TABLE IV—PROGRESS OF PARKINSONIAN FEATURES IN DIP CASES (n=48)

Change	%
Parkinsonism resolved	66
Still some parkinsonian features (despite stopping drug)	11
Still parkinsonian (drug dose reduced)	6
Parkinsonism resolved but later development of IDP	11
Died before follow-up completed	6
Not known	2

indication for the drug. In these some degree of parkinsonism may be a reasonable price to pay for a degree of "tranquillity". Thioridazine was stopped in 90% of cases and reduced in the rest.

The alteration with time in parkinsonian features in the 48 DIP cases is shown in table IV.

In the 66% of cases in whom DIP resolved, recovery was recorded after a mean of 7 weeks, but with a wide range of 1 to 36 weeks.

DISCUSSION

This study confirms that parkinsonism is not only common but also badly diagnosed by practitioners. Just over half the cases were drug induced. It is puzzling that such a common and serious iatrogenic neurological condition should have been described mainly in the psychiatric literature. Even the excellent review by Marsden et al[1] was published in a psychiatric context.

The general belief is that DIP has a different clinical picture from IDP, and Hausner[2] claimed that they were separate conditions. It is often said that typical tremor is less likely with DIP. This was not so in our series.

Although the mean time for recovery from DIP was 7 weeks, some cases took much longer. One old lady who had received trifluoperazine (for a minor fright and anxiety) for 5 weeks took 36 weeks to recover from the DIP but never managed to get home again. Hence DIP is a serious threat to old people and to hard-pressed geriatric units and residential homes.

5 DIP cases recovered from the drug-induced state but later became affected by idiopathic parkinsonism. The mean time between disappearance of DIP and occurrence of IDP was 11 months (3 to 18 months). Their features of DIP had all resolved within 6 weeks of stopping the causative drug. Goetz[3] has described 3 patients with DIP who recovered completely on cessation of the neuroleptic and yet at follow-up one to two and half years later were noted to have IDP. Goetz suggested that these patients probably had subclinical IDP and the neuroleptic aggravated the potential dopaminergic defect to produce clinical manifestations. The ages of Goetz's patients were not stated. Marsden and Jenner[4] postulated that DIP would develop in anyone given sufficient neuroleptic to block the central dopamine receptors. He also pointed out that only when the striatal dopamine has been depleted to 20% of normal will IDP occur. If there are persons with low striatal dopamine levels, they will be at risk of DIP when given a neuroleptic. The lower the dopamine level, the more prone they are to DIP. Marsden also believes that there are indications that age increases the risk of DIP—ie, the elderly are more likely to be near the critical 20% level and hence more readily "tipped over". This tipping over may be figuratively and literally correct since 60% of our DIP patients gave a history of falls.

The noteworthy findings in our study are: (1) the close resemblance between DIP and IDP in our elderly subjects; and (2) the occurrence of IDP in patients who recovered from DIP.

We suggest that these findings indicate that in some old people DIP really is an unmasking of latent IDP, hence the clinical similarity of the two conditions in this age group. DIP in younger patients may not only be a different entity from IDP but it may also be different from DIP in the elderly.

We conclude with a strong plea for extreme caution in the use of neuroleptics in the elderly, especially in patients who complain of vague unsteadiness or falls. Since DIP may last many months we urge that a diagnosis of IDP should not be made until it is certain that the condition observed cannot be related to a drug which was stopped months ago.[5,6]

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Occasional Survey

RELATION BETWEEN BREAST-FEEDING AND INCIDENCE RATES OF INSULIN-DEPENDENT DIABETES MELLITUS

A Hypothesis

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Summary The variations in incidence rates of insulin-dependent diabetes mellitus (IDDM) in childhood within and between genetically very similar Scandinavian populations and the variations in incidence rates with time are difficult to explain. Epidemiological data show that the incidence of childhood IDDM may now be declining and suggest an inverse correlation between breast-feeding frequency and IDDM in childhood. Case-control data show that diabetic children were breast-fed for shorter periods of time than their healthy siblings and the population at large and that a smaller proportion of diabetic children were ever breast-fed. It is postulated that insufficient breast-feeding of genetically susceptible newborn infants may lead to beta-cell infection and IDDM later in life.

