin	Synthetic Insulin
1.	Source – Porcine Insulin	Source – Non biological
2.	C peptide present	C peptide absent
3.	Less antigenic	Theoretically least antigenic.
4.	Monocomponent product	Claimed to be Monocomponent. E.coli (Protozoa), still an animal.

Comparison of Efficacy of Human and Porcine insulin in Treatment of Diabetic Ketoacidosis.

“Between these two groups there were no significant differences in sex, state of consciousness, age duration of insulin therapy before DKA. Basal levels in venous blood of glucose. B-OHB, acetoacetate, creatinine, calcium, phosphate, sodium, potassium and IRI. No difference were found in arterial pH, bicarbonate and base excess. (Diabetes Care 10: 49-55, 1987) (Fred E. M. G. Stoms MD. Jos A. Lutterman MD)

- ◆ There is an advantage with porcine insulin, i.e., small arms of Glucagon are also extracted - (newer Human Insulins do not contain glucagon) Glucagon in very small doses may avoid Hypoglycemia. (Professor Amiel - Wolff 1998, Lancet)

QUESTION 7:

The synthetic genetic engineered human insulins - are there any disadvantages? From theory to practice?

- ◆ The terminology applied to insulin and the structure of insulin appears to have been agreed international by default.
- ◆ Truly human insulin is only produced by human pancreas and has been divided by Deckeret and others 1981 into endogenous human insulin secreted by the pancreas in situ, and exogenous homologous human insulin derived by

pancreatic extraction or cultured islets. Normal human insulin thus best briefly described as endogenous, pancreatic or islet cultured.

- ◆ Human insulins are only human in the sense of having the amino acid sequence and tertiary structure of natural human insulin. They are fully synthetic (i.e. derived from aminoacids)

Philip Corfman, MD.

- ◆ Is synthetic Insulin better than Natural Insulin?

When “Humulin” was approved in 1982, the FDA declared that the synthetic product had not been shown to have any therapeutic improved over animal insulin. The Agency maintains this position today.

- ◆ Is Synthetic insulin not as safe as Natural Insulin?

Labeling was required by Lilly at time of approval

“A few patients who have experienced hypoglycemic reactions after transfer from animal-source insulin to human insulin have reported that the early warning symptoms of hypoglycaemia were less pronounced or different from those experienced with their previous insulin”.

This labeling makes one wonder about safety..

These words, required by Lily to be in the label of “Humulin” one year after approval in 1982, demonstrates very well that the company was aware of the problem of hypoglycemia unawareness from the very beginning.

- ◆ The Kinetics of natural Insulin is longer and “softer” than synthetic insulin. Indeed, Dr. Galloway of Eli Lilly published these finding in 1982. Diabetes Care.
- ◆ And in 1988 Galloway listed these differences between natural and synthetic insulins.

- Human insulin is more rapidly absorbed from the injection site.
- Human insulin is shorter acting than animal insulins
- For optimal treatment of children: different dosage regimens.
- Hypoglycemia is more likely.

Diabetes Mellitus 1988 J. A. Galloway.

◆ ***Possible problems with human insulin***

BM frier et al, Hypoglycaemia in clinical diabetes 1999.

- More hypoglycemic episodes
- Reduced hormonal responses
- Different symptoms of hypoglycaemia
- Impaired hypoglycaemia awareness
- More deaths from hypoglycaemia.

* ***Human insulin reduced brain signal activity during near-normoglycaemia***

Roth c, Landolf HP, Achermann P, Teuscher A, Bordely A, SLEEP 1996.

- We took EEGs in-patients on natural insulin, found that brain signal activity was reduced when they switched to synthetic insulin and returned to normal when switched back.
- We postulated that this effect may relate to hypoglycaemia unawareness seen with synthetic insulin.

* ***All night EEG power spectrum in nonREM sleep***

Roth O et al. SLEEP 1998.

- Synthetic insulin reduced signal activity in non-REM sleep.

Patients on Porcine insulin experience sound sleep longer and feel more relaxed the next day, (Human Vs Porcine Insulin in patients with IDDM - Roth C et.al, Sleep 21, 1998).

**** Different Effects of human and animal insulin on the responses to hypoglycemia in elderly patients with type 2 diabetes***

Meneilly GS et al, Diabetes 1996.

- “We conclude that beef/pork insulin results in greater awareness of hypoglycemic warning symptoms than does human insulin in elderly patients with NIDDM.”

**** Human insulin and Pregnancy***

Kuhl C. Diabetic pregnancy study Group, Copenhagen 1996.

- “Our current knowledge of hypoglycemia in pregnancy can be summarized as follows: As many as 71% of IDDM pregnancies may be complicated by severe hypoglycemia which seems to develop more quickly and often without warning signs during gestation.”

**** Human insulin and traffic***

(Canton of Zurich, Switzerland)

- Hypoglycemia unawareness has also become a problem with traffic accidents, as demonstrated in these findings from Switzerland. Insulin hypoglycemia was a rare event before introduction of synthetic insulin.

**** Unexplained deaths of type 1 diabetic patients***

Tattersall RB, Gill GV, Diabetic Medicine 1991.

- Most were diabetics aged 12-43 years who had gone to bed in apparently good health and were found dead in the morning.

- All was taking human insulin at the time of death but most had been switched from animal insulin between 6 months and 2 years earlier.

- Finally, I want to mention the “dead-in-bed” syndrome, first described in some detail by Tattersall in 1991.

QUESTION 8:

How does the anatomy, structure, curved chains & c peptides etc differ with human genetic engineered insulins - and their clinical applications if any? Is this knowledge important?

- ◆ Insulin is a protein with 51 aminoacids. There are two methods of analysis. One is X-ray analysis, which must be conducted with a crystal and the crystalline structure of the molecule. NMR is the second manner of analysis, where the structure is determined from, and a molecule in solution. Here one can only derive information on the number of atoms, which compose the molecule.
- ◆ Looking at the molecular structure human and pork insulins are almost identical. However the structure of insulin receptors is unknown, so the microscopic picture of how insulin works in the body is unknown. Structure and activity can not be easily inferred.
- ◆ In short, insulin is flexible, its structure is not froze. Microscopic function cannot be derived from the structure; for this, the crystalline structure of the insulin receptors in the body must also be known. In general it is found that mutations in the aminoacid sequence can lead to considerable changes in the structural properties in porcine insulin solution. However functional implications of such changes can only be assessed by more detailed ligand binding studies of native and mutated insulins (Dr.Meuwly).
- ◆ Insulin is injected in microcrystal form. The solubility of microcrystal form was therefore different from the solubility of microcrystal form of Porcine insulin. The beta cells in the human body do not produce crystals but rather active or precursor forms - this means a greater difference. Researchers are working now only on this aspect. The big pharma when they state that synthetic insulin is exactly the same as natural insulin was false. It was also a fact that

recombinant insulin produced by E.Coli bacteria, at first does not form properly; it is linear. Every beginner's biochemistry handbook describes the different physical and biochemical process (heat, pH etc.) required to fold the insulin molecules thus produced. So there is a difference and this proven - (Romen Leist, Biochemist).

