

Reflections on Some Mathematical Modeling in Endocrinology

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Abstract: *This is an expository paper which explores a variety of epidemiological and other quantitative approaches to research in endocrinology. It is a sample of some of the projects in which the author and his colleagues, including doctoral students, have been involved over a number of years. The medical and mathematical theories have been tested on consenting patients in clinical environments.*

Keywords: *Diabetes mellitus, Erythrocytes, Moving boundary problems, Control theory, Compartment models, Meta-analysis, Retinopathy, Glomerular filtration.*

Introduction

The initial reaction of many applied mathematicians to a practical problem has tended to be to model it with the aid of the differential calculus, and so the reflections on this research begin with some such applications. As will be seen in the actual papers the work cannot be neatly pigeon-holed, but it is a convenient way of finding a path through the work. Fig. 1 outlines the path through this expository paper. We also utilize difference equations when appropriate to the experimental data [40], generalized nets [2, 29] and fuzzy logic [cf. 15]. The common theme is the modelling of situations for which the underlying medical theory is not yet fully understood [8].

Erythrocyte sedimentation rates

The rate at which red blood cells (erythrocytes) fall in vitro is used as a common clinical haematological test, called the erythrocyte sedimentation rate (ESR), for a number of pathological conditions. Its clinical effectiveness is hampered by poor understanding of whole-blood sedimentation. The current use of this test is also cast into doubt when one finds flaws in the underlying models and confusion over fundamental issues such as the aggregation of the red blood cells (cf. [74]). It is important in endocrinology because highly specific insulin receptors have been identified on human erythrocytes [24, 52].

Research into this topic was carried out with two research degree students, Dr. Arthur Hung and Dr. Andreas Reuben. We applied certain moving-boundary problems to clarify the mechanisms so that the test can be more usefully interpreted [51]. In particular we applied the theory of Stefan moving-boundary problems. This theory was originally developed to handle heat equation problems in which one of the boundaries changes position with time. This is an illustration of the perspective which the applied mathematician can bring to the total problem in some parts of medicine.

These studies also involved extensive reviews of previous attempts to model the sedimentation of anticoagulated blood when left to stand without being disturbed. The experimental work for these studies was carried out at the Rachel Forster Hospital (Prof. Leopold Dintenfass), St Vincent's Hospital (Prof. Jim Biggs and Dr. Tony Dodds), and the CSIRO (Dr. Tony Collings).

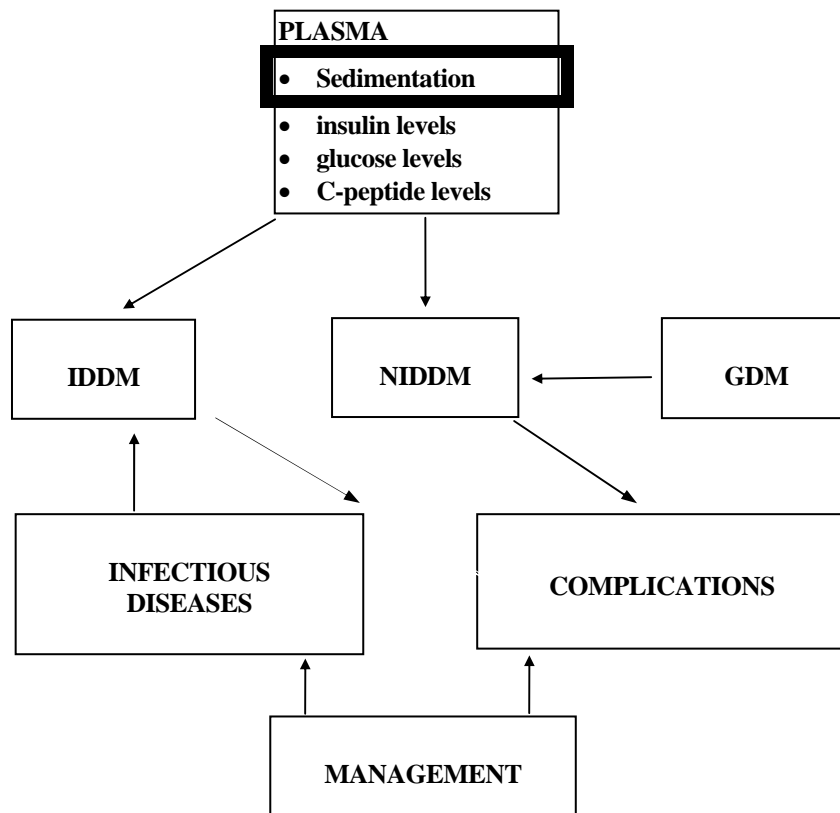


Fig. 1 Plan of the exposition

Legend: IDDM: Insulin Dependent Diabetes Mellitus; NIDDM: Non-Insulin Dependent Diabetes Mellitus; GDM: Gestational Diabetes Mellitus.

Insulin secretion rates

A not dissimilar situation to that of the previous section has existed with some issues in diabetes mellitus where, not only blood flow, but the glucose and insulin concentrations in the blood are critical components of health care. Diabetes mellitus is, in fact, a chronic state of excessive blood glucose levels (hyperglycaemia) [5]. The major regulator of blood glucose concentration is insulin, a hormone synthesised in and secreted by the beta cells of the islets of Langerhans in the pancreas [17].