INTRODUCTION

THE aetiology and pathogenesis of insulin-dependent diabetes mellitus (IDDM) is still poorly understood. Interaction between genetic, environmental, and immunological factors is required to produce beta-cell destruction and IDDM.[1] A widely accepted working hypothesis suggests that the genetic susceptibility to IDDM is conferred by two genes on chromosome 6—one associated with HLA D/DR3, one with HLA D/DR4—which act through different mechanisms. The reaction of susceptible persons to certain exogenous stimuli (beta-cell cytotropic virus, beta-cell cytotoxic chemicals) is abnormal, leading to beta-cell destruction, directly by the exogenous agents, through autoimmune mechanisms, or because of lack of beta-cell regeneration.[2]

Several epidemiological observations on childhood IDDM are, however, not easily accounted for by this hypothesis: there are striking differences in incidence rates of childhood IDDM between genetically very similar populations (eg, Scandinavian populations);[3] there are large geographical incidence variations within these populations;[4,5] and childhood IDDM incidence rates show peculiar changes with time in these countries.[3,6]

In genetically stable and similar populations variations in incidence rates of IDDM with geography and time must reflect the influence of environmental factors involved in the aetiology and pathogenesis. The hypothesis cited above suggests that susceptible individuals are directly exposed to an agent which damages beta cells. Consequently, the observed variations in childhood IDDM incidence rates should reflect changes in exposure to the damaging agent. The incidence variations may also be produced by changes in the occurrence of a factor or factors protecting against beta-cell-damaging agents.

We report here epidemiological data suggesting an inverse correlation between breast-feeding and incidence rates of childhood IDDM and case-control data supporting the relation.

SUBJECTS AND METHODS

Population Data

We obtained data on incidence rates of childhood IDDM (diagnosed before the age of 15) for the County of Oslo, Norway, for the periods 1925–54,[7] 1956–65,[8] 1966–74 (J. H. Ustvedt, unpublished), 1973–77,[3] and 1978–82 (G. Joner, unpublished), and for the region of Umeå, Västerbotten, in northern Sweden, for the periods 1938–77[5] and 1978–82 (B. Hägglöf, unpublished). Ascertainment exceeds 90% in both areas with no changes over time.

Breast-feeding data from Oslo County have been collected yearly since 1944 by Oslo Helseraad (Health Council). The data presented here are from Sagene Health Centre, serving an approximately 10% representative sample of the Oslo population (J. Steen, unpublished). Swedish breast-feeding data have been compiled on a nationwide basis from 1869 to 1975.[9] Data for 1976–82 are based on information from only 16 health-care regions, representative of a total of 37 regions (Y. Hofvander, unpublished). It has not been possible to extract data specifically covering the Västerbotten region.

The breast-feeding habits were recorded as the proportion of women who breast-fed their babies completely or partly, in Oslo for at least 3 months and in Sweden for at least 2 months.

Case-control Data

Data on breast-feeding habits of mothers of diabetic children were collected through questionnaires about the duration of complete or partial breast-feeding, administered to mothers of diabetic children from the outpatient clinics of Steno Memorial Hospital (225) and Copenhagen County Hospital, Glostrup (98). IDDM had developed in the children before the age of 18, in 1962–82. Breast-feeding data for their healthy siblings were obtained as well. All information from the questionnaires was verified by checking the records of the nurse health visitors. In Denmark each family with a newborn baby is offered visits by a specially trained nurse health visitor five to ten times during the first 18 months of life. Information on breast-feeding is recorded during such visits. There was good agreement between the mothers' answers to the questionnaires and the health visitors' records; in all cases where no exact date for cessation of breast-feeding was given in the health visitor's record, the date stated by the mother fell between two visits by the health visitor, the record of the first noting continued breast-feeding and the second noting that breast-feeding had ceased. The breast-feeding data for Copenhagen region for 1959–61[10] served as background population data.

For statistical evaluation Student's *t* test and chi-square analyses were used. The level of significance chosen was 5%.

