Opinion on problems raised by prenatal and perinatal diagnosis. Report.

N°5 - May 13, 1985

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Opinion

Congenital malformation and hereditary diseases are some of the main causes of mortality and morbidity in industrialised countries. They result in suffering for the individual, in emotional distress and an economic burden for families and society.

There has been considerable and rapid progress in medical understanding of these disorders and of their causes. In the last ten years or so, various techniques have evolved for prenatal diagnosis of a large and growing number of anomalies. These developments give hope to parents who either have already borne affected children or who know themselves to be carriers of a risk of hereditary disease for their descendants and who would otherwise have decided not to have children. When a prenatal diagnosis can eliminate the possibility of risk, the anxieties of prospective parents can be alleviated.

However, prenatal diagnosis may also reveal the presence of anomalies for which there is at present no known treatment. Medical progress has not yet made it possible to cure a great many hereditary disorders: the best that can be done is to prolong life slightly and improve its quality to a limited degree.

This gap between methods of diagnosis and available therapy may inspire concern that if frequent use is made of prenatal diagnosis procedures, social rejection of individuals thought to be abnormal may be reinforced and the slightest foetal or infant defect may become even less acceptable.

On an individual basis, prenatal diagnosis puts parents and physicians in a position where they must face the fearsome moral dilemma of induced abortion.

The choice between voluntary abortion and the birth of a more or less severely handicapped child is a difficult decision to take and depends on each individual's personal convictions regarding life and the human being.

The decision to continue or interrupt pregnancy in the last resort belongs to the parents, by right of law. "Thus the risk of collective eugenics is eliminated". The decision must take into

account a set of factual and legal concerns. Legally, according to a law dated 17th January, 1975, a "strong probability that the unborn child will be affected by a particularly severe disorder, known to be incurable at the time of diagnosis" is sufficient reason for elective abortion. The definition has to be evaluated in the light of four factual components: degree of certainty of diagnosis, severity of the potential disorder, age of onset of disease, and effectiveness of therapy.

Considering the extreme difficulties faced in some cases by those who request prenatal diagnosis and the ethical nature of the problems they may need to resolve, the National Committee of Ethics feels bound to formulate recommendations regarding the use and future developments of prenatal diagnosis methods.

1. Use of prenatal diagnosis

In the last ten years or so, progress in prenatal diagnosis has been essentially based on highly reliable biological techniques (cytogenetics, biochemistry) and applications have been developed by co-operation between those in charge of diagnostic centres with the agreement of public health authorities. In this way, thousands of tests have been performed and year by year a growing number of at-risk couples obtain a diagnosis.

In the last few years, ultrasonographic foetal imagery has led to new diagnostic possibilities. Accuracy of results depends on equipment quality and operator experience.

So that biological and ultrasonographic tests continue to be of high quality, it is recommended that special approved centres for prenatal diagnosis be created, and that no abortion decision for medical reasons be taken without prior consultation of such a centre. The centre must be organised on a multi-disciplinary basis and be attended by at least one MD trained in biology and genetics, and by an expert in foetal ultrasonography. Biological laboratories able to perform required tests must be associated with the centre.

In practical terms, physicians and technicians in these disciplines must be trained as a matter of urgency.

In legal terms, a decision to interrupt a pregnancy by reason of congenital malformation or genetic disorders as defined in the law dated 17th January, 1975, must have been approved in writing by two physicians, of which one needs to be recognised as an expert by the judicial authorities. It is therefore recommended that one at least of these two signatories should be an expert in these disciplines and be associated with an approved centre. The same rules must apply to abortions for which a decision is taken based on diagnosis performed before twelve weeks of pregnancy.

It is up to the parents to decide whether induced abortion should take place once they have been duly informed of the results of the tests. They should not be made to feel they are under pressure when they are given test results. Nor should they be blamed if they do not want a prenatal diagnosis or decide not to interrupt a pregnancy.