It has been known that about 50% of the insulin is taken up by the liver on passing through it via the portal vein after secretion from the pancreas. However, the precise value of this fractional uptake is not known, so the prehepatic insulin secretion rates cannot be readily estimated from the plasma insulin concentration levels [75, 76, 78]. The issue is further complicated because high blood sugar levels may be due to a lack of insulin in the case of the person with insulin-dependent diabetes mellitus (IDDM) and/or to an excess of factors that oppose its action and cause insulin resistance in the case of persons with non-insulin dependent diabetes mellitus (NIDDM) [29, 31].

A major difficulty with previous models has been that they require seeding with an initial guess to seed the algorithms. This can lead to ill-conditioning problems. The model mentioned does not need seeding because of the way it can be linearized [59].

By utilizing the experimental facts that insulin and connecting peptide (C-peptide) are secreted in equimolar amounts from the pancreas and that the C-peptide is not stored in the liver, a non-invasive method of estimating the pre-liver insulin secretion rate was developed [49, 53]. The basic assumption was that there is an “instantaneous” surge of insulin in response to a glucose challenge. In a global sense this is reasonable, though a detailed analysis of insulin concentration profiles sometimes shows a bi-modal, and even occasionally a tri-modal, response curve if the time intervals of measurement are close enough. It was a conscious decision to opt for the simplest scenario as the starting point for the development of the differential equation, and in most cases it turned out to be an exceptionally good fit, as measured by the coefficient of determination. The only other assumption was that the rate of clearance of the insulin from the plasma was proportional to the concentration of insulin present in the plasma, a reasonable assumption in the absence of evidence to the contrary and in the light of the results stated later where the insulin kinetics were traced with radioactive markers.

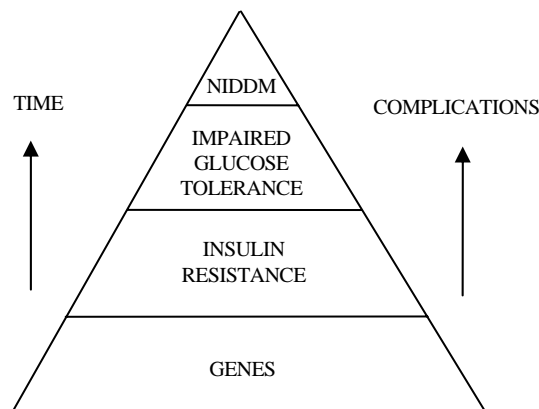


Fig. 2 The progress of type II diabetes

A compartment model was formulated and the resulting differential equation yielded a gamma variate solution which could be readily linearized. The model was tested on groups of subjects classified as normal, mild, moderate and severe diabetic, with excellent concordance between observed and theoretical values of the plasma insulin levels. The experimental work was done at the Prince of Wales Hospital, Randwick (Prof. Steve Colagiuri) and University Hospital Cardiff (Prof. David Owens *CBE* and Dr. Steve Luzio). The consequent rates for insulin secretion were consistent across the groups and were clinically meaningful. The model has even been modified for use in marine biology by Dr. Ewa Kulczykowska’s group at the Polish Academy of Sciences in Gdynia.

This study opens up ideas for further research because it seems to the author that the plasma concentration levels of the peptides following an oral glucose tolerance test (OGTT) or a meal tolerance test (MTT) must contain information about insulin secretion and insulin clearance and therefore insulin resistance.

What makes this so important is that a state of insulin resistance seems to precede impaired glucose tolerance (IGT) which can then be followed by full-blown non-insulin-dependent diabetes mellitus (NIDDM). One way of explaining this is by means of the pyramid in Fig. 2 in

which the base represents those people who have the right ‘cocktail’ of genes to be predisposed to NIDDM (or Type II diabetes). Some of these become insulin resistant, fewer still become IGT, and then a few get NIDDM (Fig. 3).

