For debate

Could the aetiology of IDDM be multifactorial?

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Epidemiologic data suggest that an infectious agent and/or nutritional factor play a role in the aetiology of insulin-dependent diabetes mellitus (IDDM). Either factor could be a confounding variable for the other or for another yet-to-be identified causative agent. Alternatively, the metabolism of a nutritional factor could be altered during an infectious illness to induce a metabolite toxic to the pancreas and/or a product that initiates an immunologic reaction against the pancreas. Others have suggested that the cause of IDDM is multifactorial [1–3].

The triggers for IDDM in most cases may be a yet-to-be-identified interaction between an enterovirus and a nutritional factor. If such environmental factors interact directly, the logical anatomical site for such interaction would be the gut. Enteroviruses generally persist in the gut for several weeks following infection. Nutrition, particularly animal protein and/or nitrosamine/nitrosamide content in the diet, during that time period may be important. Destruction of the islet cells could result from such an interaction. Subsequent enteroviral-nutritional interactions could lead to further destruction of the pancreas until there is not enough insulin producing capability to respond to a stress. During a stressful life event, e.g. trauma, other infection, pubescent growth spurt, pregnancy, the insulin requirement exceeds the capability of the pancreas leading to clinical diabetes (Fig. 1).

Early exposure to foreign protein/nitrosamine during infancy might 'prime' the small intestine for subsequent viral-dietary interactions. Vitamins, such as nicotinamide and vitamin C, might interfere with the production of a diabetogenic toxin in the gut.

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Abbreviations: IDDM, Insulin-dependent diabetes mellitus; EMCV, encephalomyocarditis virus.

Infectious factors

Several findings suggest a link between enteroviruses and IDDM. (a) In 1968 Craighead and McLane [4] reported the induction of hyperglycaemia and lesions of the pancreatic islets of Langerhans in mice infected with encephalomyocarditis virus (EMCV), a Picornavirus belonging to the cardiovirus group. (b) Gamble et al. [5] reported higher titres of antibodies to coxsackie B4 virus infection, a Picornavirus belonging to the enterovirus group, within 3 months of onset of IDDM when compared to patients with diabetes of longer duration. This led to a case-control study of neutralizing antibodies to coxsackie B viruses (serotypes B1–B5) of 162 diabetic patients compared with 319 non-diabetic hospitalized patients matched for age and time of year. They found 70% of diabetic patients with coxsackie B4 antibodies compared to 58% in the control group ($p < 0.01$). They found no differences for other infectious agents, including influenza, measles, mumps, and *Mycoplasma pneumoniae* [6]. (c) Yoon et al. [7] reported a 10-year-old previously healthy boy who presented in diabetic ketoacidosis within 3 days of onset of flu-like symptoms. He died seven days later. Coxsackie B4 virus was isolated from the pancreas at post mortem examination. Inoculation of the virus into mice produced hyperglycaemia, inflammatory cells in the islets of Langerhans and beta-cell necrosis [7]. (d) A seasonal variation of diabetes has been noted for several decades with peak incidence of IDDM in autumn and early winter [8]. The peak incidence of enteroviral infections occurs in late summer and early fall.

Table 1 shows the study sites, sample sizes, basic study design (control selection), enteroviral serotypes studied and general results of 18 seroepidemiologic studies identified by literature review. Eleven of the studies found a positive association with specific

Fig 1. Aetiology of IDDM: a multifactorial hypothesis

1–9 years of age were more likely than control subjects to have antibodies to enterovirus 71 ($p = 0.02$) [24].

coxsackie viruses and/or a greater frequency of positive serotests for several enteroviruses when comparing cases and control subjects [5, 6, 9–24]. Several of the ‘negative’ studies deserve comment. The Irish study [9] included non-insulin-dependent diabetic patients among its ‘cases’. Two German studies [12, 17] had no control subjects and concluded that coxsackie viruses could not be the aetiological agent because they could not find evidence of infection in 100 % of cases. Another study tested for antibodies to only three coxsackie serotypes out of 67 known distinct serotypes of enteroviruses [13].