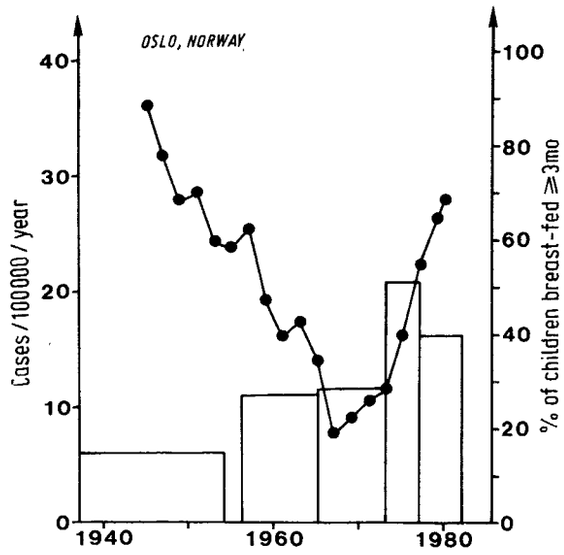

Fig 1.—Incidence of IDDM in children (aged 0–14 years) in Oslo, Norway (histogram) and breast-feeding habits in Sagene Health Centre, Oslo.

RESULTS

Population Data

Incidence rates of childhood IDDM for 1940–82 from Oslo County and the Umeå region are shown in figs 1 and 2. In both populations there was a steady increase from the 1940s to the mid-1970s. Throughout the data-collection period the incidence rate in the Umeå region was almost twice that in Oslo. During the past 5 years (1978–82) there has been a fall in IDDM incidence in both regions. The incidence rates in 1978–82 in Oslo were 22% lower than in the preceding 5-year period; the corresponding decline in Umeå was 39% but may not reflect a uniform Swedish trend.[11]

In the early 1940s about 90% of all babies in both populations were breast-fed (figs 1 and 2). In Oslo County the percentage of babies breast-fed then fell to a minimum of about 20% in the late 1960s, but has risen rapidly since then (fig 1). There were similar trends in Sweden (fig 2) but the exact position of the nadir of the Swedish breast-feeding curve could not be determined because of infrequent sampling of data.

The time lag between the IDDM incidence peak and the breast-feeding nadir in Oslo can be roughly estimated at about 9 years.

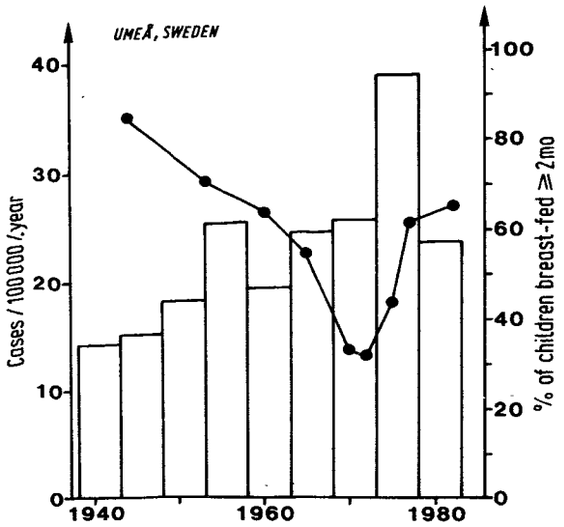

Fig 2—Incidence of IDDM in children (aged 0–14 years) in Umeå, Sweden (histogram) and breast-feeding habits in Sweden.

Case-control Data

Breast-feeding questionnaires were returned by 83% (187/225) of the mothers of diabetic children at Steno Memorial Hospital, giving information about breast-feeding for 188 diabetic children diagnosed in 1967–82 and 165 of their healthy siblings selected randomly, 1 from each family. The births of the diabetic children and their healthy siblings were evenly distributed over the period 1962–81 (median 1966). IDDM occurred in random order in the sibships studied. Using the information from the hospital records of the IDDM children, we found no differences in mother's age, child's age at diagnosis of IDDM, number of births, and socioeconomic status between responders and non-responders to the questionnaire. Identical breast-feeding questionnaires were answered and returned by 80% (78/98) of mothers of diabetic children at Copenhagen County Hospital, giving information on breast-feeding for 78 diabetic children and 65 randomly selected healthy siblings, 1 from each family. The births were evenly distributed over the period 1960–80 (median 1969).