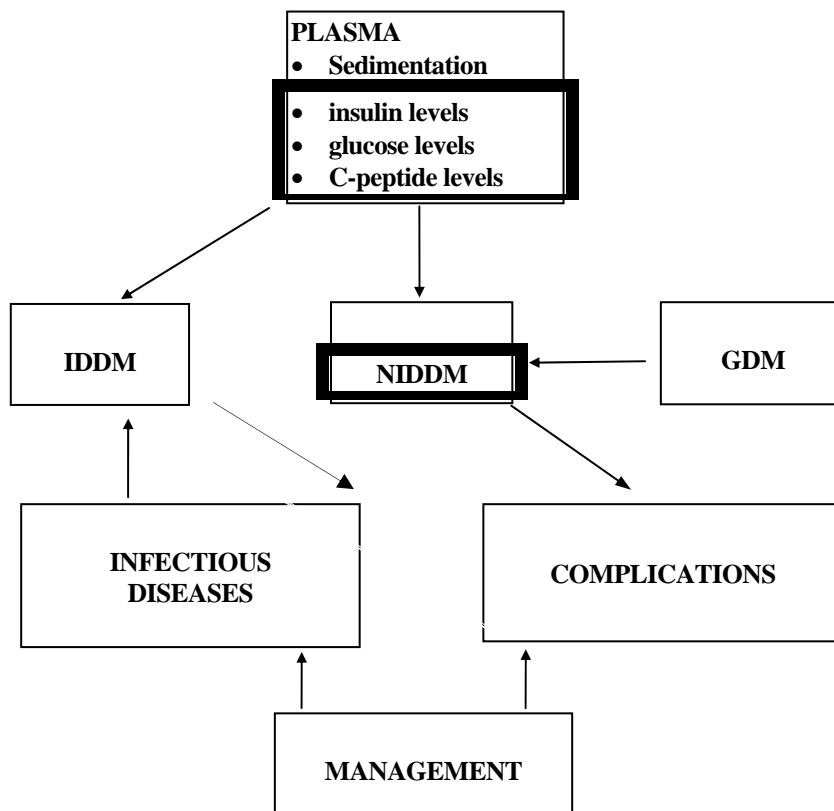


Fig. 3 Aspects of NIDDM

What could be done is to use an oral or meal glucose tolerance test with the above theory of insulin secretion on subjects known to be insulin resistant and a matched (for age and obesity) group of healthy subjects. There is also scope for statistical research into the quality control of the assays and appropriate inferential techniques to be applied to the medical data [14].

Research by the author on gestational diabetes mellitus (GDM) provides evidence, albeit circumstantial at this stage, that the diet of the pregnant mother, particularly during the last six to eight weeks of pregnancy when the adipose and islet cells are formed, can also play a role in the subsequent development of NIDDM in the offspring. This needs to be checked experimentally with diabetic rodents where the confounding elements present in normal human life can be controlled and one can cycle through many generations relatively quickly.

Control theory applied to blood glucose levels

The body is, of course, full of feedback loops, an obvious one occurring in the schematic version of the compartment model for the insulin secretion algorithm [18]. Diabetes is actually a disease in which the finely tuned feedback between the blood glucose levels and the beta-cells is disrupted [73]. The research described in this section (Fig. 4) not only follows on logically from the work of the previous section but also links with the research and development work on instrumentation designed to make the lives of people with diabetes more flexible and easier.

In all of this research attempts were being made to address four major problems associated with closed-loop systems, namely:

- the size and reliability of the glucose sensor,
- the time taken to analyse the plasma insulin and glucose concentrations,
- the sensitivity of the models,
- the mathematical analysis of the control algorithms, and
- the adaptability of the control algorithms.

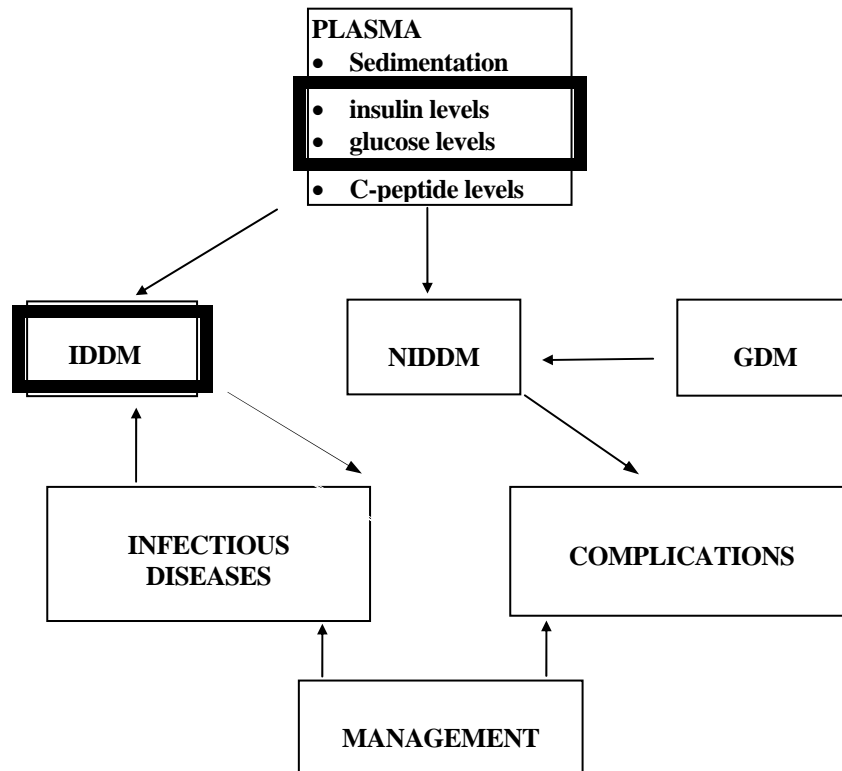


Fig. 4 Aspects of diabetes treated in Section “Control theory applied to blood glucose levels”

In [42] an adaptive control strategy for plasma glucose levels of subjects with IDDM was developed. It was also based on a compartment model specifically designed to adapt to naturally occurring changes in the glucose/insulin system caused by such factors as stress, exercise or infection [cf. 4, 16]. These factors are taken up again in a later section on hardware and software associated with a project called “Diabetes Homescan”.