- ◆ C peptide's exact function is not known - (C Peptide can be synthetically manufactured by Genetic Engineering if wanted).
- ◆ The fundamental insulin property & its accompanying solubility - Lipid solubility etc are all maintained by the curved nature and diffusion into tissues - (or else it behaves like a straight hormone) - If straightened as a straight chain the amino acid sequences may also have different effects (as an example the Growth hormone is a straight hormone - 191 amino acids).
- ◆ C Peptide also varies in different animals. C peptide have now be understood to have an influence on micro albuminuria correction and other fringe actions. C Peptide is absent in exogenous insulin administration & may need supplementation. This subject of "C Peptide" & connecting Peptides (why they are there in insulins) & the curvature of
- ◆ the molecule etc & various significance's have to be periodically updated by clinicians & Diabetologists.

QUESTION 9:

"Insulin hypoglycemia" versus human insulins and Animal insulins - and the nocturnal hypo etc and sleep rhythms - do they matter in clinical practice - clinical experiences?

** Human insulin reduced brain signal activity during near-normoglycaemia*

Roth c, Landolf HP, Achermann P, Teuscher A, Bordely A, SLEEP 1996.

- We took EEGs in-patients on natural insulin, found that brain signal activity was reduced when they switched to synthetic insulin and returned to normal when switched back.
- We postulated that this effect may relate to hypoglycemia unawareness seen with synthetic insulin.

** All night EEG power spectrum in nonREM sleep*

Roth C et al. SLEEP 1998.

- Synthetic insulin reduced signal activity in non-REM sleep.

Patients on Porcine insulin experience sound sleep longer and feel more relaxed the next day, (Human Vs Porcine Insulin in patients with IDDM – Roth C et.al, Sleep 21, 1998).

Possible problems with human insulin

BM frier et al, Hypoglycemia in clinical diabetes 1999.

- More hypoglycemic episodes
- Reduced hormonal responses
- Different symptoms of hypoglycemia
- Impaired hypoglycemia awareness
- More deaths from hypoglycemia.

** Bellagio Report 1996.*

Scientific information for Bellagio Report April 1996.

*“Human Insulin Hypoglycemia Unawareness:
Accumulated Evidence on the Phenomenon”*

Conclusions of Bellagio Report:

- Human insulin is a useful insulin formulation and many people with diabetes can happily use it. However, a substantial minority of people with diabetes feel safer, have

been hypoglycemic warning symptoms with animal insulin and fewer abrupt hypoglycemic episodes.

- A transfer back to animal insulin brings relief in most instances from severe hypoglycemic events due to loss of warning symptoms *.

- Patients who have always been on human insulin may find advantages if they are allowed to change to animal insulin (Bradley C, Report to WHO Regional Office for Europe, June 1992).

- At the Liverpool Symposium of human insulin and hypoglycemia (1992) there was general agreement for carefully designed large field studies. Until such scientific evidence can be available, 'the simple practical advice must be that patients who wish to use animal insulin should be able to have the insulin of their choice' (Diabetic Medicine 1992; 9: 579-80).

- The balance of scientific data confirms that there are differences between human and animal insulin. Several show advantages with animal insulin in controlled studies also in the elderly despite an intact counter-regulatory response and in numerous case histories. No studies show any clinical advantages of human compared to animal insulin (Alberti KGMM, Brierley EJ, Reduced awareness of hypoglycemia in the elderly despite an intact counter-regulatory responses. QJ Med 1995; 88: 439-445).

- Review of literature shows altered cognitive function and reduced autonomic nervous stimulation with human insulin. These observations are in agreement with the recent studies of brain glucose uptake in well controlled diabetic patients (Boyle PJ, Brain glucose uptake and unawareness of hypoglycemia in-patients with IDDM. New Engl. J Med 1995; 333: 1726-31) and offer an explanation for reduced awareness in some patients experiencing hypoglycemic events from human insulin treatment. This explanation comes as a relief to many doctors and patients. Adding to this the many case reports from patients or their families who have experienced to witnessed practical problems with human insulin (Insulin Dependent Diabetes Trust, Draft Report, Feb. 1996) means that the case for saying that human

insulin should not be the automatic first line choice insulin for most insulin-dependent or insulin-requiring diabetic patients is proven beyond reasonable doubt. (The International Team Residency, Rockefeller Foundation Center Bellagio, April 1996).

** Different Effects of human and animal insulin on the responses to hypoglycemia in elderly patients with type 2 diabetes*

Meneilly GS et al, Diabetes 1996.

- “We conclude that beef/pork insulin results in greater awareness of hypoglycemic warning symptoms than does human insulin in elderly patients with NIDDM.”

** Human insulin and Pregnancy*

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- “Our current knowledge of hypoglycemia in pregnancy can be summarized as follows: As many as 71% of IDDM pregnancies may be complicated by severe hypoglycemia which seems to develop more quickly and often without warning signs during gestation.”

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* 4th July 2000.

“Human” and animal insulins compared.

A report commissioned by the British Diabetic Association

Rhys Williams, Mark Airey, Cathy Bennett, Paul Martin, Pat Spoor.

Division of Public health
Nuffield Institute for Health
University of Leeds
United kingdom

Conclusions:

In our view the following conclusions can be drawn from the above synthesis:

- ◆ The small numbers of trials that do suggest an effect of “human” insulin require explanation.

The explanation could be:

Statistical: these result have occurred by chance alone

Biological: difference in response to “human” insulin exist between populations (either due to genetic factors, environment factors or genetic/environment interaction) so that research carried out in different population (of different nationalities, for example will show different conclusions.

