Antenatal genetic diagnosis: current status and future prospects

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The current status of antenatal genetic diagnosis is reviewed and the limitations of present techniques are discussed. It is suggested that multidisciplinary clinics are the most efficient means of providing this aspect of health care. Advances in cell culture techniques, in ultrasonography and in fetoscopy will extend the services available, and the impact of this will be felt by the community. Education of the medical profession and the public in this area is necessary so that informed decision-making can take place.

On fait la revue de l'état actuel du diagnostic génétique prénatal et on discute des limites des techniques utilisées à date. Le recours aux cliniques multidisciplinaires est suggéré comme le moyen le plus efficace pour pourvoir à cet aspect des services de santé.

Les progrès réalisés dans les techniques de culture des cellules, dans l’ultrasonographie et dans la fetoscopie vont permettre d’étendre la disponibilité de ces services, et l’impact s’en fera sentir dans la communauté. Il est nécessaire d’éduquer les membres de la profession médicale et le public sur le sujet afin d’en venir à des décisions éclairées.

In many Western countries there has been in the past decade increasing interest in antenatal genetic diagnosis. Among the reasons for this is that congenital anomalies are now a significant cause of infant deaths. For example, in 1976 they accounted for 25% of all deaths during the first year of life among infants in England and Wales. Technologic advances have made possible the antenatal diagnosis of chromosome abnormalities and an increasing number of biochemical disorders. More recently the practice of taking blood samples directly from the fetal circulation has widened the range of diagnostic possibilities.

At the same time, public attitudes in many countries towards selective abortion have become more liberal. Parents are aware that modern medicine gives them the option of controlling not only the number of children they wish but also, to some extent, their normality. Finally, the state has begun to look at the cost-benefit relation of the new approaches to antenatal testing for certain anomalies because of escalating costs of health care.

In most countries in the Third World, however, the problems of overpopulation and malnutrition are still pressing. It is well to remember that what is the future in medical diagnosis for the Third World is often the present for our population. This discussion therefore begins with a review of the current status of antenatal genetic diagnosis in Canada. Speculation follows as to which directions this discipline may take in the short term. The short term is emphasized because most of our current methods of dealing with our genetic problems may well be outmoded by the end of the century.

It might first be asked what value antenatal genetic diagnosis has, for if it has no value, it has no future.

Value

Ninety-five percent of families seen with indications for antenatal genetic diagnosis will be reassured that their baby does not have the genetic problem they were concerned about. This means a considerable reduction in parental anxiety. It also means that many such families who otherwise would not have begun a pregnancy or might have sought termination because of fear of the outcome can now choose antenatal testing.

At present, very few of the conditions thus diagnosed are treatable. One example is vitamin-B₁₂-responsive methylmalonic acidemia. This condition, if diagnosed antenatally, may be treated by giving large doses of vitamin B₁₂ to the mother. Similarly, if the fetus is found to have galactosemia the maternal diet can be altered to exclude lactose and avert the fetal effects of this disorder of galactose metabolism.

With many conditions that cannot be treated, appropriate management can be started on the first day of life if the diagnosis is known before birth. For example, the presence or absence of the 21-hydroxylase-deficient form of the adrenogenital syndrome can be predicted by measur-
ing the concentration of 17-hydroxyprogesterone in the amniotic fluid before 24 weeks' gestation. The sex of the fetus can also be determined so that cortisol replacement can be started at birth and the emotional trauma of sexual ambiguity be averted.

Emotional and even financial preparation may also be needed by the family that has chosen to continue a pregnancy despite the prediction of an abnormal fetus.

Third-trimester complications for the mother may be avoided with the policy of selective second-trimester termination of pregnancy when there is a condition such as intrauterine growth retardation associated with chromosome abnormalities, or hydramnios associated with anencephaly.

Finally, the problem of selective abortion must be considered. Whether one is a follower of the Messiah, of Mary, of Marx, of Mohammed or even of mammon, termination of pregnancy is a dismal admission of defeat. However, the arguments that families have given to members of our genetic team for selective abortion are as follows: One or both parents feel they could not cope emotionally with a severely handicapped child; the long-term burden on normal siblings would be avoided; the costs of health care are so high that the family cannot afford to continue an abnormal pregnancy to its outcome; or the parents already have one severely handicapped child and feel they would not have the time for the loving care of two or more such children. Disaster can be redeemed with love, but if disaster can be avoided abortion may be justified.