The research did however develop a new approach to the estimation of the adaptive parameters used in the differential equation models. The broad range of diabetic responses was reduced to a number of representative categories in the doctoral research of Dr. Richard Ollerton under the supervision of the author. The appropriate category for an individual subject can then be continually monitored and knowledge of the response category allows an optimal regimen of insulin to be prescribed.

The resulting control algorithm was applied to some subjects with diabetes at the Prince of Wales Hospital in Randwick with Prof. Stephen Colagiuri and it was found to be effective in maintaining the plasma glucose levels of the subjects within narrow physiological ranges. This work is continuing, but with the use of fuzzy logic and generalized nets [5, 8]. The

representations of these categories make the later use of generalized nets particularly appropriate [1, 65].

It is a relatively straightforward problem then to calculate the amount of insulin infused intravenously to produce the same glucose profile as the given amount of subcutaneously injected insulin. The writer has found results of between 8% and 20% which is much less than the comparable figure of 50% for rats. The results have been consistent with whatever method was used; these methods have included Cholesky decompositions, least squares methods and radioactive tracing [41, 42, 53]. This is on-going research because the results are not what medical scientists expect intuitively but there does not seem to be any counter-example to disprove our work. Another confounding issue is the difficulty of determining general subcutaneous pathways for insulin from the injection sites to the veins in a given individual. The time for activation of the insulin prior to a meal is a crucial element in the management of insulin-dependent or insulin-treated diabetes. An allied issue for further research is the relation of skin thickness and delivery kinetics. Skin thickness is primarily determined by collagen content and is increased in insulin-dependent diabetes. About all that is known is that there is some correlation between skin thickness and glycaemic control [13].

Radioactive tracing of insulin

Knowledge of subcutaneous insulin absorption is affected by many factors: the concentration of the insulin, the half-life of the insulin, the site, the method and the type of injection: needle, pump, jet injector. The rate of absorption is also affected by the rate of clearance of insulin [54]. While the research [60] opens up possibilities for the further study of clearance rates, it was decided to try to determine insulin absorption by labelling the insulin with a radioactive tracer I^{125} [63] which previous studies had shown is not normally degraded at the injection site [50] (Fig. 5).

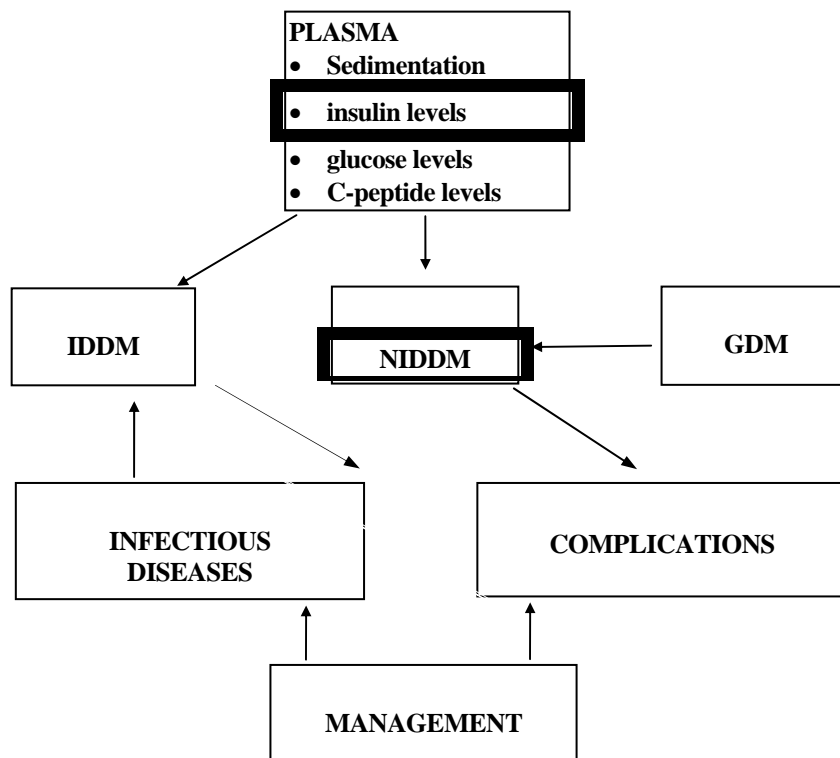


Fig. 5 Aspects of diabetes treated in Section “Radioactive tracing of insulin”

To assess the relationship between insulin absorption and subcutaneous blood flow the latter was measured by the disappearance of 99M technetium [26, 27]. A theoretical compartment model was postulated with a subcutaneous distribution pool and a plasma pool. While this is an oversimplification of the biological process since it assumes that all subcutaneous insulin is immediately available for transcapillary absorption, the agreement between the theoretical predictions of the resulting differential equations and the experimentally measured values gave coefficients of determination in excess of 0.95. The basic assumption were based on some pilot experiments and seemed to justify the use of an essentially exponential model. The resulting graphical curves also conformed to the gamma variate model found in our work on the endogenous secretion of insulin.

This simple study illustrates how biomathematical modelling of whole body systems can be greatly assisted by the increased sophistication in the production of short-lived radionuclides and tracer probe preparation using rapid synthetic chemistry [32].