In the largest and most recent case-control study evaluating the associations of enteroviruses and IDDM, investigators collected sera from 128 newly diagnosed IDDM patients and 120 hospitalized endocrinology patient-control subjects matched for age, sex, and date of blood sampling [24]. Sera were tested for IgM monoclonal antibody-based capture enzyme immunoassays for 14 enteroviral serotypes. Overall, 89 % (114/128) of diabetic patients and a similar 87 % (104/120) of control subjects tested positive to one or more viral serotypes. However, diabetic patients had higher rates for each of the 14 serotypes ($p < 0.05$ for 8/14 serotypes). The 144 diabetic patients tested positive to a median of 4 serotypes (range 1–14) whereas the 104 control subjects tested positive for a median of 3 serotypes ($p = 0.03$). Diabetic children 13–18 years of age were more likely than control subjects to be positive for 9 of 14 serotypes ($p < 0.05$). Diabetic children 10–12 years old were more likely than control subjects to be positive for echovirus 34 ($p = 0.02$), and diabetic children

Nutritional factors

Breast-feeding. In 1984, Scandinavian researchers suggested that there was an inverse relationship between duration of breast-feeding and IDDM. They proposed that breast-feeding provides maternal antibodies to prevent diabetogenic infections [25]. Three studies from Italy, New York, and the United Kingdom failed to support the hypothesis [26–28].

Twelve case-control studies of breast-feeding and/or early infant diets and IDDM were identified and reviewed; seven reported an association between breast-feeding duration and/or ‘early’ exposure to animal protein and subsequent development of IDDM (Table 2). The associations found in those studies suggesting a link to duration of breast-feeding are marginal with odds ratios in the 1.4 to 1.8 range [25–35].

There are numerous limitations in interpreting those data. It is difficult to reconstruct breast-feeding practices of mothers several years prior to interview because of recall bias. The studies vary in sample sizes, breast-feeding and nutritional history questionnaires, and in control selection. However, it is intriguing that most studies suggest some association between early feeding habits of infants and subsequent development of IDDM.

Childhood nutrition. Several epidemiologic observations suggest that ‘enhanced’ nutrition during childhood and adolescence predisposes one to IDDM. (a) A reduced incidence of diabetes was observed in Germany and Sweden during World War II [36]. (b) Studies in Finland and Estonia show large differences in

Table 1. Studies of IDDM and enteroviral infection

Study site	No. cases	No. controls	Description of control subjects	Enteroviral serotypes tested	Reference (Year)
<i>Positive association found between enteroviral infection(s) and IDDM on seroepidemiologic studies</i>					
UK	123	155	Diabetic patients > 2 years' duration	Coxsackie A 2, A 5, A 10, A 16, B 3–B 5.	5 (1969)
UK	162	319	Age- and time-matched HPs	Coxsackie B 1–B 5	6 (1973)
USA	9	36	Multiple matched control subjects	Coxsackie B 1–B 6	10 (1974)
Japan	103	101	Age- and sex-matched out-patients	Coxsackie B 1–B 5	14 (1982)
UK	28	290	Elective surgery patients	Coxsackie B 1–B 6	15 (1983)
Sweden	24	24	Multiple matched surgical patients	Coxsackie B 1–B 5	18 (1985)
UK, Austria and Australia	122	204	Various groups of HPs	Coxsackie B 1–B 5	19 (1985)
Sweden	108	46	Surgical or other patients with viral infections	Coxsackie B 1–B 5	21 (1992)
USA	84	71	Age- and sex-matched children of case-parent's friends	Coxsackie B 1–B 5	22 (1992)
Finland	96	96	Pregnant mothers of non-diabetic subjects	Coxsackie B 3–B 5, Coxsackie A 9, and Echovirus 1	23 (1995)
	22	110	Siblings		
	90	90	Age, sex-matched unrelated children		
USA	128	120	Multiple matched HPs on endocrine service	[Coxsackie B 1–B 6, A 9, Echovirus 4, 6, 9, 11, 30, 34, and Enterovirus 71]	24 (1995)
<i>No association found between enteroviral infection and IDDM on serology</i>					
Ireland	58 ^a	121	Age-matched HPs	Coxsackie B 1–B 6	9 (1972)
UK	27	27	Non-diabetic identical twin	Coxsackie B 1–B 5	11 (1975)
Germany	83	0	None	Coxsackie B 1–B 5	12 (1978)
USA	33	33	Multiply matched selected from viral surveillance programme	Coxsackie B 3–B 5	13 (1982)
USA	> 100	57	Siblings	Coxsackie B 1–B 6	16 (1983)
Germany	166	0	None	Coxsackie B 1–B 6	17 (1983)
Sweden	98	94	Multiply matched children chosen from population register	Coxsackie B 1–B 6	20 (1989)

^a Cases include a mix of IDDM and NIDDM; HP, Hospitalized patients (non-diabetic) as control group

incidence rates between two genetically similar populations and suggest a relationship between higher socioeconomic status in Finland and IDDM [37]. Children in the highest socioeconomic echelon are at least equally represented among diabetic patients in the United Kingdom [38]; and whites had higher rates of IDDM than African-Americans in Allegheny County, Pennsylvania [39]. (c) The increase in IDDM among migrant populations in Polynesia and Micronesia suggest a relationship to nutritional status [40]. (d) Swedish paediatricians reported an association between high linear growth rates among children and an increased risk of IDDM [41]. (e) A case-control study among Swedish children found an association between high protein content and high nitrosamine content in the diet and increased risk of IDDM [3, 42].