If it is accepted that antenatal genetic testing has merit, the current status of genetic diagnosis should be examined and areas identified where progress and improvement are needed.

**Current status**

At present, the indications for antenatal genetic diagnosis are as follows: maternal age 35 years or more, parental chromosome rearrangement, or a family history of a chromosome anomaly (trisomy 18 or 21), a neural tube defect, an inborn error of metabolism, an X-linked disorder, a hemoglobinopathy or a dysmorphogenesis syndrome.

Any woman who has a child, a sibling, a spouse or any other relative with a neural tube defect is advised to undergo amniocentesis for the detection of raised α-fetoprotein (AFP) concentrations in the amniotic fluid as well as careful ultrasonographic examination of the fetal vertebrae at around 18 weeks' gestation. Other causes of raised AFP concentrations in the amniotic fluid include threatened abortion, duodenal atresia and congenital nephrosis, and it may be difficult to exclude these.

Recently the United Kingdom collaborative study on AFP in relation to neural tube defects showed that AFP values in the mother's serum at 16 to 18 weeks' gestation were raised to 2.5 times the normal median value in 88% of cases of anencephaly, 70% of cases of open or closed spina bifida and 3% of normal singleton pregnancies. A voluntary screening program such as the one in that study may be tested in Canada, but it is likely that this new method of antenatal diagnosis will be greatly debated. More data will be required about the cost-effectiveness and reliability of such a program, as well as the awareness, understanding and acceptance of it by the public and by physicians.

Davidson and Sheffield recently pointed out in an editorial in the Journal that carefully monitored pilot studies must be done before wide-scale screening of AFP concentrations is begun, otherwise we may be providing answers for patients who have no questions.

At present only 80 biochemical disorders of the fetus can be diagnosed, but this is one area where rapid advances are being made. The specific enzyme deficiency is now known for approximately 130 genetic diseases, most of which are lysosomal disorders.

The X-linked disorders include conditions such as hemophilia and Duchenne muscular dystrophy. Until recently, all that could be offered was antenatal determination of the sex of the fetus and abortion if it was male. There have been reports, however, of the ability to exclude the diagnosis of Duchenne muscular dystrophy by testing the blood of a male fetus for creatine phosphokinase activity. Two affected fetuses have been identified on this basis, and after abortion both were found to have histologic changes suggestive of the disease. Further research on creatine phosphokinase activity in the normal fetus is needed, as is perfection of fetal blood sampling techniques, before this test can be universally applied.

It is now also possible by means of fetal blood sampling, via either fetoscopy or placental aspiration, to diagnose β-thalassemia and sickle cell disease in utero. In our unit α-thalassemia has been diagnosed in one instance and β-thalassemia in four instances from fetal blood samples obtained by fetoscopy. In February 1978 the sickle cell branch of the United States National Heart, Lung, and Blood Institute sponsored a symposium in Los Angeles, where investigators from all over the world met to assess the current status of the antenatal diagnosis of hemoglobinopathies. At that time 470 cases had been studied throughout the world. Further progress in both fetal sampling and blood analysis is likely.

Finally, through direct fetal visualization by fetoscopy or ultrasonography some conditions may be diagnosed on the basis of a morphologic anomaly such as polydactyly or syndactyly. The Ellis-van Creveld syndrome, for example, has been diagnosed antenatally by Mahoney and Hobbins. In our unit right upper hemimelia, arthrogryposis multiplex congenitans and Laurence-Moon-Biedl syndrome have been excluded by fetoscopy, the last when normal digits were observed. It is likely that ultrasonography will be improved so that better fetal viewing by a non-invasive technique will enable limb anomalies as well as abnormalities of the brain, the heart and the kidneys to be diagnosed. Polycystic kidney disease has already been diagnosed by this means.
Amniocentesis for genetic diagnosis has proven to be a safe technique, and the fears expressed in the early part of this decade of serious maternal infection or hemorrhage have not been realized. Furthermore, the risk of abortion due to amniocentesis is apparently negligible in skilled hands when there has been ultrasonographic placental localization. However, even in the best centres, problems arise.