Finally, so that medically unjustifiable use is prevented as well as errors which might result from general recourse to "kits" sold for diagnosing the sex of the future child or genetic diseases from nine weeks of pregnancy onwards, it is recommended that such genetically applicable reagent kits should be sold according to legislation based on principles similar to those applying to marketing of new or dangerous drugs.

2. Developments in prenatal diagnosis

Because of the hopes aroused by prenatal diagnosis, new developments are both desirable and predictable.

Difficulties mentioned above should inspire a similarly cautious approach as regards extension and generalisation of new techniques.

For this reason, use of prenatal diagnostic techniques should only be encouraged if the probability of error of a test is so low that the presence of a genetic disease is certain or almost certain. It is recommended that government authorities should only encourage prenatal diagnosis - and therefore support the cost of it - if such conditions prevail. Such financial support aims to give equality of access to frequently very costly procedures.

In cases where diagnosis is reliable and the disease is frequent and particularly severe, it may be desirable to encourage a general extension of prenatal diagnosis methods. Premarital and prenatal check-ups could include - if couples wished it - tests giving a more accurate assessment of risk factors and, if appropriate, diagnosis of carriers of recessive gene disorders.

A public health programme for the collection of data on hemoglobinopathy (sickle-cell anaemia and thalassemia) would be feasible as of now in areas where it is frequent, and will soon be a possibility for certain X-linked disorders. Further extension could be considered as soon as possible to the diagnosis of frequent, grave, and intractable genetic diseases (such as cystic fibrosis), taking into account inter alia the cost of testing.

3. Screening for predisposition

When screening for predisposition to certain diseases, some of which are severe and fairly frequent, is possible through perinatal, postnatal, and even in certain cases prenatal testing, then the Committee would make identical recommendations as regards financing, limiting to diseases for which a certain or quasi-certain diagnosis of predisposition can be made, and to those for which effective palliative or curative therapy is available if given early enough. Frequency and severity of diseases as well as the cost of testing must also be taken into account. Finally, confidentiality of data collected is mandatory.

4. Consequences of prenatal diagnosis

Hereditary diseases for which prenatal diagnosis is made at the present time are mostly lethal in childhood, before the age of reproduction.

There is concern in some quarters about the dysgenic consequences of medical progress which prevents normal "natural selection" and increases the "genetic burden". Others are opposed to eugenic undercurrents in public health genetic policies.

All existing genetic population studies have shown that although it is possible to reduce notably the numbers of those born with hereditary diseases, medical knowledge for the moment cannot do very much about modifying genetic heritage.

New possibilities offered by judicious and sober use of prenatal diagnosis can only be of benefit to patients, their families, and the population as a whole.

Report

For centuries, medicine concentrated on therapy. Nowadays, the ultimate aim is to prevent rather than cure disease. Prevention implies prediction, and the first step to preventive medicine is identification of predisposition.

This is not a totally new attitude, however, since medical geneticists have been trying for several years to diagnose in utero malformations and hereditary diseases. Furthermore, government authorities long ago began to organise collective prevention campaigns, such as vaccination programmes.

From an ethical point of view, there has been a broad consensus approving methods used and advice given by medical geneticists.

So it may seem surprising that there should be renewed interest in this branch of biomedicine. However, some new facts have come to light:

1. Because of new molecular biology techniques it is now possible to diagnose in utero some hereditary diseases which have dire consequences for the affected individuals and for their families. The method will certainly be extended soon to other single gene hereditary defects.

2. The diagnosis can now be obtained by simple sampling through the vaginal route of a tiny fragment of chorionic villus containing the molecule which dictates the whole hereditary biological programme, i.e. DNA.

If this sampling technique turned out to be low risk for the foetus, it could be performed as early as the tenth week of pregnancy.

3. Biologists are aware of predisposition "markers" for certain more complex hereditary diseases which are caused by the unfortunate simultaneous presence in an individual of several genes which are deleterious when combined. If such individuals can be screened, prevention or early treatment becomes a possibility and preventive medicine becomes a reality.