The Swedish Childhood Diabetes Study was established to evaluate risk factors for IDDM and included a study of different nutrients and food additives. An official Swedish population register traced 339

children aged 0–14 years who had recently developed IDDM and 528 control children matched for age, sex, and county of residence. Their parents filled out questionnaires regarding their children's frequency of consumption of various foods. Foods were classified according to their content of protein, fat, carbohydrates, sugars, nitrosamines, nitrates and nitrites, vitamin C, and fibre. The frequency of intake was categorized as high, medium, and low. Perinatal events, breast-feeding history, and aspects of social environments were also evaluated [3].

The Swedish investigators found a dose-response relationship between the frequency of intake of foods rich in meat protein, complex carbohydrates, nitrosamines and nitrates/nitrites and IDDM. Increased milk consumption was not associated with IDDM [1, 42]. Further analysis of the Swedish data led to exploration of possible determinants of IDDM assuming a multifactorial model. A ten-fold increase in risk was observed when a variable measuring infectious disease in the last year was combined with a measure of

Table 2. Studies of breast-feeding (BF), infant feedings and IDDM

Study site	No. cases	No. controls	Description of control subjects	Characteristic tested	Reference (Year)
<i>Positive association found</i>					
Norway/Sweden	266	230	Healthy siblings	Duration BF	25 (1984)
Australia	194	753	School classmates	Duration BF	29 (1988)
USA	268	291	Physician-based patients	Ever breast fed	30 (1988)
	268	188	Childhood cancer patients	Ever breast fed	30 (1988)
Sweden	339	528	Age, sex, county-matched children	Duration BF	31 (1989)
Finland	103	103	Birth-date, sex-matched country-wide	Duration BF	33 (1991)
USA	205	205	Healthy siblings	Ever breast fed and milk substitutes	34 (1992)
USA	164	145	Age, sex, ethnicity-matched children	Early exposure to cow's milk	35 (1993)
<i>No association found</i>					
Italy	396	6702	Background population	Duration BF	26 (1985)
USA	95	289	Siblings/matched peers	Duration BF and onset of solids	27 (1986)
UK	34	27,446	Age-matched cohorts	Duration BF	28 (1987)
Canada	161	321	Neighbourhood friends/emergency-room patients	Ever breast fed	32 (1989)
Sweden	339	528	Age, sex, residence-matched children	Duration BF	3 (1991)

frequency of consumption of foods containing nitrosamines [3]. This report is the first suggesting a viral-nutritional interaction as the aetiology of IDDM.

Animal study. An epidemic of IDDM in an area of Iceland known for its traditional feasts of nitrosamine-containing foods, particularly smoked mutton, led to animal challenge studies with those foods. Helgason et al. [43] supplemented the diet of parent CD1 mice with Icelandic mutton cured with nitrate and nitrite before mating and during pregnancy, and the diet of offspring from day 19 until killing 1–5 weeks later. Thirty-five of 302 (12%) progeny in the experimental group developed glucose intolerance and insulinopenia compared with none of 106 progeny of mice fed standard Oxoid RM1 pellets. Histologic changes in pancreatic beta cells were noted in the diabetic progeny mice.

Toxic factors

Chemical toxins can produce IDDM in humans. Some poison pancreatic beta cells directly; others trigger an autoimmune process [1, 44]. There have been over 300 case reports of IDDM, over 250 in Korea, following accidental and/or intentional ingestion of Vacor, a rat poison containing the active ingredient, N-3-pyridylmethyl- N'-p-nitrophenyl urea. Survivors show sustained IDDM [1, 45]. Several other chemicals can sporadically cause mild hyperglycaemia and glucose intolerance, including calcium

channel blockers, cimetidine, corticosteroids, indomethacin, pentamidine, and vincristine [1, 44].