Technical difficulties may include failure to obtain amniotic fluid, the necessity for repeated ultrasonography, failure of amniotic fluid cells to grow and inability to view the fetus or to obtain a blood sample from it.

Problems with interpretation arise when there are conflicting data; for example, a high AFP concentration in the amniotic fluid but a normal fetal ultrasonogram. More sophisticated techniques are required to obviate these difficulties.

At present there is 3 weeks of anxious waiting for results of culture of amniotic fluid cells. Future work in this area is necessary.

Difficulties occur even in well organized units when too many patients must be seen and clinics can appear to be nothing more than “factories” processing people. More centres will be needed as the inevitable demand increases. Because amniocentesis has to be done after 15 weeks’ gestation and it may be 19 weeks before an answer is available, decisions must be made at a time when the mother definitely feels quickening; this can cause her many problems.

Prevention and treatment, not abortion, should be the aim of antenatal genetic diagnosis. We must make sure that research in these areas is not overlooked or neglected in our zeal to use the latest gadgets and techniques.

**Future developments**

**Organization**

There are various ways in which services for antenatal genetic diagnosis may be made available to the pregnant woman in the future. The solo doctor, armed with a copy of McKusick’s latest list of genetic disorders, may perform an amniocentesis in the office, send the fluid (preferably not blood-stained) to a private laboratory and deal with the outcome personally. No one of us, in my view, has sufficient training for this approach. One cannot be a good genetic counsellor, have the time to perform accurate and safe amniocenteses, do ultrasonography, be a good fetoscopy and have the time and the expertise to follow-up and counsel patients. However, many patients are now dealt with in this way.

In other centres geneticists and obstetricians work independently, communicating only occasionally, and then by letter. Without cooperation between these experts, patients receive less than optimal care because so many decisions must be made during counselling and its aftermath. The private family doctor as the primary care physician is in an excellent position to advise which patients would benefit from antenatal diagnosis. However, most have not had the requisite training, and as a result many feel uncomfortable. So it is to be hoped that multidisciplinary groups will be formed with increasing frequency to deal with the often complex problems that arise. In this way the best care should be provided in the future.

With the multidisciplinary approach a family is referred by the primary care physician to a central office. There the details of the family’s problem are recorded and reviewed, and data from other pregnancies, autopsies, other counselling services and so forth are collected by the clinic coordinator. This person holds the key to the team approach. In our unit a specially trained public health nurse/genetic counsellor fills this role. Although there are few such paragons now, there will probably be similarly trained personnel in most major centres in the future.

The family is then given an appointment with the clinic, where it receives genetic counselling based on all the available data; an obstetric evaluation is also done. A decision is made as to whether genetic testing is needed. If it is and the results are normal, the referring doctor is informed and looks after the patient in the future. A follow-up call is made to the physician after the expected date of delivery to check on the outcome of the pregnancy.

If the results of genetic testing are abnormal, however, they are discussed at a weekly interdisciplinary meeting where geneticists, ultrasonographers, technicians, cytogeneticists, biochemists, obstetricians and any other personnel involved with the family are present. The referring doctor is advised of the abnormality; if he or she decides, as many do, to let the team continue management, further counselling is given to the family. Their decision is followed by appropriate action, again coordinated by the nurse/counsellor. Termination of pregnancy, if this is deemed appropriate, is performed by members of the team; autopsy of the fetus is also carried out by a team member, a pathologist with special interest and training in this area. Counselling after such a disaster is undertaken by the geneticist who originally saw the family in the clinic. Our team members have found that, with this approach, patients appear to benefit from the expertise of the many disciplines involved.

Families referred for genetic counselling need an enormous amount of empathetic support and informed discussion. They need facts, not a pat on the head. A paternalistic approach is not what is required. The aim is to help families come to the right decision for them, and to try to make sure that they will be able to live with that decision.

If it is agreed that the team approach, as the most efficient and helpful way to provide antenatal genetic diagnosis, should be more widely used, the next point to be made is that this would be accompanied by an increase in workload for team members and for laboratory staff. Such an increase at one of our associate chromosome laboratories is shown in Fig. 1. Soon each group would find that there was a point beyond which resources were over-
strained, efficiency fell and the patients suffered. At that point, or preferably before, satellite groups would be formed in peripheral areas to provide the services locally, so that only complex problems would need to be dealt with centrally. This would involve a financial commitment from the state. Funds would be needed for material, staff and space for clinics, laboratories and the various departments involved and for communications. Efficient organization would also be needed to ensure that testing was accurate, safe and easily available. How society deals with these problems in the future will determine the effectiveness of genetic services.