- ◆ The evidence does not support the contention that treatment with ‘human’ insulin per se affects the frequency, severity or symptoms of hypoglycemia. However, a number of studies, mainly those of less rigorous design, describe an

effect when people are transferred from animal insulin to 'human' insulin. It is not possible to state how common this is or whether the phenomenon is specific to 'human' insulin or an effect resulting from stricter glycaemic control (perhaps compounded, in some cases, by neurological complications in long-standing diabetes). This remaining uncertainty makes it essential that insulin from animal sources continues to be available so that clinicians and patients may retain this choice of treatment

- ◆ The evidence summarized in this report is clearly an unsatisfactory in many ways. It is likely that not all of the evidence available is in the public domain.
- ◆ For example, the largest double blind RCT (Anderson 1990) is available only in abstract form. Other important data may exist but only as unpublished scientific reports or as documents kept confidential by commercial organisations. Further work in this area needs to build upon the above analyses as more information becomes available.
- ◆ Progress in the statistical aspects of meta-analysis may take it possible to combine the results of the double blind crossover RCTs available in the literature will be valid.
- ◆ Qualitative description of patients' experiences following changeover from animal to "human" insulin is almost completely lacking in this body of evidence. Some case reports and case series come close to this but, in general, this is a largely unexplored area. Such investigations could be incorporated into a well-designed crossover Rct with three periods of intervention to explore the effect of change back from the second intervention to a further period on the first intervention.

STATEMENT FROM IDDT

Jenny Hirst, Co-chairman
July 7 2000.

- ◆ In September 1999 Novo Nordisk, one of the three major suppliers of insulin in the world issued a press statement that included the following:

Novo's Admission

- ◆ “Historically improving Glycaemic control with soluble Human Insulin has been associated with an increased risk of Hypoglycemia”
- ◆ So Now you know
- ◆ But of even greater concern is a statement from Aventis's, another large insulin manufacturer, dated April 24th 2000 that includes the following:

Aventis Admission

- ◆ “Human Insulin therapy may be associated with Hypoglycemia, worsening of diabetic retinopathy, Lipodystrophy, skin reactions (Such as Injection – site reactions, pruritus and rash), allergic reaction, sodium retention and edema”.
- ◆ The statements were put in the public domains by the insulin manufacturers and not by IDDT. These statements cause us concern because the adverse reactions that may occur with ‘human’ insulin therapy, as listed by Aventis and Novo Nordisk, are very much in line with the evidence from a large number of patients in various countries. These reactions largely regress with a change to animal insulins.

◆ National Institute of clinical excellence (NICE). The final draft guideline on Type 2 diabetes – glycaemic control, is currently on the NICE website 2002 April. Page 59 in the section on the use of insulin in the treatment Type 2 states the following:

◆ “Despite the lack of an evidence-base to support current practice, the group recognized that usual insulin therapy both for people with diabetes starting and continuing insulin now utilized human species insulin rather than beef or pork. However the purified forms of these latter species of insulin are appropriate options for clinical and patient choice.”

◆ Professor Alberti’s statement

“Personally I care less about what sort of insulin is available, and more that it is accessible, affordable, of reasonable quality – and works.” (IDDT, Summer Newsletter, Issue no 33 July 2002)

◆ In general Hypoglycemia can easily occur in synthetic Human Insulin & Hypo unawareness & Warning Syndromes may be absent - because Human synthetic Insulin said to be less Lipophilic - & does not reach the Hypothalamus – easily. "Silent Hypo" common.

◆ Hypoglycemic symptoms were fewer in number in patients taking human insulin, meaning patients on Human insulin are at higher risk of suffering from hypoglycemic unawareness (Science 1 2001, Elphinstone Conference, UBC).

◆ Nocturnal Hypo - Dead in Bed syndrome at night. Dead in undisturbed Bed syndrome (BMJ) - said to be common in 1980- 90 period. Tight control cases of IDDM mostly.

Addendum (SGPM). In Indian scene severe Hypo is not observed as major problem with human insulin. Broadly because we are using lower doses of human insulins and not a strict control regimen and many sleep laboratory reports have not been studied.

At this juncture we should not forget, after 80 years usage with animal insulins there were no reports on Hypo-unawareness. When we are getting highly purified Bovine at RS. 65 and monocomponent Porcine at RS. 135 Why we should not provide this cost-effective solution to our diabetics (SGPM).

QUESTION 10:

Insulin & weight gain human insulin - versus animal insulin ? It is apparent or real in clinical experiences?

- ◆ In general insulin is an "anabolic hormone".
- ◆ Insulin is a growth hormone in foetus - Foetus has its own Growth hormone & also foetal insulin - (Hyper insulinaemia in foetus can produce Macrosomia).
- ◆ Insulin weight gain in IDDM & NIDDM. Is it different? In IDDM weight gain is only proportion to weight loss - In Type2 weight gain can occur - (obese Type2 Probably more weight gain) - some small controversy exists. Many agree on this weight gain - even some of the Sulphonylurea can cause weight gain in NIDDM - Lean NIDDM - No weight gain.
- ◆ The subject of weight gain requires a differential study.
- ◆ "Spontaneous Hypoglycemia" in non-diabetes: Healthy non-diabetes can develop hypo glycaemia episodes - after an early breakfast. Postbreakfast Hypo settles well after a second break fast.

- ◆ In general weight gain is more with synthetic Human Insulin - rather than animal Insulins - with Bovine Insulin much less - no weight gain (experience based) not evidence based).

QUESTION 11:

Selective clinical situation example (pregnancy) etc (allergy to one or other species) are all selective situations- individual ideas with individuals experiences?

- ◆ Pregnancy - an exclusive situation with Diabetes - known Diabetic going through Pregnancy as well as Gestational Diabetes, may need short term Insulin therapy.
- ◆ Many considerations are taken into account - Insulin does not cross the placenta - But Insulin antibody complexes (Water-soluble) can cross & produce Macrosomia. Even minimal antibodies can cause problems unlike in Non pregnant (non-pregnancy no problems).

The reality

- Animal insulin Vs Human insulin

N = 170 mothers 39.

Macrosomia (>90 percentile) & ponderal index similar

Obst Gynecol 1991 78 (4), 590-3.

Even in pregnancy, no difference has been observed in terms of neonatal Macrosomia and ponderal index between users of bovine and synthetically produced insulins (Kochu Pillai, AIIMS).