Two animal models of toxin-induced IDDM exist. In 1943, alloxan was the first diabetogenic toxin discovered. Alloxan toxicity specific to the pancreatic beta cell is almost universal among vertebrates [1, 46]. Streptozotocin is a wide-spectrum antibiotic and a nitrosamide. Streptozotocin selectively destroys the pancreatic beta cells in several mammals. The toxicity is dose-dependent. With chronic exposure to lower doses of streptozotocin, an autoimmune phenomenon develops leading to beta-cell destruction and gradual onset of diabetes. With single high doses of streptozotocin in rats, the beta cells of the pancreas are selectively degranulated after a few hours, then necrosed. An initial transient hypoglycemia is followed by rebound hyperglycaemia, and eventually insulinopenia and ketosis [1, 47].

Discussion

I postulate that the cause or triggering exposures for the cascade of immunologic events leading to IDDM is a complex, yet-to-be-identified interaction between enteroviral infection and nutritional factors in susceptible hosts. The concept of interactions of viruses and chemicals leading to specific diseases is not new. In 1938, Rous and Kidd [48] showed that rabbits developed a greater number and a different appearance of tumours following exposure to tar and papillomavirus than when they were exposed to either agent alone. In 1984 Micha Levy [49] proposed that

underlying viral diseases may increase patients' susceptibility to adverse drug reactions by altering the metabolism of drugs.

The best known example of a modification of drug effects occurring in virus-infected individuals leading to disease is probably Reye's syndrome. Initially investigators speculated that Reye's syndrome represented either a new viral disease or an adverse reaction to salicylates. Although the mechanisms by which salicylates and varicella-zoster and influenza B viruses interact to produce Reye's syndrome are still not clear, publicizing the epidemiologic association of aspirin with this syndrome led to a marked decrease in salicylate use for febrile children and a concomitant decrease in the incidence of the disease [50].

If IDDM is triggered by an enteroviral-protein/nitrosamine interaction in the gut, several prevention strategies could prove useful. (a) Enteroviral vaccines could be developed for many serotypes and tested in high-risk populations. Increasing handwashing by food handlers and diners, especially toddlers and children, should reduce enteroviral infections. (b) Heavy protein/nitrosamine dietary intake should be discouraged, especially during and for several weeks after any febrile illness. There may be ways to prepare foods to decrease their content of the yet-to-be-discovered offending dietary factor. (c) Breast-feeding should be encouraged. Delayed introduction of animal protein in the diet of infants may prove beneficial. (d) Daily vitamin supplements may be protective, especially during acute febrile illness.

More research on the aetiology of IDDM is warranted. This hypothesis is only one of several possible combinations of environmental factors associated with IDDM. One way to support a role for an individual factor in causation would be to develop and test an intervention strategy. Animal models challenged with various combinations of factors may provide useful information. Surveillance for enteroviral infections and incidence of IDDM should be monitored in several developed and developing countries. Advancements in measures for enteroviral infections should be incorporated into study designs [51]. Anthropologic studies of the cultural differences in diet, eating habits, and handwashing practices before eating may yield information germane to explaining the different rates of IDDM across countries. More studies of dietary intake of diabetic patients before diagnosis is warranted. Concentrated studies in Iceland and other areas where the incidence of IDDM is high should be pursued.

Identifying the aetiology of a multifactorial disease requires co-operation and communication across several scientific disciplines. However, if the pathways can be elicited, it may lead to ways to prevent and treat a disease which results in significant morbidity and mortality worldwide.

