Middle Articles

CONTEMPORARY THEMES

Families Referred for Genetic Advice

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There has been an increasing demand for genetic and cytological investigations in recent years, and many patients are being referred to newly established university departments of human genetics. Little has been published in this country on genetics clinics, and it was thought that an account of the experience of the staff at this unit would be of some interest.

Each year several thousand patients are seen by the staff of this unit in the course of *ad hoc* studies. However, in addition, about 200 families are referred for genetic consultation to the unit or to one of the five clinics held in the hospitals of the Oxford Regional Hospital Board. These clinics were started on average about five years ago and patients are seen mainly at the request of the consultant medical staff, but some are referred direct by the general practitioners, or by the medical officers of the local health authority departments.

By the end of September 1966 a total of 1,064 families had been referred for genetic investigation or advice. This number does not include those patients who were seen at the clinics but who had been ascertained in the course of specific studies. Table I lists the conditions which determined referrals of these families. The reasons for referral are shown in Table II, and Table III sets out by whom the families had been referred.

Types of Conditions Determining Referral of Families

Single gene traits were segregating in a quarter of the families—279 in all—as is shown in category A of Table I. Relatively few families with muscle disorders or blood-coagulation defects were seen at the clinics, as a majority of cases in the area had already been seen in course of special investigations.

The anomalies listed in category B represent a very heterogeneous group and some recessive gene traits are probably included in the group of "syndromes," but as these have not been fully differentiated this aetiology cannot be ascribed with certainty.

Category C includes the families, where a grossly malformed child had been stillborn or died shortly after birth, who were referred for genetic advice. The children with cleft palate, or with harelip with or without cleft palate, were mainly living, and this group of cases included some of the syndromes associated with lip and palate defects. The small number of cases of congenital heart disease is due partly to the relatively low familial incidence, and partly to the frequent association of congenital heart disease with other malformations, and many with cardiac malformations have been included in the group of multiple malformations or in category E, which contains the chromosomal anomalies.

Recurring abortions and moles have been subjects of special study in this unit, but only 19 families (category D) which had not previously been investigated were referred.

Category E, showing those families where one member at least had a chromosomal abnormality, is dominated by mongolism. Except for confirmation of the diagnosis, cytological studies are seldom carried out in families where the mother of a mongol child is over 30 years of age. All these families were seen when the condition was first diagnosed or suspected, and a series of 44 cases from a mental deficiency institution who were also investigated have been excluded from this report. It is perhaps of interest to note that of 20 children in whom the clinical diagnosis was in doubt 12 were found to have normal karyotypes. Even with the aid of dermatoglyphics clinical diagnosis of mongolism in young babies can be extremely difficult in a minority of cases. About 200 other index cases were referred as having a suspected autosomal anomaly as well as some congenital defect, but were found to have normal chromosomes and are included in the preceding categories.

Altogether 139 patients were referred as having a suspected sex chromosome abnormality, but of these only 35 were found to have some anomaly of one of the sex chromosomes (categories E and F). Sixty-six women with primary amenorrhoea or other menstrual irregularity were referred, and 14 of these were found to have clinical and cytological features typical of Turner's syndrome.

The final category, G, contains those families referred for miscellaneous reasons, and is of interest only to show the variety of conditions for which genetic advice may be sought.

Reasons for Referral of Cases

It is not easy to classify the reasons why many of the families were referred. In many instances it was because of a family history of a disorder which had aroused the interest of the doctor referring the case, but we have always stressed that we should be interested to see any patients with congenital or hereditary disease, even if the patient was the only one in the family affected and the condition was not rare or of serious consequence to the subject. As will be seen from Table II, more than one-third of the patients were referred primarily for cytological diagnosis and a further 300 families were seen for estimation of risks to subsequent conceptions that may or may not have required cytological investigations.