- ◆ Fifty insulin dependant pregnant diabetic women were treated from presentation at an antenatal clinic at the Royal Maternity Hospital, Glasgow. The data presented in the paper by J.M. Lieper et al clearly shows that there is no difference in the group treated with highly purified porcine insulin as regards to blood glucose, control birth weight or neonatal complications as shown in Tables.

Table: Clinical Characteristics and progress of Mothers and Babies Studied.

	Human Insulin Treated	Pork Insulin Treated
Age (Years)	26.9 ± 5.1	27.9 ± 4.8
Duration of diabetes (years)	9.1 ± 5.7	10.4 ± 8.5
Gestation of presentation (weeks)	12.0 ± 6.6	11.5 ± 6.5
Gestation of delivery (weeks)	37.3 ± 2.1	37.4 ± 1.7
Maternal HbA _{1c} at presentation (%)	9.8 ± 2.1	10.0 ± 2.9
Maternal HbA _{1c} at 26 weeks gestation (%)	7.7 ± 1.5	7.8 ± 1.0
Maternal HbA _{1c} at delivery (%)	7.3 ± 1.4	7.5 ± 0.8
Birth Weight ratio	1.04 ± 0.2	1.07 ± 0.2
Macrosomia (cases)	4	5
Neonatal hypoglycemia (cases)	4	4
Major congenital abnormalities	Pyloric stenosis, congenital heart disease	Anencephaly, neonatal hyperthyroidism
Results are expressed as mean ± S D		

No difference between the groups attained statistical significance.

Table: Insulin Dose (mean S.D.) at 20 Weeks Gestation, Pre-delivery (Mean Gestation 37 weeks) and 5 Days Post-Partum.

	Human Insulin	Pork insulin	
20 weeks gestation	n = 19	n = 18	
Morning Soluble	14.5 ± 2.6	14.3 ± 3.0	NS
Isophane	25.2 ± 1.7	24.7 ± 2.8	NS
Evening Soluble	8.0 ± 1.9	8.7 ± 1.7	NS
Isophane	26.5 ± 1.8	17.0 ± 2.8	p<0.01
Pre-delivery	n = 21	n = 21	
Morning Soluble	22.6 ± 2.6	21.5 ± 3.7	NS
Isophane	35.4 ± 2.6	33.0 ± 3.7	NS
Evening Soluble	14.2 ± 3.1	13.7 ± 2.6	NS
Isophane	32.3 ± 3.0	19.9 ± 2.6	p<0.005
5 Days post-partum	n = 19	n = 17	
Morning Soluble	7.6 ± 0.7	8.4 ± 1.3	NS
Isophane	16.1 ± 1.3	15.8 ± 1.4	NS
Evening Soluble	4.7 ± 0.5	4.5 ± 0.8	NS
Isophane	13.1 ± 1.4	7.9 ± 1.8	p<0.01

◆ At 20 weeks gestation, pre-delivery and at 5 days post-partum significantly those required more evening Isophane

insulin on human insulin. Otherwise morning and evening insulin doses were similar. Two women receiving human insulin had to change to a thrice-daily regimen (bedtime Isophane insulin) in the third trimester to avoid nocturnal hypoglycemia and fasting hyperglycemia.

- ◆ A comparative shorter time action of human Isophane insulin was suggested by the increased requirement for Isophane insulin in the evening injection (to maintain fasting normoglycaemia) and the necessity in two cases to delay the evening Isophane injection until bedtime. These findings are consistent with the known characteristics of biosynthetic Isophane insulin, both in formal pharmacokinetic studies and in clinical trials in non-pregnant diabetic subjects. This information was not available at the time the study was carried out. Increasing the dose of evening Isophane insulin in order to control fasting blood glucose levels carries the risk of including nocturnal hypoglycaemia. These problems might be avoided by the use of **longacting** human insulin preparations.

Medicine update 2002 Dr. Anil S. Bhoraskar.

- ◆ In practice if for any reasons if it is not possible to use porcine Monocomponent or human, any insulin have highly purified may be suitable to correct the metabolism.
- ◆ In allergy - also one or other variety may be changed - allergy to any insulin is noted. Even Genetic Engineering Human insulin can produce allergy. (any therapy with insulin allergy is usually not permanent).

Allergic Reactions to Animal Insulin

- ◆ Allergic reactions including urticaria and anaphylaxis occurred with early insulin preparations, but as these were very impure, the antigen may not have been insulin. Immediate-type systemic hypersensitivity reactions to insulin are rare now and they will virtually disappear once patients switch over to highly purified insulins. In insulin

allergic patients insulin specific IgE values are often 10-20 fold higher than in-patients without allergy. A major problem is the cross-reactivity that occurs between anti-insulin antibodies and the various animal and human insulin preparation in-patients presenting with allergy to animal insulin. In non-allergic cases positive skin test to human insulin do not necessarily have any clinical significance, because as many as 40% to 50% patients receiving conventional insulin therapy showed wheal-and-flare responses and intra-dermal testing. (Guntram Scherntianer Diabetes Care, 1993; 16.)

- ◆ Another manifestation of insulin allergy, which is also now relatively rare, is a delayed local injected insulin which is seen as tender subcutaneous lump that develops at the injection site 30 minutes after injection and lasts for 12-24 hours. This is local Arthus-type reaction, mediated by IgG rather than by IgE and is attributable to the compliment activation by insulin - IgG immune complexes. The exact frequency of allergic reactions to animal insulin preparations is unknown. However, after reviewing the entire literature on this subject one can safely conclude that the frequency has been reduced 30% to < 5% in the past half century.

Allergic Reaction to Human Insulins

- ◆ In view of the wide spectrum of immune-mediated complications of insulin therapy, much attention has been directed to the reduced immunogenicity of highly purified forms of animal insulins and more recently available recombinant and semi-synthetic form of human insulin. Delayed-type insulin allergy and especially immediate-type were extremely rare in type1 and type2 diabetic patients who were treated exclusively with human insulin in many centers.
- ◆ As human insulin preparations are not totally non-immunogenic, local and acute systemic responses to

exogenous human insulin have occasionally been reported. There are occasions where a patient with a known history of anaphylaxis to animal insulin may also develop similar reaction to human insulin. Recently Ganz et al described a type 2 diabetic patient who manifested both severe insulin resistance and persistence systemic allergy despite treatment with recombinant human insulin. However, in this cases symptoms of insulin allergy had already emerged several months after initiating therapy with mixed bovine-porcine insulin. After switching to recombinant human insulin, generalised urticaria with pruritus, significant eosinophilia, and diffuse lymphadenopathy reminiscent of serum sickness like response occurred. This case illustrates that a wide array of clinically significant responses to human insulins occurs when it is used in insulin allergic patients (Timon W. Van Haefen Diabetes Care 1989; 12 (9)).