Curve-fitting of clinical data arrays

In most of the foregoing research there has been a constant interplay between theory and observation on the one hand, and between mathematical and medical sciences on the other. In all of this there is always the danger of trying to fit a good model to poor data or vice versa. In [20] some curve-fitting techniques were applied to some data for measuring insulin sensitivity by two different methods. The curve-fitting approach is seen as a natural complement to the compartment modelling described earlier since it is based on the assumption that a differentiable function can represent the glucose and insulin profiles [42]. It is then feasible to express this function as a Taylor series and to seek the coefficients in the series with a polynomial approximation. The principal advantage of this approach was in analysing the results of those patients who did not fit the insulin secretion algorithm well.

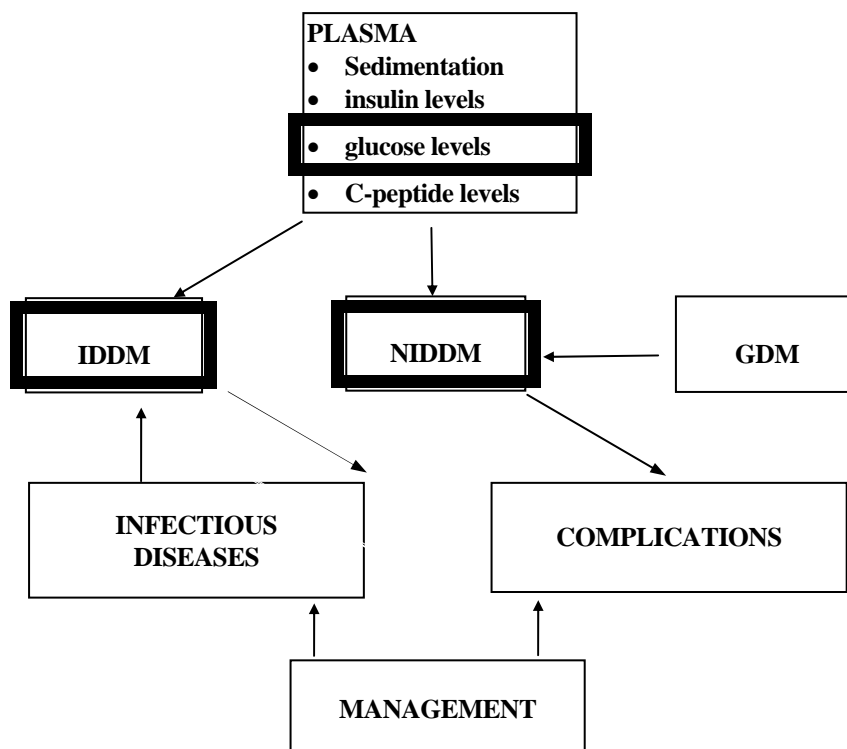


Fig. 6 Aspects of diabetes treated in Section “Curve-fitting of clinical data arrays”

While some of the issues of accuracy and precision are independent of the main thrust of this exposition, they should nevertheless be seen as supplementary to the application of ideas from the mathematical sciences to problems which arise in the diagnosis, analysis and management of diabetes mellitus [58, 61]. [10] discusses the establishment of criteria for validating kinetic models of experimental data.

Insulin sensitivity and insulin resistance are two key indices in the management of each patient's diabetes if the time of injection, the site for the injection, the duration of action, and the amount and type of insulin are to be known reasonably accurately. These factors are particularly important for the person with "brittle" diabetes. The experimental work reported here pointed to variations in these properties in the same individual from day to day and during the course of any one day. These variations point to the advantages of trying to utilize the collective "memory" of the body's cells by means of fuzzy logic and generalized nets [1, 3, 66, 72].

Metabolic problems in newly-diagnosed patients with NIDDM

It is becoming clearer through epidemiological studies that by the time many patients with NIDDM are diagnosed many of the complications of diabetes have already taken hold. This, together with the problems of often having to change life-long habits of diet and exercise, makes the early identification of those likely to acquire NIDDM very important for their care and in the control of healthcare costs. Ideal statistical randomisation is rarely possible in the actual clinical situation where patients are examined and treated on presentation. Thus a major part of data analysis is how to adapt statistical techniques that are robust in some ways, but sensitive in others [37].

In [45], multiple linear regression techniques were applied to the results from more than a hundred newly diagnosed, previously untreated patients with NIDDM. The justification for this was based on the then successful use of the gamma variate function. Much data are routinely collected at initial presentation and the more information which can be justifiably extracted from this wealth of information the more immediate help can be given to the patients with a probable reduction in later pathology. Among the major conclusions from this study was that increasing fasting plasma glucose levels were related to a deteriorating beta cell response in the glucose tolerance tests. There was also an independent association between retinopathy and glycaemic response, body mass index and renal function, all of which are facets of diabetic complications to which references are made in other studies in this submission. There was a curious difference between men and women in terms of correlation between body mass index and age. For men these were positively and negatively correlated respectively with gender, while the reverse was found for women. The overall results tend to suggest that atherosclerotic risk factors are more important in men with NIDDM, with weight control an essential feature of their management.