Techniques

The main problem in the detection of chromosomal anomalies is the 3-week wait for amniotic fluid cells to grow. It is essential that this long culture time be reduced, but not at the expense of accuracy.

One way of speeding up the diagnosis of chromosome anomalies would be to use some form of computer analysis to recognize anomalies. It might be possible to identify specific chromosomes or parts of them by chemical testing. It might even be possible to study chemical reactions of uncultured cells rather than of the chromosomes; this too would shorten the time for diagnosis. Finally, methods for analysing chromosomes may be improved in the future so that chromosomes that look normal by present methods will prove to be abnormal. In this way more conditions will be diagnosable.

One problem that is likely to become increasingly common is the request by parents to have the sex of their fetus determined for no other reason than that they have had or want only children of a particular sex. Our group is adamantly opposed to the use of amniocentesis for this reason. It may be, however, that what is unacceptable in Canada will be accepted in other areas of the world.

More tests to detect biochemical disorders of the fetus will become available, so that diseases whose causative enzyme abnormalities are not yet known will be diagnosable in utero.

The use of single cell analysis of enzyme activity has been reported recently by Hosli. In this technique biochemical ultramicromethods needing only very small amounts of tissue and small amounts of chemicals are used, and the results are considered more accurate than those with conventional biochemical methods. Microchemistry is combined with cell cultivation, visual cell selection and cell isolation techniques. An alkaline phosphatase induction test has been developed that can screen single fetal cells either from amniotic fluid or from maternal blood to detect lysosomal storage diseases and numerically unbalanced chromosome disorders. The fact that fibroblast cultures from chromosomally abnormal patients show increased alkaline phosphatase activity when treated for 2 days with a solution of isoproterenol, ascorbic acid and theophylline could mean that a biochemical test for chromosome anomalies in a single cell will be available soon.

Glick has recently suggested the use of several microanalytic methods, of potential interest in laboratory medicine, for single cell analysis:

1. Dilatometry, in which enzyme assay is done by measuring the change in volume or density accompanying a chemical reaction in solution.
2. Spectrophotometry, which is used to measure oxygen uptake for the functional assay of cells.
3. Luminometry, in which the light emitted by excited molecules in chemical or biologic reactions is measured.

Galjaard and coworkers in Rotterdam have shown that single cell analysis may be feasible by microscale spectrophotometry and spectrofluorometry for the antenatal diagnosis of inherited enzyme deficiencies. They have already diagnosed 15 genetic metabolic diseases within 2 weeks after amniocentesis.

Another development that may aid the future diagnosis of certain conditions is the observation of Wyatt and Cox that fibroblasts from patients with Duchenne muscular dystrophy when cultured and studied by electron microscopy revealed characteristic inclusion bodies that distinguished them from normal cells.

It has also been possible to use molecular hybridization to make an antenatal diagnosis. In a pregnancy at risk for homozygous α-thalassemia Kan, Golbus and Dozy cultured fibroblasts from amniotic fluid, then measured the number of α-globin genes in the deoxyribonucleic acid (DNA) by hybridization with radioactive DNA complementary to α-globin sequences in messenger ribonucleic acid. It is likely that other diagnoses will be made by similar techniques in the future. The main advantage would be that one would be able to detect cellular products that were not usually produced by that cell. Hemoglobin, for example, could be produced by “turning on” globin genes in skin fibroblasts, so that amniocentesis would give the results that fetal blood sampling does now.

It is already possible to sort fetal cells in maternal blood by a complex cell sorter using a laser that analyses the fluorescent intensity of each cell.

Should it become feasible to identify and isolate fetal cells from the
maternal blood, a whole series of tests could be performed on those cells. This would herald the introduction of antenatal genetic screening of the general population for the major genetic disorders.

As yet what kind of fetal cells these are has not been determined, nor is it known whether they will grow and so produce a chromosomal karyotype or be useful for enzyme assay.