- ◆ Patients who are intermittently exposed to insulin because of **irregular administration** appear to be at a higher risk for more persistent and severe allergic reactions.

Lipoatrophy

- ◆ The phenomena of lipoatrophy, in which there is a loss of fat at insulin injection site was previously quite common, being reported in 10% - 55% of patients treated with conventional bovine/porcine insulin. Patients with lipoatrophy usually have high circulating insulin antibody titers. An immune basis for this condition has been suggested by the immunohistochemical demonstration of both insulin and IgG subcutaneous tissue biopsied from lipoatrophy areas. *Lipoatrophy is now very rare with highly purified porcine insulins.* (Guntram Scherntianer Diabetes Care, 1993; 16.)

- ◆ Thus individual ideas & individual experiences may prevail in these situations.

QUESTION 12:

The so-called "Availability of animal Insulin crystals" - as a subject what is the reality in animal insulins across the Globe?

- ◆ The problem of shortage of animal insulins in U.S. was raised even over 20 years ago (Podalsky et al). The problem of Limited Insulin supplies Globally. 15000 pigs & 18500 cows → 800 pounds of Pancreas, yield one pound of insulin, to serve 750 patients one-year supply. But the concern is the increase in the number of patients year after year.
- ◆ The big Pharma has withdrawn bovine insulins in India and their long term strategy to discontinue animal insulins remains unchanged. Their existing production of animal insulins will gradually be converted to the production of semisynthetic human insulin. E.g. biobras/NN production in Brazil. What this means that they will make "human" insulin from animal insulin. Hence the name semisynthetic. That is how human insulin was first made in 1980's.
- ◆ In reality American National Advisory Board 1978, WHO 1980 feels that there would not be any insulin shortage and no such problems will arise. Insulin manufacturers own studies are believed to confirm that most pig pancreases remain unharvested (Teuscher and Diem 1980, DECKERT et.al 1981) and pig pancreases alone can meet the current demand. Chemically modified human insulin (enzyme modified pork) depends on animal pancreatic insulin as its starting material. Assured production thus cannot be a reason for a development of this insulin (K.G.M.M. Alberti).

Animal insulins are freely available in India at most affordable prices. These extensive promotional activities like this, will certainly reassure the practicing diabetologists the availability of animal insulins in the Indian market.

QUESTION 13:

Are there any extra environmental influences" - like "mad cow diseases" "Prion diseases" - pig encephalitis viruses etc - are they real impediments - or created ideas etc what is the problem and what is the reality? Discussion?

Defining CJD:

Classical Cretzfeldt-Jakob Disease (CJD) is a rare (< 1: 1,000,000:yr) and fatal brain disorder characterized by rapidly progressive dementia and associated neurological disturbances. The disease produced microscopic vacuoles in neurons that appear "sponge-like" and is often referred to as spongiform encephalopathy.

Originally thought to be caused by a virus, recent research has pointed to a new type of pathogen called a proteinaceous infectious particle (prion), which is capable of transforming normal benign protein molecules into infectious, deadly proteins by altering their shape and consequently, their function. There is currently no evidence that persons diagnosed with any form of CJD carry infectious prions in their blood.

- ◆ Sometimes the other aspects of disease in animals have been invoked as problems (Mad cow disease, Spongiform encephalopathy & pig encephalitis Virus etc).
- ◆ Generally Viruses reaching the Pancreas is protected (RSG Leslie) unless it is pancreatotrophic - (in general virus Diseases have a tropism). In general in medicine the virus

disease have a Big Tropism – like skin Tropism – Parotid Tropism – Hepatic or Pancreatic or Brain Tropism. Thus we are shut up with “Mumps” – breakdown with “Measles” – or Jaundice with Hepatitis etc – without Tropism usually the organs are not affected. Hence no possibility of BSE in pancreas.

- ◆ In general animal meat – Beef is so highly processed that it is highly unlikely that they contain any protein.
- ◆ In general the manufacturing process of Insulin from animals involves several elaborate steps of purification, sterilization and certifications. The large 254 BSE amino acids would be filtered out by the 4th of 14th filter steps in manufacturing.

Scientist: ‘Mad Cow’ May Not Cause Human Illness

10/24/01

Mad cow disease and the illness thought to be its human equivalent might not be linked after all.

George Venters, an expert in public health medicine in Hamilton, Scotland, believes the rogue prion brain protein that causes mad cow disease, or bovine spongiform encephalopathy (BSE), does not cause new variant Creutzfeldt-Jakob Disease (vCJD) – a degenerative brain disease found in humans.

But Venters said there is no direct evidence that the prion responsible for BSE and other animal diseases is infectious in humans.

Prions in animals and human are different, he argues, and humans do not get other animal prion diseases such as scrape – found in sheep – from eating lamb.

BSE is not a transmissible disease.

It is also incorrectly described as an infection. There can be no infection without a virus or bacteria, as there are neither it is clearly a poisoning. A poisoning cannot produce a transmissible disease but it can be transplanted from one animal to another and made to appear transmissible.

Transmission is an illusion.

Proof that all spongiform diseases are produced endogenously has been confirmed by animal research.

When cats, mice, sheep, pigs, goats, monkey, etc., are experimentally inoculated with BSE (2), yet all naturally occurring forms of spongiforms disease when microscopically examined have a species specific recognisable pattern. When a different genotype is used to donate the feed or inoculums it produces what is referred to by SEAC as the “Donor species effect” (2) a mouse with induced BSE for example (2) produced a mutant form of BSE as the induced poison is simply being transplanted from the donor to the recipient as these articles (3)(4) clearly demonstrate. Bradley R., Experimental Transmission of BSE, 1996, Elsevier, Paris. TSE, SEAC. London HMSO. September 1994. P 62. Brown P., Carleton Gajdusek D., et al. The New England Journal of Medicine, Sept 19, 1985, p 728.

To successfully reproduce the true disease the induced genetic material must come from same species as the recipient.