4. At the same time, since parents can now control their fertility and therefore the number of children they give birth to, they wish to improve the prevention of severe birth handi. These sometimes categorical demands are being made at a time when elective abortion is becoming more commonplace.

The social impact of such diseases merits emphasis as do the suffering and tragic repercussions on individuals or families.

Aims to be achieved are clear :

- further alleviate the condition of patients,
- enable couples who voluntarily refrain from child bearing to do so in a satisfactory way while making sure that:
- care and counsel given them is of high quality,
- unnecessary, abusive or erroneous recourse to elective abortion is limited,
- and medical confidentiality remains the rule.

1. Data

To be clear, a distinction must be made between :

a) chromosomal aberrations (e.g. Down's syndrome) and congenital malformations which are not hereditary but which can be diagnosed in utero.

b) recessive or dominant genetic diseases (sex-linked or not), many of which can only be treated with palliative therapies (e.g. cystic fibrosis, haemophilia, myopathy). More often than not, they are due to the alteration of a single gene.

c) diseases which only appear if and when an environmental factor is added to a genetically predisposed susceptibility (e.g. insulin-dependent diabetes, multiple sclerosis, ankylosing spondylitis). These are more complex hereditary diseases and generally involve several genes (polygenic).

A. Tests methods

In the last few decades, medical geneticists have developed a whole new range of investigative tests and methods :

- to diagnose a disease in utero at the earliest possible time,

- to detect adult carriers of deleterious genes in the heterozygous form (i.e. only one gene in the pair is defective),

- and more recently, to detect susceptibility of individuals to the third category of diseases, i.e. complex hereditary disorders.

Foetal investigations have gradually improved so that a very early and thorough prognosis can now be made for the unborn child.

- Ultrasonic *echography* allows for detailed vision of foetal morphology and mobility as early on as twelve or thirteen weeks into pregnancy.

- *Foetoscopy* , that is in situ vision, with the help of a probe through the abdomen to find less obvious anomalies (this practice has almost disappeared).

- *Amniocentesis* which consists in sampling a small quantity of amniotic fluid, can be performed early in the seventeenth week. Foetal cells are obtained in this way.

- Direct *sampling* of foetal blood from the umbilical vein must be performed by highly trained experts.

- *Chorionic villus sampling* , which consists in sampling trophoblasts from foetal villi which link the child to the maternal placenta, is still experimental. With this method, foetal cells could be sampled as early as eight to ten weeks into pregnancy through the vaginal route.

Many tests can be performed on this foetal material :

- Display chromosomes to discover major anomalies such as Down's syndrome (90% of diagnoses).

- Biochemical examination of proteins (e.g. haemoglobin or various enzymes).

- Biochemical examination of genes with the help of molecular biology (detection or location of defective genes).

The range of tests and techniques grows day by day so that there is constant progress in the feasibility of diagnosing certainties, probabilities, or sometimes only predisposition.

After birth or in adults, some of these tests allow, inter alia, screening of carriers of heterozygous defective genes (i.e. located on only one of two homologous chromosomes).

B. Diseases diagnosed

Medical advance has led to an amazing decline of infant mortality in industrialised countries (in particular because of progress in prevention and treatment of infectious diseases).

The first two above mentioned categories, congenital malformation and genetic diseases, are now the principal causes of infantile pathology in these countries particularly:

- lethal diseases in childhood (before the age of 20) for which medical treatment is non existent and care only serves to prolong survival with poor quality of life;

- pronounced mental deficiencies.

1. Chromosomal anomalies

Trisomy 21 or mongolism (1 : 700 live births). It mostly occurs with relatively older mothers (38 years), and is the most frequent chromosomal anomaly. But there are other types of trisomies, trisomy 13 (1 : 9 000), trisomy 18 (1 : 5 000).

Sex chromosome aberrations: Turner's syndrome (1 : 2 500), fragile X syndrome

(1 : 1 500 boys).