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References

1. Leslie RDG (1993) Causes of diabetes: genetic and environmental factors. Wiley, Chichester New York Brisbane Toronto Singapore
2. Palmer JP (1996) Prediction, prevention and genetic counseling in IDDM. Wiley, Chichester New York Brisbane Toronto Singapore
3. Dahlquist G, Blom L, Lonnberg G (1991) The Swedish Childhood Diabetes Study – a multivariate analysis of risk determinants for diabetes in different age groups. *Diabetologia* 34: 757–762
4. Craighead JE, McLane MF (1968) Diabetes mellitus: induction in mice by encephalomyocarditis virus. *Science* 162: 913–914
5. Gamble DR, Kinsley MJ, Fitzgerald MG, Bolton R, Taylor KW (1969) Viral antibodies in diabetes mellitus. *BMJ* 3: 627–630
6. Gamble DR, Taylor KW, Cumming H (1973) Cocksackie viruses and diabetes mellitus. *BMJ* 4: 260–262
7. Yoon JW, Austin M, Onodera T, Notkins AL (1979) Isolation of a virus from the pancreas of a child with diabetic ketoacidosis. (Virus-induced diabetes mellitus). *N Engl J Med* 300: 1173–1179
8. Gamble DR, Talyor KW (1969) Seasonal incidence of diabetes mellitus. *BMJ* 3: 631–633
9. Hadden DR, Connolly JH, Montgomery DAD, Weaver JA (1972) Cocksackie B virus and diabetes. *BMJ* 4: 729 (Letter)
10. Huff JC, Hierholzer JC, Farris WA (1974) An "outbreak" of juvenile diabetes mellitus: consideration of a viral etiology. *Am J Epidemiol* 100: 277–287
11. Nelson PG, Pyke DA, Gamble DR (1975) Viruses and the aetiology of diabetes: a study in identical twins. *BMJ* 4: 249–251
12. Schmidt WAK, Brade L, Munterfering H, Klein M (1978) Course of coxsackie B antibodies during juvenile onset diabetes. *Med Microbiol Immunol* 164: 291–298
13. Palmer JP, Cooney MK, Ward RH, et al. (1982) Reduced coxsackie antibody titre in type 1 (insulin-dependent) diabetic patients presenting during an outbreak of coxsackie B3 and B4 infection. *Diabetologia* 22: 426–429
14. Sakurami T, Nabeya N, Nagaoka K, Matsumori A, Kuno S, Honda A (1982) Antibodies to coxsackie B viruses and HLA in Japanese with juvenile-onset type 1 (insulin-dependent) diabetes mellitus. *Diabetologia* 22: 375–377
15. King ML, Shaikh A, Bidwell D, Voller A, Banatvala JE (1983) Cocksackie B virus-specific IgM responses in children with insulin-dependent (juvenile-onset/type 1) diabetes mellitus. *Lancet* i:1397–1399
16. Orchard TJ, Atchison RW, Becker D et al (1983) Cocksackie infection and diabetes. *Lancet* ii:631 (Letter)
17. Mertens TH, Gruneklee D, Eggers HJ (1983) Neutralizing antibodies against coxsackie viruses in patients with recent onset of type 1 diabetes. *Eur J Pediatr* 140: 293–294
18. Frisk G, Fohlman J, Kobbah M et al. (1985) High frequency of coxsackie B virus-specific IgM in children developing type 1 diabetes during a period of high diabetes morbidity. *J Med Virol* 17: 219–227
19. Banatvala JE, Schernthaner G, Schober E et al. (1985) Cocksackie B, mumps, rubella, and cytomegalovirus specific