This “Donor Species effect” (2) visibly demonstrates the disease cannot be transmitted to other species. New variant CJD was never new and never variant. It has always been simply CJD. If a new disease was immerging in Britain related to eating British beef the “species effect” would reveal from what animal the disease originated. The missing ‘Donor species effect”, in all forms of spongiform encephalopathy not induced by scientists, proves the disease did not breech the species barrier.

The endogenous origins of spongiform encephalopathy.

Spongiform diseases occur in both animals and humans. The disease is given a different name according to the species, such as CJD in humans, Scrape in sheep, BSE in cattle, and CWD (chronic wasting disease) in deer and elk. The disease in vegetarian elk or deer, therefore eating meat cannot cause it in cows, sheep, humans, or any other species. Eating British beef cannot possibly cause new variant or any other form of CJD. We can also prove that it was never experimentally, what appeared to be transmitted was in reality induced putrid protein poisoning. Bio-accumulated neurotoxic residues that survived in the fat component of the newly introduced solvent-free fat extraction process.

Endogenous Origins of SEs

Dioxins

“Dioxins” for just one example refers to a group of chemical compounds that share certain similar chemical structures and biological characteristics. Dioxins are present in the environment all over the world. Dioxins are released into the air from combustion processes such as waste incineration and from burning fuels. Dioxins can also be formed when household trash is burned forest fires. Animals can take up dioxins deposited on plants and concentrated in the food chain so those animals have higher concentrations than plants, dioxins tend to accumulate in fat. About 95% of exposure to dioxins occur through consumption of food, especially food containing animal fat.”

Conclusions

Our proposition could again be tested and proven by conducting a simple experiment which would involve treating two samples of organs from a cow. Dry clean and process one sample with a solvent used in the feed manufacturing process i.e. trichloroethylene and compare the toxic residues of each.

Only the non-solvent treated sample will contain the predicted neurotoxic residue.

We prove the disease is not transmissible. A poisoning is not a transmissible disease it is an injury. The prion is a symptom not the cause.

MAD COW DISEASE

<http://www.suite101.com/article.cfm/4866/71780>

Author: Juan C. Mendible

Published on: June 12, 2001

Prions are proteins, and in order for the ones from cows to cause disease they have to go through your gastrointestinal tract, your blood stream and cross what is called the blood barrier, whose function is to stop big molecules from going into the brain.

Now, in the GI are protease's, enzymes that destroy—digest—most of the proteins that you eat. This is one of the reasons it has not been possible to design a way to take insulin orally—it is destroyed in the GI. Insulin is a much smaller protein than prions.

Even if the prions should make it through the GI system and into the blood, they should be destroyed by your immune system; and if they survive all that, they still have to cross the blood-brain barrier, enter the cells, find the normal prions and convert them to pathogenic. Aren't they stretching it too much?

- ◆ In their statement of 16 April 1996, The European Medicines Evaluation Agency (EMA) concluded inter alia that for all active ingredients or reagents used in the manufacturing process, the measures detailed in existing European guidelines guarantee that medicinal products containing bovine tissue are safe. There are no recorded

cases of variant Creutzfeldt Jacob Disease (vCJD) that have been linked to the use of pharmaceuticals containing bovine derivatives.

However, it is important to note that after rigorous surveillance efforts and scientific scrutiny by leading scientific investigators as well as government and regulatory agencies, a large body of evidence demonstrates that there is no credible support for transmission of CJD, including vCJD, from person to person through blood or plasma-derived products. Therefore, any risk must be considered as theoretical.

QUESTION 14:

If all the insulins are available and if their action are more or less the same - is the cost important? Or the marginal advantages and disadvantages matters ??

- ◆ If all insulins are available - mono species and Purity are the Supremes - no doubt insulin action will be the same - They all will sit on receptors & act well.
- ◆ Analogues of insulins sit well & act - when synthetic analogues act well - why not natural Insulin analogues Bovine / Porcine & Human.
- ◆ In that case, of course cost will be the important factor - although some may not care for the cost - at least say so.
- ◆ Marginal disadvantages & advantages between the insulins always were there even earlier.
- ◆ But Physicians & Diabetologists must be aware of all the aspects of Bovine, Porcine & Human & apart from these

clinical animal Insulin. "Animal Insulinology" - has become a big subject in Basic Diabetological sciences-

- ◆ When animal Insulinology is progressing this question is inevitable.

QUESTION 15:

Some of the synthetic insulin analogues have serious potential problems. Mitogenesis & Carcinogenicity etc - even if incidence is not high can it be taken into account. For instance "Pro insulin" - clinical trials - myocardial toxicity - with drawn etc - many other instances also. What are the collective ideas - enthusiastic ideas and non enthusiastic ideas?

- ◆ Replace Human Insulin by human insulin was the motto in the newer Insulin Era -
- ◆ Now because Genetic Engineering has been advancing, the focus on Insulin analogues began & pharma companies & Insulin Researchers go on speculating on various analogues - short acting & long acting analogues.
- ◆ Pro insulin for clinical usage was produced as an earlier analogue & now with drawn quickly owing to myocardial Toxicity.
- ◆ Now many short acting & Long acting Insulin analogues are devised - Insulin Aspart, Insulin Lispro, Insulin Glargien - Lantus Insulin & so on -
- ◆ Discover an analogue & then find & Build up a usage for it - is the usual pathway.
- ◆ Regarding Clinical trials of analogues - various contradicting ideas can occur - as an example Insulin

"Lispro" in 1998 etc. New Eng. Journal of Medicine published so many problems in usage of "Lispro" "in pregnancy" - so many frightening foetal anomalies etc & again last year 2001 same NE Journal of Medicine published and announced results with Lispro as safe in pregnancy even same reported authors (Jovanovich) - Probably one will lose confidence in "evidence Based Medicine" - across U.S.

- ◆ Brent Hoadley's Insulin Patent Research and Findings:
Feb 28, 2001 - Hoadleygold, inc, Brent hoadley PhD.

In his book 1984, George Orwell wrote about "newspeak". This is now the language used by the pharmaceuticals to create billions of dollars in profit from genetically engineering insulin-like molecules.

Pharmaceuticals will tell you the foreign protein insulin source is the pancreas of a pig or cow. When given names such as humalog, lantus or novorapid by giant corporations, a foreign protein becomes a wonder 'analog' of human insulin. The truth is all three of these substances are foreign proteins - in some cases not even an insulin molecule. All could be considered new growth hormones with very little being known about long term effects. Diabetics need to apply for long-term guinea pig status.