2. Congenital malformation

- Defects in formation (anencephaly and spina bifida) and other anomalies of the central nervous system (hydrocephalus), in total 1.4 : 1 000.

- Congenital heart disease (about 4 : 1 000)

- Defects of the urinary tract and genitalia (about 4 : 1 000).

3. Genetic diseases

These may be classified according to their mode of transmission as follows:

- *dominant inheritance* : only one of the parents is a carrier for the deleterious gene which is passed on to half of the offspring. These are rare disorders, such as for instance Huntington's disease which leads to inexorable dementia at the age of 40.

- *recessive inheritance* : both healthy parents carry only one identical defective gene (heterozygous). One child in four is affected because that child has received the defective gene from each parent, i.e. twice (homozygous).

The most frequent condition of this category in France is cystic fibrosis which affects 1 child out of 2 000 or 2 500. Phenylketonuria affects (1 child in 15 000).

Hemoglobinopathies are very serious conditions. Sickle-cell anaemia is most frequent in West-Indian and African populations. Thalassemia is found in Mediterranean populations.

X-linked hereditary diseases, by which is meant linked to the X chromosome (men have one X chromosome and women have two). These diseases are evident only in men who have inherited an X chromosome containing the defective gene. A woman carrying the gene on one of her two X chromosomes is healthy, but is known as a carrier since she will pass the disease on to one son out of two.

- fragile X syndrome (mentioned above)

- haemophilia types A and B (1 : 10 000 boys)

- muscular dystrophy (1 : 5 000 boys).

Apart from these typical examples, a vast number of other genetic mutations exist (up to 3 000 of them have been listed). It is true that they are rarely encountered, but consequences for individuals and families can be dramatic.

The sum of diseases mentioned so far represent a considerable burden on the sick, on their families, and on society as a whole.

The proportion of live births and still born children affected by congenital malformation and hereditary diseases is estimated at approximately 3%.

4. Diseases occurring against a background of hereditary predisposition

These conditions are inherited in a less systematic and more complex fashion. Such diseases (see table 2) are:

- juvenile onset insulin deficient diabetes;

- multiple sclerosis;

- rheumatoid arthritis;

- autoimmune diseases,

to quote but a few of the more severe diseases, in medical and social terms, which afflict the population in high proportions.

5. Therapeutic possibilities

Unfortunately, the diseases which can benefit from therapy are only rarely those which can be diagnosed in utero. As a consequence, the medical outlook is not identical to what is usually found in the profession. When an anomaly of the foetus is diagnosed, in consultation with parents, voluntary abortion may be considered.

However, experience acquired in the last fifteen years through more than half a million diagnoses world wide, has demonstrated that the number of normal cases exceeds the number of foetal defects diagnosed. This is true for all indications and the difference is frequently very pronounced.

A few possibilities of treatment at the present time are:

- Surgical treatment at birth for some malformations.

- Disastrous effects of phenylketonuria (profound mental debility) can be avoided with a special diet which must be strictly observed during the first five or ten years of life.

- Haemophiliacs can nowadays lead a normal life but need continuous and very costly treatment.

- Prognosis for hemoglobinopathies is still very severe in spite of improvements in transfusion therapy.

But there is a clear discrepancy between detection and therapy. One only needs to observe

the dramatic situation in some families due to: cystic fibrosis, in which affected children gradually deteriorate to an early death before adulthood; muscular dystrophy (Duchenne and Becker) with similar consequences; the fragile X syndrome, the consequences of which are severe mental retardation in individuals who are otherwise perfectly formed. There is no effective therapy for any of these three conditions.

2. The problems

For the sake of clarity, although some of the problems are common to both categories, a distinction will be made between:

- prenatal diagnosis for congenital malformation and genetic diseases;

- diagnosis, frequently postnatal, of predisposition to complex hereditary diseases.

A. Prenatal diagnosis

Problems arise in fact because of the close link between prenatal diagnosis and voluntary abortion.