Glomerular filtration rates

Authors in [39] continued the discussed above approach with multiple linear regression and the established Cockcroft-Gault Formula to develop an estimation of glomerular filtration rates (GFR) from a combination of simple parameters in a large group of patients with NIDDM. GFR is largely driven by increases in plasma flow and capillary pressure and increases in GFR indicate alterations in renal circulation. These changes appear early in diabetes and many years before the onset of diabetic nephropathy [37]. Most patients with diabetes show a progressive decline in GFR with the duration of diabetes.

According to the hemodynamic hypothesis to account for this, damage to some glomeruli causes changes in the microcirculation that result in hyperfiltration occurring in the remaining glomeruli. In turn this single-nephron hyperfiltration with intraglomerular filtration is itself damaging. In our study 122 newly presenting, previously untreated patients with NIDDM had their GFR determined from the plasma clearance of ⁵¹Cr-EDTA and simultaneous measurements of demographic variables including fasting plasma glucose, HbA1c, blood pressure, lipids, age, weight, body mass index, body surface area, urea and plasma creatinine. We were able to come up with a simple equation for GFR using age and plasma creatinine which is quicker and less expensive than standard methods against which it was validated. Furthermore, we were able to classify GFR values into three ranges which reveal the nonlinear characteristics of GFR in relation to other demographic variables since there has been some confusion about this in the literature. This classification was analogous to the ESR categories found in Section “Erythrocyte sedimentation rates”. Further studies have confirmed that microalbuminuria is a strong predictor of overt diabetic nephropathy which results in end-stage renal disease. Treatment of this with transplantation or dialysis is very expensive and deleterious to the patient's quality of life, including earning ability. Angiotensin converting enzyme (ACE) inhibitors, good glycaemic control and dietary protein restriction are effective in reducing the albumin excretion rate (AER) [64, 69].

Retinopathy in newly-presenting NIDDM patients

Diabetic nephropathy seems to precede diabetic retinopathy which is the major cause of blindness in Australian adults under the age of 60. Whereas the prevalence of diabetic retinopathy is much greater in patients with IDDM, the largest population of retinopaths is found among patients with NIDDM [38]. The contribution of the writer as a statistician was to postulate various factors as contributors to the aetiology and pathology of retinopathy [45, 46]. 129 previously untreated patients with NIDDM were given meal tolerance tests (MTT) and oral glucose tolerance tests (OGTT) on successive days (cf. [44]).

As well as Student's unpaired t-tests and analyses of variance, the variety of categories made it appropriate to employ a multivariate logistic regression analysis in order to explore whether the prevalence of retinopathy is associated with certain qualitative as well as quantitative risk factors. A stepwise progression made it possible to determine the smallest subset of the risk factors which are all significantly correlated to the presence of retinopathy. Both forward selection and backward elimination were used in an APL program written by the author and Dr. Aage Vølund of Novo Nordisk A/S in Copenhagen, Denmark. This utilized both iterative maximum likelihood estimation and asymptotic likelihood ratio tests for the analysis. The various retinopathy probabilities were related in the best fitting logistic model to the mean insulin response during the MTT and the systolic blood pressure. These results were further confirmation of our belief that beta-cell function is central to the vascular complications in patients with NIDDM.

Research in progress is also looking at the relationship between retinopathy and the results of home blood glucose monitoring over a number of years. Patients and their physicians can accumulate a wealth of data relevant to that patient but which is rarely used other than for adjusting base doses of insulin. One of the writer's first forays into diabetes research was to show how time series analysis could be used to discern patterns not otherwise obvious in such data; currently this is being extended with the use of neural networks which are ideal for “learning” about an individual patient.

Mass screening for diabetes

The usefulness of mass screening for many diseases has come under increasing scrutiny in recent years [57]. For example, there are many questions now surrounding the effectiveness of screening for prostate cancer in men and for breast cancer for women (cf. [30]).

The basis of screening is either to review all those with relevant risk factors or to seek volunteers for mass screening, for instance in shopping malls. Later those who show up as positive on the initial screening test are invited to undergo a definitive diagnostic test. If the risk factors are not sufficiently specific for the disease in question, or if the mass screening selection is too biased, then the screening has inherent problems. These are often compounded by a poor response to the invitation to attend the follow-up diagnostic test, either through apathy or ignorance or fear (“the worried well”).

In [35], the results of 23 228 capillary blood glucose (CBG) tests were reviewed. These results came from community screening tests coordinated by the then Diabetic Association of New South Wales (now Diabetes Australia – NSW Branch), although the Association had no control over who conducted the tests or their training or level of expertise. The correlation coefficients linking the main variables and the t-tests used the pooled standard deviations were calculated with SPSS on a Honeywell Level 66 computer. 3.7% of the subjects who were screened (and who were not previously known to have diabetes) had an abnormal result (CBG > 8.0 mmol/l). They were advised to take the result to their doctor for further assessment. Of these only 53.4% subsequently responded to our questionnaire and, despite statistical correlations between the various sub-groups, the suspicion remained that the responders were biased towards the diagnosis of diabetes because of symptoms, family history or curiosity.

The question of follow-up to a screening process is problematic for most diseases, and is complicated in the case of diabetes by lack of consensus about the effectiveness of treating the pre-symptomatic stage of diabetes in a non-pregnant adult. However, the study prepared us for a study of the effectiveness of screening for diabetes during pregnancy, a meta-analysis of which is described later.