QUESTION 16:

In many insulin - Blood glucose controls & complication trials no analogues were used and the available Routine Insulins also good enough? What are the comments?

- ◆ In Insulin analogues - the usual question Basic asked is Do we need the various analogues? The straight answer will be

- No - Not necessary - round about answer may be - yes in selective areas of Insulin practice.

- ◆ Many of the given classical Trials DCCT or UKPDS - or Kumamoto - did not use the Insulin analogues - There was no necessity and Tight control of Blood glucose can be achieved without it.
- ◆ So it looks as if Insulin analogues are for "Coined usage" (again a coined Terminology) not absolutely essential - (still may have its own usage in selective areas).

QUESTION 17:

In general what are the individual ideas and final opinion and concluding messages in this subject of animal insulins versus human insulins and GE insulin.

- ◆ As daunting as the over all costs of diabetes care the day to day challenge for individuals with diabetes and policy makers relates to choices in diabetes care. What benefits do various choices of insulin provide and at what cost. Whether these questions are asked at an individual or national level, knowing the answer is fundamental to cost effectiveness.

India presents classic example,
In 1998,

Cost of Insulin therapy/year/person	\$350
Cost of non insulin therapy/year/person	\$ 70

17.5 MN diabetics in India,

Total cost of diabetes in India	\$ 2.2 Bn.
Total healthcare budget for entire India	\$ 720 Mn.

Percapita expenditure for all health cares	\$ 21
- including water and sanitation.	

Nearly 400 Mn Indians live in absolute poverty.

The availability of cost effective animal Insulins is mandatory in the Indian Sene. (Nearly 400 Mn Indians live in absolute poverty) and in developing countries (where 80% of the population consumes 20% of world production of insulin).

- Since Purity - Purity has been conquered in animal insulins they may be otherwise equable - why not have all of them. Cost effectiveness is important for regular and continued use of insulin especially because there is no medical insurance coverage in Indian Medical Sene.
- The debate on these differences has continued since the introduction of treatment with human insulin and, unfortunately, very often the patients' experiences have been classed as "only anecdotal" and of little value.
- Research has already demonstrated that human insulin has no clinical advantages for patients. When insulin is needed animal insulin should be considered as first choice treatment for all those were hypoglycemia is our special concern. This may include the following:-
 - Children;
 - Elderly;
 - Those reporting severe and/or frequent hypoglycemia;
 - Those with severe cardiovascular disease or long term complications;
 - Those who do not have access to frequent blood-glucose monitoring, e.g. in developing countries;
- In this connection human insulin hypo and animal insulin hypo differences are to be critically studied and reviewed and various syndromes will be looked into. Is it real or artifactual? Such as :-

Unexpected hypo.

Hypo unawareness.

Hypo and sleep abnormalities

Hypo and traffic accidents

- In spite of over 20 years the cost reduction of synthetic insulin was very much expected and announced. But it did not take place. Why? Why? Why?
- The Antibody v/s various insulins have been critically studied and they do not pose big problems as various studies have revealed it.
 - Thus many imaginary conditions of availability of animal insulins in future and animal insulin crystals, invoking animal diseases (BSE risk) are not at all stumbling blocks for animal insulin usage.
 - If cost is an important factor considering the minor clinical advantages with human insulin, natural animal insulins with highest level of purity must be available for clinical usage in both commonsense based diabetology and experience based medicine which we have popularized in a vast country like India. (United States of India) in general, apart from evidence based medicine popularized in USA.
 - All these do not mean that G.E insulin process is Halted. That the progress will go on in the post post newer insulin era in spite of having a relook into animal insulins.

After all we all live to learn.

E.P. Joslin

- ❖ *Learn as if you have to live forever.*
- ❖ *Live as if you have to die tomorrow.*
- ❖ *Long live insulin and insulinology.*

Appendix to Panel Discussion

A Few Dictums about "Relook into Animal Insulins" & "Lessons from animals Diabetes" & "Animal Insulinology"

1. The subject of relook into animal insulins in the post - post-newer Insulin ERA is interesting.
2. The porcine - Beef - (Bovine) & - Mixed animal insulins have been in long usage since 1922 the discovery of insulin.
3. In no other endocrine products, we use the animal biological products so much as in the insulin in Diabetes and it has stood the test of time till genetic engineering check in after 1970 - 1972.
4. Comparative animal Pancreatology pancreas evolution in animals - vertebrates is all the prelude in this subject.
5. "Lessons" from "Animal Diabetes" has been incorporated in the subject of Human Diabetology and actually in ever IDF meeting since 1982 - the "Presatellite IDF meeting" on lessons in animal Diabetes for 2 days prior to main IDF meet has been the routine.
6. In general pancreatic islets are unique to vertebrates and lacking in non - vertebrates (Not exactly true). But in MOLLUSES (Non vertebrates) collip in 1923 discovered islets - Thus insulin is also found in non - vertebrates.
7. Thus insulin is found in invertebrates & insects of even red ants in brain area.
8. The "Amphox" is the border line animal between vertebrates & in vertebrates.
9. Thus "Comparative Animal pancreatology" - a coined terminology is very much talked about & animal insulinology has come into existence.
10. In fact no other hormone (except insulin) has been so much studied as insulins and even as many as 45 animal

insulins (elephant rhinoceros down tomice) have been studied in detail with regard to amino-acid sequences etc.

11. In Avian birds - the Glucagon in high +++ in secretion of & Insulin + low on & blood glucose in domestic fowls normal is around 220 mgs % alpha cells predominate - this has been worked out in Calcutta university Zoology Department (current science magazine).
12. Thus again to emphasize the comparative Animal insulinology has emerged as a big subject and as many as 45 amino acids - elephant Rhinoceros - Monkeys & dogs & even horizontal animals like rats pigs & cattle have been studied in insulin structure & amino acid sequence.
13. Few peculiarities in animal insulins - two insulin genes in guinea pigs and two different types of insulin (a native insulin & a porcine type insulin) has been known - reasons not well understood - but interesting.
14. Some other animals like porcupine - some rodents etc also different insulin types - some of them relate to dimer and monomeric form of Insulin (& even enabling quick erection of porcupine spines).
15. Lessons from Animal Diabetes involve the study of induced experimental diabetes and the spontaneous diabetes in some animals & also the diabetes drug trials in experimental diabetes and the spontaneous diabetes in some animals and also the diabetes drug trials in experimental animals etc.
16. Again - unfortunately the steps in the purification of animal insulins is very elaborate about ten steps from collection of frozen pancreas down to crystallise & purified etc.
17. Purification of animal insulins - big procedure gel purification & chromatographic purification and mono

chromatography & twice chromatography "Single Peak" - "Mono Component" MC insulins have all been various terminologies in purification of animal insulins and their declaration.