The law on voluntary abortion specifically allows it for a foetus afflicted by disease or malformation whereas previously, only the mother's state of health was considered.

Problems arising nowadays are :

- *ethical*

- to allow parents to take an unobstructed decision in the light of as complete and clear information as possible;

- to allow physicians the possibility of refusing voluntary abortion if they have conscientious objections to performing the procedure.

- *logistic*

- to guarantee that the population gets good quality service, and

- to avoid abuse which is still a potential danger.

1. Prenatal diagnosis

Experience has demonstrated that one cannot simply confront parents with uncertainty. In practice, therefore, prenatal diagnosis is made only if it is technically possible to arrive at total or almost total certitude.

Unless this is so, it seems undesirable to extend it to other disorders.

The problem is becoming increasingly acute because of methods used in molecular biology. DNA probes are not always direct, i.e. they do not specifically point at the defective gene which is the cause of the disease. In some cases, the probe acts indirectly by settling on a nearby gene on the same chromosome. Depending on the distance between the two genes, there is more or less of a probability that they have both remained on the same chromosome. In such cases, the geneticist can only give probabilities. It is hoped however that it will soon be possible to arrive at almost complete certainty for the three most common genetic diseases in France: cystic fibrosis, muscular dystrophy, and the fragile X syndrome.

In X-linked diseases, diagnosis of the sex of the foetus is of the utmost importance in decision making. Sex determination is now possible by an examination of chromosomes in cells sampled by amniocentesis in the 18th week.

Using chorionic villus sampling techniques, examination will in many cases be possible as early as the 10th week in the near future. This will make a considerable difference because it will then be possible to avoid the serious psychological consequences of late abortion, and if it must be performed, the situation will be much improved.

It is easy to imagine however that such techniques might well lead to convenience abortion since sex determination becomes a possibility before the voluntary abortion deadline.

2. Screening for heterozygotes

When this is a possibility, there are enormous advantages :

- individuals who do not carry the defective gene can be reassured, in particular sisters of patients suffering from X-linked diseases;

- women who are carriers can use prenatal diagnosis for each pregnancy.

If there is no such possibility, certain couples are voluntarily infertile.

So, far from leading to a greater number of voluntary abortions, prenatal diagnosis already makes it possible to enjoy a greater number of wanted pregnancies and in the future, this effect will be amplified.

Up until now, when the sister of a young muscular dystrophic patient has witnessed the agonised progression to his death of her little brother, she refuses to give birth to a boy. Soon, it should be possible to let her know whether she is in fact a carrier and whether the male foetus she bears is affected.

When should screening for heterozygotes take place?

- systematically in at-risk families, either as part of a prenuptial check-up or else early in pregnancy;

- screening for heterozygotes can be extended to a whole population who will be willing to accept such constraints if the disease is known to be of dire consequence (this is the case in Sardinia or Cyprus for hemoglobinopathy).

3. Problem of medical confidentiality

There are two obligations in this respect :

- It is essential that confidentiality be strictly observed as regards the presence in an individual or in a family of a hereditary anomaly such as a defective gene or a chromosomal defect, e.g. balanced translocations (1 : 300 individuals) ;

- at the other extreme, it is also essential that such defects be recorded so as to be able to match conditions in a family and avoid unnecessary repetition of tests.

At present, such files are kept by specialised centres and they exchange data.

But knowledge is being gained at such speed that this personal data may take huge proportions, unpredictable at the present time. Therefore, methods must be developed to

store the data and limit access strictly so that it can only be used for the benefit of patients and excludes access by third parties who could draw conclusions damaging to the freedom and best interests of the patient (employers, insurers).

B. Diagnosis for predisposition

The procedure in this case aims at discovering at any time in the life of an individual, but preferably during childhood, or even in utero, a genetic arrangement which favours the onset of a particular disease.