The background population data gave information on the frequency and duration of complete or partial breast-feeding for 6245 babies (3213 boys and 3032 girls) born in the Copenhagen region during the period 1959–61[10] (ie, representing a time period close to the beginning of the birth period, 1962–81, of the diabetic children).

BREAST-FEEDING HABITS FOR DIABETIC CHILDREN, NON-DIABETIC SIBLINGS, AND BACKGROUND

—	Average duration of breast-feeding (mo)	No (%) never breast-fed	No (%) breast-fed ≥3 mo
SMH			
IDDM patients (n = 188)	2·47	18 (*10*)	33 (*18*)
Healthy siblings (n = 165)	3·17	8 (*5*)	44 (*27*)
GH			
IDDM patients (n = 78)	3·30	7 (*9*)	21 (*27*)
Healthy siblings (n = 65)	4·05	5 (*8*)	25 (*38*)
SMH plus GH			
IDDM patients (n = 266)	2·69	25 (*9*)	54 (*20*)
Healthy siblings (n = 230)	3·41	13 (*6*)	68 (*30*)
Background population			
(n = 6245)*	2·99	. .	1584 (*25*)

SMH = Steno Memorial Hospital; GH = Glostrup Hospital; NS = not significant.
*Compared with SMH IDDM patients only, because of a better time fit than with GH patients: $p<0·02$ for comparison of duration of breast-feeding; $p<0·02$ for no breast-fed ≥3 mo.

Children in whom IDDM later developed were completely or partly breast-fed for significantly shorter periods of time than their healthy siblings ($p<0·01$ for Steno Memorial Hospital, Glostrup Hospital, and both together) and the background population ($p<0·02$; see table). IDDM patients were less likely ever to have been breast-fed than their healthy siblings, though this trend was not significant, and fewer diabetic children were completely or partly breast-fed for more than 3 months than their healthy siblings ($p<0·05$ for Steno Memorial Hospital; $p=0·14$ for Glostrop Hospital; $p<0·02$ for patients from both hospitals) or the background population ($p<0·02$; table).

DISCUSSION

A declining incidence of childhood IDDM has not been reported previously. The changes are too large to be explained by possible effects of genetic counselling or migration of IDDM-prone families. Since each of the years 1978–82 in Oslo County and in Umeå showed lower incidence rates of IDDM than the average of the preceding 5 years (data not shown), the declines in these two separate populations are likely to be real. The decline in Umeå, however, may not reflect a uniform Swedish trend.[11] Breast-feeding habits have varied considerably over the past few decades in Scandinavian populations. There seems to be an inverse covariation between breast-feeding and IDDM incidence, suggesting that breast-feeding and childhood IDDM susceptibility may be connected. Our case-control data support this suggestion.

Admittedly, our suggestions are based on raw epidemiological data. The data were not prospectively collected with the purpose of studying the possible existence of such relations. Furthermore, the incidence rates from Oslo County are based on data from the whole population, while the breast-feeding data were derived from only a 10% representative sample. The Swedish breast-feeding data represent a nation-wide survey, but the IDDM incidence data are from the Umeå region only. Furthermore, the background population data do not apply to exactly the same time period as the data from the diabetic families. The bias this may introduce is probably less important than the statistically significant difference between the diabetic children and their healthy siblings. Births of patients and siblings were evenly distributed over 1962–81, IDDM occurred randomly in the sibships studied, and the breast-feeding habits within families varied less with time than in the background population.

The pattern that emerges is clear, however. When the breast-feeding frequency is high, IDDM incidence is low. IDDM incidence seems to peak some years after the nadir of the breast-feeding curve, and when breast-feeding frequency is increasing, the IDDM incidence is declining (figs 1 and 2).