18. It has been frankly and accepted that Bovine - Porcine & Human Insulins are virtually mutual natural insulin analogues and this declaration has opened many venues regarding analogues.
19. This appreciation has led to the big-big subject of insulin analogues in this era and various insulin analogues have been studied.
20. After the advent of genetic engineering - various manufactures of Insulin & amino acid sequences have been tampered with the production of newer and newer insulin by GE method have been evolved - so called "Tailoring of Insulins" Tailoring of Insulins etc.
21. Human minds & Human research and Pharma research are restless & go on trying to manufacture more and more insulin analogues short action & long action & so on - with genetic engineering & even at enormous cost.
22. In fact it is strange that Insulin analogues have been more than twice costlier than G.E. Human insulins. How come?
23. Apart from genetic engineering - Human insulins - even "Humanised Insulins" - from Porcine Insulin - modification of amino acid and changing amino acids is in usage.
24. Practically there is no difference between Human GE Insulins and Humanised Porcine Insulins.
25. Purity - Purity & Purity by various standards have been the catch words of animal insulins in this era.

26. Thus at one point of time we go on advertising in journals "Replace Human Insulin by Human Insulins" and at the same time we go on dabbling with Insulin analogues & even mixture of analogues + Human Insulin all difficult to understand - anyway taking place.
27. In this era in this connection - even islet cell transplants have also been studied in animals & human & even CMC Vellore has been experimenting on animal islet transplants and Hetero animal transplants.
28. Human islet cell transplantation and harvesting dead fetal islets after MTP in pregnancies have been all done - but restricted by "Embryo ethics" - USA.
29. At the same time "Cloning" and "Cloning" - much studied in animals & in Zoology & sheep & pigs - In pigs etc predominant cloning of oviducts have been done - Human experiments not yet successful.
30. The advantages & Disadvantages of the insulin analogues have been clearly appreciated.
31. In this regard a reanalysis of animal insulin & antigens & antibodies have been all studied & the binding of antigen antibody complexes is even an evolved subject.
32. Since the supreme importance of purity - purity in animal insulin has been set - animal insulins have also the same advantage as Human insulin.
33. The cost - Benefit of animal insulin's in Indian setting & "Socio economic burden in diabetes" - well talked about and also the so called "Insulin economic burden" has led to the continuation of animal insulins in day to day practice as long as it lasts.
34. This does not mean & does not advocate against genetic engineering human insulins and its derivatives at all - &

actually the progress in genetic engineering will continue in all directions.

35. Insulin has been the "trend setter" in genetic engineering of other hormones as well as (growth hormone - or somatostatin) etc.
36. Thus again insulin & insulinology as a specialty has come to stay (on par with Aspirin or Aspirinology & "statinology & soon).
37. There are many interesting things about the hormone insulin - Insulin is a physiological hormone and is indeed a "GUT Hormone" with predominant metabolic action at one end of spectrum, while at the other end is "Gastrin" - almost exclusively gastrointestinal activity etc.
38. It is also appreciated that genetically malformed insulin - Insulin malformation & Ghost insulin in some individuals & some families have been appreciated so called even "Insulinopathies" seen in some NIDDM type2 insulins in particular.
39. Intra uterine fetal insulins may differ from adult insulin in some respects. Insulin in fetus also acts as an additional growth hormone apart from foetal growth hormone.
40. It is some times not realised by doctors & patients that insulin is a "God given Gift to man" and in deficiency we have to go after insulin manufactures to replace us this natural gift and by them at enormous cost - especially human insulin.
41. Thus Human insulin & animal insulins will be relative used in Indian scene for long periods and studying their mutual advantages and especially enabling the cost benefits in Indian insulinology.
42. Thus a Relook into animal insulins in the background of newer insulins and genetic engineered insulins in this era is

particularly important scientifically quite apart from pharma companies introducing animal insulins.

43. In insulin therapy we talk of "Insulin Replacement" therapy as in IDDM type 1 patients and insulin "Supplemental therapy in NIDDM type 2 patients and soon.
44. It is also good that a few pharma companies have boldly reintroduced the animal insulin - ensuring "Purity" - "Purity" - as a hall mark as supreme standard apart from spies and that has also incidentally evolved the study of "Relook" into animal insulin's.
45. In normal individuals whatever the quality and quantity of food that we eat the available insulin endogenous matches the food intake - but once you are "Diabetic" you have to match the food intake to the available "exo" or endogenous insulin - This is indeed called the scientific philosophy of diabetes.
46. It is stated that Insulin may improve the so-called "Quality of Life" (which is difficult to define) in many NIDDM when administered even for short periods - individual ideas may differ in this area.
47. In this connection it is a good argument that API all India annual meet in 2002 has taken up plenary session on "New Look into animal Insulins" to be in Madras 2002.
48. IDDM type, is reckoned as form of "Pure Diabetes" - a pure endocrine disease - with total deficiency of Insulin.
49. While NIDDM is a "Hotch Potch" disease with so many diseases within it & soon and is highly heterogeneous.
50. Insulin is the leader of "Metabolic orchestra & hence in IDDM become a "Chaotic" metabolic disease with complete absence of Insulin.

51. Obesity in animals also studied & Diabetes & Obesity = Diabesity in animal studies & Humans.
52. Various diabetes drug trials experiments on animals (eg) Aldose reduction in neuropathy etc.
53. In veterinary Diabetology for example in "Bovine Ketosis" studied in cattle. There are even human counterparts of "Bovine Ketosis like ketosis" in human lactating pregnant diabetes.
54. Even many animal diabetologists have evolved in veterinary specialists - even "RAT Diabetologists" are known in ISRAEL & many of them take part in IDF pre satellite meetings. On lesson from animal in debates.
55. Thus evolving subject such as Animal comparative pancreatology comparative islets study & comparative insulinology & comparative diabetology - have all been interesting subjects - Thanks to "New look into Animal Insulins".