Meta-analysis and multiple injections of insulin

The report [55] on diabetic microangiopathy was one of the earliest studies in which meta-analysis was applied to clinical medical literature. The originality of this work, which was done with a grant from the Kellion Foundation, was in the application and extension of a novel statistical technique in a new field. In this technical note the results from two major studies were converted to standardized mean differences in order to emphasize the otherwise not-obvious consistency of their results that two injections of insulin per day were more effective than one in reducing glycosylated haemoglobin in patients with diabetes [23]. (Glycosylated haemoglobin is often used as a marker, or even a gold standard, for indicating glycaemic control.)

The major points about meta-analysis are that it provides a qualitative approach to, as well as a quantitative means of, comparing and combining the results from many studies of the same phenomena [67]. There is firstly a systematic coding of the major variables, and then, if it is justified, a numerical comparison of the data by reducing them to the same metric. This is usually an odds ratio, or in the case of the studies referred to above, the standard deviation units of the control population. More sophisticated approaches use conventional multilevel modelling and hierarchical Bayesian models to address the combination of evidence from disparate types of study [48].

The objectives of meta-analysis in medicine are:

- to demonstrate an effect in a direction of interest by overcoming the obscuring effect of sampling variations in a large number of small studies;
- to add quantitative effect sizes (and their uncertainty) to the qualitative results of traditional narrative literature reviews;
- to encourage systematic collation and review of individual studies and explicit reporting of the criteria used to give an overall summary of diagnostic accuracy;
- to determine if diagnostic accuracy estimates depend on the study validity of the primary studies;
- to identify areas for further research.

One of the first promoters and developers of meta-analysis was Gene V Glass. He and his colleagues [22] argue, and illustrate their arguments, that meta-analyses should include poorly-controlled studies as well as well-controlled ones because their general trends are usually in the same direction as the results of the better experiments. The effect sizes may be smaller with the poorer studies, but that does not invalidate them: it may simply make them less useful. Nevertheless, it is becoming customary in medical meta-analyses to qualify trends with the quality of evidence ratings [33, 34] (Table 1).

This four point scale has been recommended by the National Health and Medical Research Council of Australia after adaptation from the United States Preventative Services Taskforce. It in turn needs to be qualified by the level of explicitness which is quite a separate issue.

Table 1. Quality of evidence for meta-analysis

| Levels | Controlled Trials | Epidemiological Evidence |
|--------|---|--|
| I | Systematic review of all relevant randomized controlled trials | Systematic review of all relevant population-based studies |
| II | At least one properly-deigned randomized controlled trial | A well-designed population based study or representative cohort study |
| IIIA | Well-designed, but not randomized, controlled trials | Well-designed case-control study, cohort study, or less well-designed population based study |
| IIIB | Well-designed cohort or case-control analytic studies, preferably from more than one centre | |
| IIIC | Multiples time-series with or without intervention | |
| IV | Opinions of experts based on clinical experience or descriptive studies | Descriptive case studies, clinical experiences, respected authorities |

The deletion of porcine insulin from the Australian Commonwealth Schedule of Pharmaceutical Benefits on 1 December 1989 and the subsequent transfer of more than 40 000 patients to human (semi-synthetic) insulin provoked much controversy in the Australian media. Many patients, for instance, claimed that they were getting asymptomatic hypoglycaemic reactions and comas because of the new insulins [44]. Some physicians and general practitioners echoed these claims. In some cases there may well have been some causal link, though part of the explanation could also have been that asymptomatic hypoglycaemic reactions are associated with the length of time patients have had diabetes. This hypothesis is supported by the evidence of Hepburn *et al.* [29] who retrospectively surveyed symptomatic awareness of hypoglycaemia in 189 patients with type 1 diabetes (IDDM) who had been transferred from highly purified animal insulin to human

insulin in the preceding 24 months. 23% complained of chronic hypoglycaemic unawareness before their change of insulin species. 6% complained of a reduction in hypoglycaemic awareness following transfer to human insulin and 3% reported heightened awareness. The mean durations of diabetes of these latter two groups were 24 ± 10 years and 15 ± 10 years, respectively [60].

Some research also seemed to support the view that higher fasting blood glucose levels and glycosylated haemoglobin levels are associated with human insulin compared with porcine insulin. Other studies suggested the reverse, and still others found no difference. This is a situation where meta-analysis can be a most appropriate tool for sifting through the evidence. Twenty studies were found in the literature of I, II, or IIIA quality level [28]. The results of this meta-analysis are summarized in Table 2.

Table 2. Comparison of insulins

| Study type | HbA1c | Significance |
|------------------------|-------|--------------|
| Double-blind crossover | H > P | n.s. |
| Double-blind parallel | H < P | n.s. |
| All studies | H < P | n.s. |

H: levels associated with human insulin-treated;
P: levels associated with porcine insulin-treated.

For instance, with all studies it was found that the standardized mean difference was 0.10 standard deviation units lower with human insulin than with porcine insulin. This difference was less than the 0.2 standard deviation units required for significance at the 5% level with a power of 90% and the (combined) sample size of 521. Thus it was concluded that human and porcine insulins are therapeutically equivalent on the basis of glycaemic control.