Given that it will be possible to diagnose many more enzyme deficiency diseases in the future, the next step is to try to treat them. Dean and colleagues\(^1\) transplanted skin from a sibling to a child with Hunter's syndrome, and found an increase in the recipient's production of the deficient enzyme (sulfol-L-iduronate sulfatase). It may be possible, then, to treat such a fetus in utero by transfusing it with compatible cells that will produce the necessary enzyme.

Ultrasoundography already plays a part in antenatal diagnosis, and with technical advances it will become more important. An ultrasonic B scan represents a cross-section of a single slice of tissue. The echoes from different interfaces appear on the screen as dots.

Methods of displaying the sonar echoes include the static scanner system. This uses a single transducer that is moved across the skin, producing a string of echoes until a complete cross-sectional picture is built up. The scan takes several seconds and has to be recorded on videotape or photographed since the visual image does not persist. Modern static machines produce pictures of fairly high quality, but measurement of fetal parts, for example, can be very difficult.

Therefore, it is likely that there will be developments in this field, such as a three-dimensional ultrasound scanner that would enable stereo images to be produced.\(^2\)

Another method of scanning is the real-time system. Here the B scan is generated with a linear array probe. This probe, which looks rather like a harmonica, has a number of separate elements, often about 64, that in sequence produce sound pulses. The strings of echoes displayed on a screen are perceived by the eye as a complete image with discernible movements.

Real-time systems are already very popular because the equipment is small enough and simple enough to use in antenatal clinics. At present, however, the poor quality of the picture and the difficulty of accurate measurement make further developments necessary. Grouping the transducers and focusing the ultrasonic beam to improve resolution may overcome some difficulties. It is likely that this noninvasive technique for intraterine fetal viewing will soon be so improved that it can be used to identify even small fetal structures, such as fingers, toes and genitalia. It may be feasible to visualize defects by this method before 16 weeks' gestation. It may even be possible to use ultrasound with computerized axial tomography, so that much more accurate information could be obtained.

It is to be hoped that a lot of time, energy and money is not expended in trying to detect fetal abnormalities that are not lethal or are often compatible with normal life. What will be done, for example, when cleft palate is readily diagnosable antenatally? Is there any point in making that sort of diagnosis? Or is there a case to be made for screening women who have had offspring with cleft palate to prepare them for the outcome of pregnancy?

Where progress is needed in ultrasonography is in the area of recognition of cardiac abnormalities, many of which are incompatible with life. Systems are already in use for cardiac imaging in the adult. Fetal cardiac lesions could then be diagnosed in the first half of pregnancy, as could renal agenesis and polycystic kidney disease. The diagnosis of urethral valve syndrome, with subsequent hydronephrosis and hydronephrosis, ought to be possible; early induction of labour could then allow perinatal surgical repair to be done before irreversible renal damage had taken place. Exomphalos, encephalocele and anencephaly have already been diagnosed antenatally by ultrasonography. It has even been suggested that ultrasonographic screening of all pregnancies be carried out at 16 weeks' gestation to exclude such gross abnormalities.\(^3\) The cost, however, is likely to be prohibitive, at least with present screening methods.

Yet another technique that is currently available and will play a greater part in the diagnosis of fetal anomalies is fetoscopy. Here a narrow-gauge telescope is inserted directly into the uterine cavity so that the fetus can be observed and samples taken of amnion, skin or blood from the fetal surface of the placenta. In our unit 17 completed pregnancies have been monitored by this technique. The instruments used are shown in Fig. 2.

Biopsy forceps can be inserted under visual guidance. Video recordings may be made by camera systems attached to the optic needle, so that permanent records of anatomic details can be reviewed later. The diameter of the needle currently used is 1.7 mm, and that of the cannula 2 mm. Smaller versions will undoubtedly be designed to reduce the risk of spontaneous abortion, which is now about 4% and is presumably related to the size of the needle.

Used in conjunction with real-time scanning, fetoscopy can delineate fetal parts, and with experience it is possible to achieve total visualization in a small proportion of cases. At 16 weeks' gestation, when the amniotic fluid is clear and the fetus relatively small, one can identify and photograph fetal hands (Fig. 3), toes (Fig. 4), mouth, genitalia, cord (Fig. 5) and placenta (Fig. 6).

With care, a small sample (0.5 to 1 mL) of fetal blood can be taken under visual guidance from the placenta, and it is occasionally possible to obtain pure fetal blood for analysis. Already 470 pregnancies throughout the world have been monitored for thalassemia major or sickle cell disease with the use of either this technique or "blind" placental aspiration.