HLA tissue groups are for the moment almost the only "markers" available. Predictive power of a test is provided by a relative risk value (RR). For example, HLA-B 27 individuals are 87 times more likely to be affected by ankylosing spondylitis than non B27 individuals. A male B27 is 600 times more likely to be affected than a non B27. It can be noted, however, that apart from this spectacular example, relative risk is usually low.

Nevertheless, these tests may be eminently useful in previously afflicted families. This is the case at present for idiopathic hemochromatosis since it is possible to give preventive treatment to homozygous children. This may in future be the case for insulin-deficient diabetes, a frequent and serious disease, for which regular supervision and early prescription of effective treatment might become possible.

At present, such diagnosis is marred by a high degree of uncertainty because the "marker" genes are no more than near to the causative genes.

But the technology is promising since genetic markers will become increasingly accurate and problems such as those mentioned above will become topical.

There is obviously little point in revealing a morbid predisposition and provoking anxiety if no particular precaution can be taken or if there is no preventive nor even palliative therapy available.

Furthermore, medical confidentiality issues are identical in this case to those previously mentioned and should be dealt with in a similar manner to avoid the possibility of abuse by, for instance, some employers or insurance companies.

3. Public health policy issues

For the moment, only prenatal diagnosis need be considered, but in future predisposition diagnosis may require consideration.

A public health policy is essential in order to :

- protect pregnant women from hasty or even erroneous conclusions arrived at by the use of any prenatal diagnosis method, in particular sole use of ultrasonography,

- be sure that such tests which are frequently costly, are made available to everyone, so that there is complete equality of access by the whole population.

- achieve quality in genetic testing and counselling.

A. An extension of the number of *Prenatal Diagnosis Reference Centres (Centres de référence de diagnostic prénatal*) cannot be too highly recommended. About thirty of them already exist in France. Official approval would be granted to centres and they should be particularly well staffed with competent medical and technical personnel, and supplied with appropriate equipment. Special training must be organised for the staff.

It would be advisable to reduce the maternal age (37) at which cytogenetic diagnosis is offered to couples in order to detect chromosomal anomalies.

As regards genetic diseases, financing should take into account :
- severity of disease ;
- age of onset ;
- frequency in population ;
- cost of testing.

B. It is also advisable to establish regulations for the availability and use of "genetic diagnosis kits" which are already marketed in some other countries; one such kit serves to determine the sex of a foetus at 10 weeks. Sex determination should be restricted to medical purposes in connection with research on X-linked genetic diseases.

C. To protect medical confidentiality and nevertheless facilitate prenatal diagnosis, it is essential to establish special computerised records. Their use must be strictly regulated.

A final word on predisposition diagnosis: in this case also, only tests leading to effective preventive measures or therapy should be financed. Juvenile insulin-deficient diabetes could become the object of systematic screening.

D. The effect of prevention on the frequency of hereditary diseases and on the human genetic heritage should be measured.

Hereditary diseases for which in utero screening is performed up to the present day, are mostly diseases leading to death during childhood, before the age of reproduction.

In some quarters there are concerns regarding possible dysgenic consequences if medical progress were to impede natural selection processes and increase the "genetic burden". Others disagree with any eugenic element underlying genetic public health policies.

All existing genetic population studies demonstrate that medical progress in its present state of advancement is incapable of either noticeably deteriorating our genetic heritage or of eradicating hereditary diseases.

Conclusion

It can be stated that the National Consultative Committee of Ethics' consideration of issues raised by new technology for pre and postnatal diagnosis is timely, since prospective developments are exceptionally far reaching.

It can only be hoped that such new possibilities will be used wisely and soberly with the sole aim of benefiting patients, their families, and society as a whole.

Until such time as specific therapies are discovered, predictive medicine can prevent many sorrows and alleviate much suffering.

It is the first step to personal preventive medicine which will be less expensive and more effective.

Who should keep the records ?

With a view to allowing maximum flexibility for organising and keeping records on the one hand, and to provide maximum security on the other hand, legal and administrative procedures should be avoided where possible but data acquisition and processing should be restricted, whatever their status, to a small number of organisations whose activities would be approved by the authorities after consulting a Committee of Ethics.