- IgM responses in patients with juvenile-onset insulin-dependent diabetes mellitus in Britain, Austria, and Australia. *Lancet* i:1409–1412
20. Tuvemo T, Dahlquist G, Frisk G et al. (1989) The Swedish childhood diabetes study III: IgM against coxsackie B viruses in newly diagnosed type 1 (insulin-dependent) diabetic children – no evidence of increased antibody frequency. *Diabetologia* 32: 745–747
 21. Frisk G, Nilsson E, Tuvemo, Friman G, Diderholm H (1992) The possible role of coxsackie A and echo viruses in the pathogenesis of type 1 diabetes mellitus studied by IgM analysis. *J Infect* 24: 13–22
 22. D'Alessio DJ (1992) A case-control study of group B coxsackie IgM antibody prevalence and HLA-DR antigens in newly diagnosed cases of insulin-dependent diabetes mellitus. *Am J Epidemiol* 135: 1331–1338
 23. Hyoty H, Hiltunen M, Knip M et al. (1995) A prospective study of the role of coxsackie B and other enterovirus infections in the pathogenesis of IDDM. *Diabetes* 44: 652–657
 24. Helfand RF, Gary HE, Freeman CY, Anderson LJ, Pallansch MA, Pittsburgh Diabetes Research Group (1995) Serologic evidence of an association between enteroviruses and the onset of type 1 diabetes mellitus. *J Infect Dis* 172: 1206–1211
 25. Borch-Johnsen K, Mandrup-Poulsen T, Lachan-Christiansen B et al. (1984) Relation between breast-feeding and incidence rates of insulin-dependent diabetes mellitus. *Lancet* ii:1083–1086
 26. Nigro G, Campea L, DeNovellis A, Orsin M (1985) Breast-feeding and insulin-dependent diabetes mellitus. *Lancet* i:467 (Letter)
 27. Fort P, Lanes R, Dahlem S, Recker B et al. (1986) Breast feeding and insulin dependent diabetes mellitus in children. *J Am Coll Nutr* 5: 439–441
 28. Golding J, Haslum M (1987) Breast feeding and diabetes. *Med Sci Res* 15: 1135–1137 (Letter)
 29. Glatthaar C, Whittall DE, Welborn TA et al. (1988) Diabetes in western Australian children: descriptive epidemiology. *Med J Aust* 148: 117–123
 30. Mayer EJ, Hamman RF, Gay EC et al. (1988) Reduced risk of IDDM among breast-fed children. *Diabetes* 37: 1625–1632
 31. Blom L, Dahlquist G, Nystrom L, Sandstrom A, Wall S (1989) The Swedish childhood diabetes study: social and perinatal determinants for diabetes in childhood. *Diabetologia* 32: 7–13
 32. Siemiatycki J, Colle E, Campbell S, Dewar RAD, Belmonte MM (1989) Case-control study of IDDM. *Diabetes Care* 12: 209–216
 33. Virtanen SM, Rasanen L, Areo A et al. (1991) Infant feeding in Finnish children less than 7 years of age with newly diagnosed IDDM. *Diabetes Care* 14: 415–417
 34. Kostraba JN, Steenkiste AR, Dorman J et al. (1992) Early infant diet and risk of IDDM in blacks and whites. *Diabetes Care* 15: 626–631
 35. Kostraba JN, Cruickshanks KJ, Lawler-Heavner J et al. (1993) Early exposure to cow's milk and solid foods in infancy, genetic predisposition, and risk of IDDM. *Diabetes* 42: 288–295
 36. Dorner G, Thoeke H, Mohnike A, Schneider H (1985) High food supply in perinatal life appears to favor the development of insulin-treated diabetes mellitus (IDDM) in later life. *Exp Clin Endocrinol* 85: 1–6
 37. Kalits J, Podar T (1988) Incidence and prevalence of type 1 (insulin-dependent) diabetes in Estonia in 1988. *Diabetologia* 33: 346–349
 38. Tarn AC, Gorsuch AN, Spenser KM, Bottazzo GF, Lister J (1983) Diabetes and social class. *Lancet* iii:631–632 (Letter)
 39. LaPorte RE, Tajima N, Dorman JS et al. (1986) Differences between blacks and whites in the epidemiology of insulin-dependent diabetes mellitus in Allegheny County, Pennsylvania. *Am J Epidemiol* 123: 592–603
 40. Elliot RB (1992) Epidemiology of diabetes in Polynesia and New Zealand. *Pediatr Adolesc Endocrinol* 21: 66–71
 41. Blom L, Persson L-A, Dahlquist G (1992) A high linear growth and risk for diabetes. *Diabetologia* 35: 528–533
 42. Dahlquist G, Blom L, Persson L-A, Sandstrom A, Wall S (1990) Dietary factors and risk of developing insulin dependent diabetes in childhood. *BMJ* 300: 1302–1306
 43. Helgason T, Ewen SWB, Ross IS, Stowers JM (1982) Diabetes produced in mice by smoked/cured mutton. *Lancet* ii:1017–1022
 44. Wilson GL, Ledoux SP (1989) The role of chemicals in the etiology of diabetes mellitus. *Toxicol Path* 17: 357–363
 45. Prosser PR, Karam JH (1978) Diabetes mellitus following rodenticide ingestion in man. *JAMA* 239: 1148–1150
 46. Dunn JS, Sheehan HL, McLetchie NGB (1943) Necrosis of the islets of Langerhans produced experimentally. *Lancet* i:484–487
 47. Wilander E, Gunnarsson R (1975) Diabetogenic effects of N-nitroso methylurea in the Chinese hamster. *ACTA Path Microbiol Scand* 83: 206–212
 48. Rous P, Kidd JG (1938) The carcinogenic effect of a papilloma virus on the tarred skin of rabbits. I. Description of the phenomenon. *J Exp Med* 67: 399–428
 49. Levy M (1984) The combined effect of viruses and drugs in drug-induced diseases. *Med Hypotheses* 14: 293–296
 50. Remington PL, Rowley D, McGee H, Hall WN, Monto AS (1986) Decreasing trends in Reye syndrome and aspirin use in Michigan, 1979–1984. *Pediatrics* 77: 93–98
 51. Graves PM, Norris JM, Pallansch MA, Gerling IC, Rewers M (1997) The role of enteroviral infections in the development of IDDM: limitations of current approaches. *Diabetes* 46: 161–168