The diagnosis of hemophilia will be made in future by studying factor VIII concentrations in fetal blood.
This was attempted in our unit in one case, but the sample of blood obtained contained both fetal and maternal blood and therefore was of no value for analysis. How to obtain a pure sample of fetal blood remains a problem.

The conditions that ought to be diagnosed once fetal blood samples have been obtained are listed in Table I. Increased public awareness of the diagnostic potential of fetal blood sampling through fetoscopy will inevitably cause increased demand. The availability of other types of specimens from the fetus, such as skin, nail, hair and muscle, should make the diagnosis of other conditions possible.

Developments in ultrasonographic techniques will probably make fetoscopy for fetal viewing obsolete, but, until it does, fetoscopy will be used to detect various phenotypic defects, especially those associated with more severe generalized abnormalities such as the Laurence-Moon-Biedl syndrome. We once used this procedure to resolve a difficulty in a case in which the AFP value in the amniotic fluid was raised and the sonogram of the fetal vertebrae was slightly abnormal. At fetoscopy a meningomyelocele was visualized and photographed (Figs. 7 and 8). The lesion was proven at autopsy.26

No account of the future of antenatal genetic diagnosis would be complete without passing reference to antenatal genetic screening. It is already possible to screen the nonpregnant population for genetic diseases such as sickle cell trait, sickle cell anemia, thalassemia and Tay-Sachs disease, but now that AFP concentrations in the mother’s serum can be
measured, a new era of antenatal diagnosis has been entered. It is likely that more disorders of the fetus will be diagnosable by maternal blood testing. Pilot studies to assess the feasibility of antenatal screening for particular conditions are essential. Tests will have to be sensitive, specific, safe, simple, accurate and not too expensive. They will also require quality control. But more than this is needed. Networks will have to be set up to provide the necessary genetic counselling to communicate results to all concerned and to follow up all cases. The screening procedures should be available to all persons in the community, not just those who can readily pay for testing. Antenatal genetic screening, however, must not be mandatory, because mandatory genetic counselling is a contradiction in terms.

Effects on society

The following pertinent questions require answers. Will antenatal diagnosis affect family composition? Will it affect how society or families treat the abnormal child? Will the state opt out of paying for the health care of those who have elected not to have antenatal testing or those who, in full knowledge of the presence of a severe abnormality, did not terminate the pregnancy? What should the priorities be for antenatal testing? Resources are finite, so money is important in these matters. Attempts to answer some of these questions have been made.25

The future impact of antenatal genetic diagnosis will be felt by the following:

1. Those who oppose abortion and will always oppose antenatal genetic diagnosis.

2. Women in whom the risk of antenatal testing may be physical, but will also involve psychologic stress.

3. Medical personnel whose fear of misdiagnosis will necessitate fail-safe systems for the collection and transmission of specimens. The legal hazards facing our profession may well increase; for example, the risk of inadvertently causing the death of a healthy fetus is real in any antenatal test. The risk of causing non-lethal damage to the fetus may also be present. There may also be legal risks of negligently failing to diagnose a defect in a fetus.

4. Those who would otherwise not have undergone testing and will be under pressure to do so.

5. Minority groups with high rates for carrying certain diseases, whose self-esteem may be affected.

There may need to be government regulation of the circumstances under which antenatal diagnosis may be carried out.

More studies are needed to try to answer the question, What does the community really want? What is at stake is control of ourselves and of the power of these new techniques. This control must lie in the hands of those who should benefit from it — the general population, not the scientists or the doctors. But the public will be able to make the appropriate decisions only if they are aware of the potential of antenatal genetic diagnosis. Therefore, the challenge for those who work in the field is to