This Committee of Ethics should :

1) make sure that epidemiological research or preventive action for which it is proposed to collect and process data is truly pertinent,

2) verify that the proposed research justifies such data acquisition and processing, with due regard to the interests of those individuals who are directly concerned and public interest in general,

3) make sure that organisations in charge of data acquisition and processing are under the responsibility of physicians whose proven competence and high moral rectitude is indisputable,

4) verify that such organisations operate in full conformity with whatever rules are established for them.

Table I

Approximately 3 per cent of children, born live or stillborn, are affected by congenital malformations.

The most frequent and severe in metropolitan France are :

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a) Chromosomal anomalies

1 living new born child out of 175 carries a chromosomal aberration

Trisomy 21	1 : 700
Trisomy 13	1 : 9 000
Trisomy 18	1 : 5 000
Turner's syndrome	1 : 2 500
Fragile X syndrome	1 : 1 500 garçons

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b) Congenital malformation

- Neural tube defects (anencephaly, spina bifida) and other central nervous system defects (hydrocephalus...)

1.4 : 1 000 births

- Congenital heart disease

4 : 1 000 births (approx.)

- Defects of the urinary tract and genitalia

4 : 1 000 births (approx.)

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c) Genetic diseases

Cystic fibrosis	**1 : 2000 to 2 500 births**
Phenylketonuria	**1 : 15 000 births**
Duchenne's myopathy	**1 : 5 000 boys**
Haemophilia	**1 : 10 000 boys**

Hemoglobinopathies
Sickle cell anaemia
Thalassemia

Table II

HLA and disorders

Disorders	HLA	Frequency (%)		Relative risk
		Patients	Control group	
Hodgkin's disease	A1	40	32,0	1,4
Idiopathic hemochromatosis	A3	76	28,2	8,2
Behçet's disease	A3	41	10,1	6,3
Congenital adrenal hyperplasia	B 47	9	6	15,4
Ankylosing spondylitis	B 27	90	9,4	87,4
Reiter's syndrome	B27	79	9,4	37,0
Acute anterior uveitis	B27	52	9,4	10,4
Subacute thyroiditis	B35	70	14,6	13,7
Psoriasis vulgaris	Cw6	87	33,1	13,3
Dermatitis herpetiformis	D/DR3	85	26,3	15,4
Coeliac diseases	D/DR3	79	26,3	10,8
	D/DR7	equally high		
Sjögren's syndrome	D/DR3	78	26,3	9,7
Addison's disease	D/DR3	69	26,3	6,3
Basedow's disease	D/DR3	57	26,3	3,7
Diabetes mellitus	D/DR3	56	28,2	3,3
	D/DR4	75	30,5	6,4
	D to DR2	10	28,2	2
Myasthenia gravis	D/DR3	50	28,2	2,5
	B8	47	24,6	2,7
SLE (Systemic Lupus Erythematosus)	D/DR3	70	28,2	5,8
Extra-membraneous glomerulone-phritis	D to DR3	75	20,0	12,0
Multiple sclerosis	D to DR2	59	25,8	4,1
Optic neuritis	D/DR2	46	25,8	2,4
C2 deficiency	D/DR2 B18			
Goodpasture's syndrome	D to DR2	88	32,0	15,9
Rheumatoid arthritis	D to DR4	50	19,4	4,2
Pemphigus	D to DR4	87	32,1	14,4

Hydralazine SLE	**D / DR4**	**73**	**32,7**	**5,6**
Hashimoto's disease	**D to DR5**	**19**	**6,9**	**3,2**
Pernicious anaemia	**D / DR5**	**25**	**5,8**	**5,4**
Juvenile rheumatoid arthritis				
- pauciarticular	**D / DR5**	**50**	**16,2**	**5,2**
- polyarticular	**D to DRw8**	**23**	**7,5**	**3,6**