In follow-up research on this issue, Colagiuri, Miller and Petocz [12] carried out a double-blind crossover study to see if there were differences between human and porcine insulin in the frequency and characteristics of hypoglycaemic episodes among patients who reported a reduction of awareness of hypoglycaemia after changing treatment. Each patient was on human and porcine insulin for two months each over a four month period. There were thus six different permutations. Among the results was the fact that only 2 of the 50 patients who completed the trial correctly identified the species of insulin used during the study. By chance alone, 8 or 9 patients should have correctly identified the insulin. This provided further evidence in support of our previous research.

A meta-analysis of gestational diabetes mellitus

Shannon *et al.* [57, 68, 70] carried out a major meta-analysis of gestational diabetes mellitus (GDM) commissioned by the New South Wales Health Department. GDM is carbohydrate intolerance of variable severity first diagnosed during pregnancy. The appropriateness of the meta-analytic technique in this context is evidenced by its growing popularity in obstetrics and gynaecology [46]. The research set out to answer three questions:

- Is GDM significantly related to maternal and perinatal morbidity and mortality?
- How can GDM be effectively diagnosed?
- What are the effective treatments for reducing these complications?

There has been debate among epidemiologists about whether GDM is a disease or merely a risk factor for various complications associated with pregnancy. Nevertheless, there is general agreement that this pregnancy condition can be linked to adverse pregnancy outcomes and may be associated with subsequent diabetes in the non-pregnant state.

A 10 step procedure was developed for conducting this meta-analysis [68]. Medline was used to identify as many suitable studies as possible.

Usually in looking for those most likely to acquire a disease one tries to isolate risk factors. Risk factors in isolation are problematic though. Obesity, for example, is neither a necessary nor a sufficient condition for NIDDM, since although the vast majority of NIDDM patients are obese, most obese people do not develop NIDDM. However, there is a close relationship between obesity and other risk factors for NIDDM. Furthermore, historical and clinical risk factors have a low specificity for GDM because they are so highly prevalent among healthy subjects. Thus risk factors are not sufficiently predictive to use as the basis for testing.

In considering then the relative merits of screening for GDM with a glucose challenge test (GCT) and diagnosing GDM with an oral glucose challenge test (OGTT) the results from 13 studies were combined to produce a population with a total size of 20 000 subjects. A sensitivity of 0.95, a specificity of 0.78, but a positive predictability of only 0.14, was found. That is, the GCT is highly specific in that it does not miss many women who have GDM, but any degree of under-diagnosis is problematic with GDM given the relatively short period of time in which effective management of the condition can be carried out. If the prevalence of GDM in this population was 4% then the test would only have missed 3 false negatives in a sample of 1000 patients. However, if the prevalence were 6% then the test could miss about 25 out of 1000. The problem is that the prevalence in each sub-population is also usually one of the unknowns.

That is, although specificity and sensitivity are characteristics of the screening test, their real values in practice are not independent of the prevalence of the condition. A recommendation from this research was that universal diagnostic (OGTT) testing of all pregnant women be introduced if they had no prior history of diabetes. In New South Wales this would cost less than Aus\$2million annually. At a Workshop on GDM for General Practitioners which was addressed by the writer there was surprisingly less objection to this recommendation (except from a couple of hospitals on the grounds of convenience), than there was to recommending that GDM be defined as fasting plasma glucose level > 5.5 mmol/l and/or plasma glucose level 2 hours after administration > 7.8 mmol/l following a 75 g OGTT.

It was also found that GDM is predictive of subsequent NIDDM. By using resistant lines we calculated that about 50% of GDM mothers would have NIDDM within about 10 years of the index pregnancy. While the evidence for the development of NIDDM in the offspring is less conclusive, there is compelling circumstantial evidence of a high risk of obesity and later NIDDM in the offspring of mothers with poorly managed GDM.

The originality in this study was in the use of a wide range of appropriate techniques, particularly from exploratory data analysis, to synthesize the results of the various studies of different aspects of GDM. This also enabled us to identify a number of areas for further research [54]. One of these is a randomized controlled trial which has two problems. One is ethical in that there is a problem of assigning some women with GDM to a no treatment protocol. The second problem is statistical in finding enough subjects for a design with appropriate power.

Concluding comments

An underlying theme which pervades the research outlined here is “how do you persuade yourself that a statement is true or an answer is correct? How do you persuade someone else?” [25]. When does qualitative common sense take over from quantitative analysis? Fisher was troubled by Mendel’s experimental data because they fitted the theory too well! [19]. Compare Newman’s argument that we tend to be less convinced by pure logic than by a convergence of probabilities [36], or do we need Level I evidence to know that jumping out of an aeroplane without a parachute is hazardous? [71]! Considerations about the appropriate use of parametric tests or distribution-free assumptions cannot be ignored, though the cumulative effect of combining studies, even those which are poorly designed, can reveal a trend which individual studies might obscure or even contradict [7, 11]. Meta-analysis, in particular, goes beyond primary and secondary analysis in order to compare studies as statistical units themselves and to combine studies when justified [21]. In the last analysis, the presentation of facts to the human mind calls for persuasion: “and if you would persuade, you must have some idea of how people’s minds work, of the ideals which move them and the prejudices which contain them”! [77].

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