Table I—Conditions potentially diagnosable by fetal blood testing

<table>
<thead>
<tr>
<th>Disease</th>
<th>Mode of inheritance</th>
<th>Method of detection</th>
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<tbody>
<tr>
<td>Hematologic</td>
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<tr>
<td>Erythrocytes</td>
<td>Autosomal recessive</td>
<td>Study of globin synthesis</td>
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<tr>
<td>Hemoglobinopathies</td>
<td>Autosomal recessive or X-linked</td>
<td>Enzyme assay</td>
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<tr>
<td>Enzyme deficiencies</td>
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<td></td>
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<tr>
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<td>Autosomal recessive</td>
<td>Granulocytes absent</td>
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<td>Agranulocytosis</td>
<td>X-linked</td>
<td>Nitroblue tetrazolium dye test</td>
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<td>Chronic granulomatous disease</td>
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<td>Characteristic granules</td>
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<td>Chédiak-Higashi disease</td>
<td>Autosomal recessive</td>
<td>Platelets absent</td>
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<tr>
<td>Platelets</td>
<td>Autosomal recessive</td>
<td>Platelets absent</td>
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<tr>
<td>Thrombocytopenia, with absent radii</td>
<td>X-linked</td>
<td>Decreased factor VIII or IX concentrations</td>
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<td>Wiskott-Aldrich syndrome</td>
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<td>Plasma</td>
<td>X-linked</td>
<td>Increased adenosine deaminase activity</td>
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<td>Hemophilias</td>
<td></td>
<td>Decreased uridopyrophosphoribonucleotide synthetase activity</td>
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<tr>
<td>Nonhematologic</td>
<td></td>
<td>Decreased heme synthetase activity</td>
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<td>Erythrocytes</td>
<td>Autosomal recessive</td>
<td>Study of membrane phosphorylation</td>
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<td>Severe combined immunodeficiency</td>
<td>Autosomal recessive</td>
<td>Lymphocytes absent</td>
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<td>Porphyria</td>
<td>X-linked</td>
<td>Study of creatine phosphokinase activity</td>
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<td>Protoporphyria</td>
<td>Variable</td>
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<td>Duchenne muscular dystrophy</td>
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<td>Leukocytes</td>
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<td>Muscular dystrophy</td>
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FIG. 7—Fetoscopy photograph of neural tube defect at 19 weeks' gestation.

FIG. 8—Diagrammatic explanation of photograph in Fig. 7. AF = amniotic fluid; M = meningomyelocele; FS = fetal skin over lumbar region.
educate not only the lay public but also all medical and paramedical personnel who are involved with the health care of families.

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INDICATIONS

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Dermovate should not be used in the eye. When used over extensive areas for pro-longed periods of time, systemic side-effects may occur. Systemic absorption may take place to give rise to systemic effects. If advisable, therefore, to use Dermovate for short periods, and to discontinue its use as soon as the lesion has cleared up. Do not use more than fifty grams of Dermovate per week. Patients should be advised to inform subsequent physicians of the prior use of corticosteroids.

PRECAUTIONS

Topical corticosteroids should be used with caution on lesions close to the eye. Posterior subcapsular cataracts have been reported following systemic use. Although hypersecretion reactions are rare with topically applied steroids, the drug should be discontinued and appropriate therapy initiated if there are signs of hyper-secretion. In cases of bacterial infections of the skin, appropriate antibacterial agents should be used as primary therapy. If it is considered necessary, the topical corticosteroid may be used as an adjunct to control inflammation, erythema and itching. If a symptomatic response is not noted within a few days to a week, the local application of corticosteroid should be discontinued until the infection is brought under control. Significant systemic absorption may occur when corticosteroids are applied over large areas of the body, especially under occlusive dressings. Because of the degree of absorption, clobetasol 17-propionate when used under occlusive dressing has not been measured, its use in this fashion is not recommended. Because the safety and effectiveness of Dermovate has been established in children, its use in children is recommended.

ADVERSE REACTIONS

Local burning, irritation, itching, skin atrophy, striae, change in pigmentation, secondary infection, hypertrichosis and adrenal suppression have been observed following topical corticosteroid therapy.

DOSAGE AND ADMINISTRATION

Dermovate Cream and Dermovate Ointment are applied thinly to cover the affected area, and gently rubbed into the skin. Frequency of application is two or three times daily, according to the severity of the condition. The total dose of Dermovate applied weekly should not exceed fifty grams. Therapy should be discontinued if no response is noted after a week or as soon as the lesion heals. It is advisable to use Dermovate for brief periods only. Note: If maintenance therapy is required, a lower strength topical steroid, such as Betnovate, is indicated.

DOSAGE FORMS

Dermovate Cream and Dermovate Ointment are available in 15 and 60 g tubes, and in 100 g jars. Product monograph available on request.