The time lag (approximately 9 years) between the nadir of the breast-feeding curve and the incidence peak of childhood IDDM in Oslo is very close to the average age of onset of IDDM in this population (9·3 years; G. Joner, unpublished). Because the data were collected infrequently in Sweden, no time lag estimate can be made. This infrequent reporting may explain why no nation-wide fall in IDDM incidence is yet apparent in Sweden.[11]

We find it difficult to imagine how large differences in childhood IDDM incidence rates between[3] and within[4,5]

genetically very similar Scandinavian populations, which are constantly present despite the variation with time in IDDM incidence rates reported here, can be fully explained by variations in direct exposure to a beta-cell-damaging agent.[2] We think a lack of factors protecting against the effects of such agents is a more feasible explanation. Breast-milk may provide such protection. Breast-feeding habits vary greatly within and between populations,[12] and, as we have demonstrated, with time in a way that could fit childhood IDDM incidence variations. Breast-milk protects the newborn infant against infections through specific secretory IgA antibodies, specifically sensitised cytotoxic T and B lymphocytes, and non-specific defence factors (eg, complement components) by way of a homing mechanism between lymphoid tissue associated with the gut and respiratory tract and the mammary gland.[13] Another explanation may be that formula feeds contain chemicals or a protein load[14] capable of damaging the beta cells.

We postulate that lack of protection due to insufficient breast-feeding of genetically susceptible newborn infants may lead to beta-cell infection, beta-cell destruction, and IDDM later in life. IDDM may be the result of a neonatal infection of the beta cells by a slowly replicating virus. Hence, heterogeneity of IDDM as related to HLA DR3 and DR4[15] would simply reflect differences in host response to the putative neonatal infection.

It is tempting to speculate that a virus (or viruses), against which antibodies would be demonstrable as specific secretory IgA antibodies in breast-milk as well as IgM and IgG antibodies in blood drawn before and at diagnosis in children with IDDM, may be the common diabetogenic agent (or agents) in man.

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DNA in Medicine

DNA JUGGLING IN THE IMMUNE SYSTEM

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IT is in the immune system that DNA in chromosomes shows its most versatile facet—ie, the ability to rearrange itself in different ways in different individual cells. This ability is the secret of survival in higher organisms because it provides the almost infinite diversity required to combat a plethora of infective agents. As a technological spin-off it has provided the means for molecular biologists to create new antibodies in the test tube using recombinant DNA methods. Unfortunately, however, the DNA rearrangement of antibody gene systems has also acquired a lethal aspect because it is used by other genes (those now called oncogenes because they have been associated with cancer) to aid tumour formation. These three related but different topics will be dealt with in this article.

DNA REARRANGEMENTS IN B AND T CELLS

The immune system operates largely through two types of lymphocyte—the B cells (so called because they mature in the bursa of Fabricius in chickens) and T cells (that mature in the thymus). Both types of cell can pick out and recognise specific foreign molecules (antigens) using a protein on their surface called an antigen receptor. The structure of these receptors is complex; the B cell receptor is antibody.

The B cell receptor is made up of two protein chains which are bound together and which are designated heavy (H) and light (L) chains on grounds of size. These proteins come from genes that are inherited as a complex set of small DNA fragments (V, D, J, and C) that move around in the chromosomes of individual B cells to produce the mature functional genes (fig 1). The genes that result from this DNA shuffling in two separate cells are unlikely to be the same because of the complexity of the pieces available for joining. The part of the final gene that will be involved in "seeing" foreign molecules is made from V, D, and J pieces; the C piece is constant.

The system is an ingenious way of achieving variability by mixing small pieces of DNA in many combinations (for example, ten V pieces and ten D pieces alone could give a hundred different combinations). Incredibly, this mixing is achieved by breakage of chromosomes, DNA rearrangement, and rejoining of the chromosomes. On top of this mixing, the pieces can themselves have their DNA sequence altered by somatic mutation. Single-point mutations in the DNA result in new sequences and in a new protein, adding further diversity to the range of antibodies that can be made by an individual. These are not the only ways in which the DNA that codes for antibodies can be altered. Yet another way is that when the chromosomal rearrangement takes place the points at which the rejoining occurs are not precise. The result of this imprecision is the creation of yet more sequences, and yet more different antibody types.

The T cells have an analogous protein which recognises foreign molecules. The genes responsible—at least for one chain of the T cell receptor—are very similar to those for B cells and consist of V, D, J, and C pieces which are rearranged in the chromosomes of individual T cells to produce a fully mature gene. (The scheme depicted in fig 1 for B cell genes could just as well have been for T cell gene rearrangements.)

The two sets of genes performing these remarkable acrobatics in the production of protein variability belong to a "super" family of genes which includes those present in the major histocompatibility locus (the transplantation antigens). They are related to a common ancestral gene and they have retained many structural features in