Source of Referrals

Not unexpectedly, nearly half of all the families seen were referred by paediatricians for either cytological diagnosis or genetic advice (Table III). The majority were those in Table I, categories A, B, C, and E, while gynaecologists referred all those

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in category D and most of those women suspected of having a sex chromosome anomaly.

Discussion

It is agreed by the medical staff of this unit that seeing patients and their families is both interesting and useful. It keeps us in touch with our colleagues in hospital or general practice and enables us, by helping them a little, to repay some of the debt which we owe to them for constantly assisting us to ascertain cases of various conditions which are essential for our systematic population studies. Many families have proved

to be of considerable interest and have either led to intensive study and publication of the findings or been the starting-point for population and mutation frequency studies.

In many families biochemical and serological investigations beyond the range of a routine laboratory service are required, and the co-operation of specialized centres in Oxford and elsewhere has to be enlisted. No one department of human genetics could ever be large enough to undertake all the types of investigation required for hereditary disorders which occur in every system and in every immunological and metabolic process in the body.

There is no doubt that the demand for cytological investigations and advice to patients concerning the implications of hereditary disease for themselves and their future offspring is increasing. The majority of cases currently referred come from a minority of the doctors practising in each branch of medicine, but in our experience when the facilities become known and cases have been referred from one source more cases follow. In the last 12 months almost 300 families have been referred.

TABLE I.—Conditions Determining Referrals of 1,064 Families

Groups of Conditions	No. of Families
A. Single gene traits	279
Inborn errors of metabolism	40
Connective-tissue defects	20
General skeletal defects	32
Local	7
Disorders of muscle	26
Traits mainly affecting the skin and its appendages	50
Disorders of development of teeth	6
Traits affecting the eyes	45
Traits affecting the central nervous system	17
Blood dyscrasias	5
Blood-coagulation defects	15
Miscellaneous and generalized syndromes	10
Testicular feminization	6
B. Anomalies where the nature of the genetical contribution is less clear	180
Eye conditions	14
Anomalies of skin, hair, or teeth	30
Mental illness	14
„ defect	42
Deafness	7
Familial malignant tumours	6
Epilepsy	4
Allergies	5
Syndromes (probably many due to single genes)	43
Miscellaneous disorders	15
C. Gross morphological congenital malformations	222
Malformations affecting mainly:	
The skeletal system	26
The urogenital system	4
The gastrointestinal tract	9
Lip and palate	26
Cardiovascular system	19
Central nervous system (mostly neural tube defects)	74
Many systems—multiple malformations	64
D. Recurring abortions, hydatidiform moles, etc.	19
E. Chromosomal abnormalities	204
(a) Autosomal anomalies:	
Down's syndrome* (4 mosaics, normal/trisomy 21, 2 D/G translocates, 1 G/G translocate)	156
Trisomy E (6 trisomy E, 1 mosaic trisomy E/normal)	7
Deletion of short arm of chromosome No. 5 "Cri-du-Chat" syndrome	1
C group trisomy	1
A/C translocate	2
Other definitely abnormal karyotypes difficult to classify	3
(b) Sex chromosome anomalies:	
Phenotypic females:	
Turner's syndrome (12 XO, 6 mosaics XO/XX, 1 mosaic XO/XY, 1 X-isochromosome X)	20
XXX, XXXX, and mosaic XX/XXX	3
Mosaic XO/XY/XXXY	1
Mosaic XX/XY	1
Phenotypic males:	
Klinefelter's syndrome (3 XXY, 1 mosaic XY/XXY)	4
XXXXY	1
Mosaic XX/XXY/XXYY	1
XXYY (both of a pair of identical twins)	1
XYY	2
F. Abnormalities of sexual development with normal chromosome complement	105
"Male pseudohermaphroditism"	6
"Female pseudohermaphroditism" (excluding 6 families with XY chromosome females classifiable as testicular feminization and included in A.)	5
Hypospadias	7
Males with hypogonadism, azoospermia, or oligospermia	27
Primary amenorrhoea or menstrual irregularity	52
Malformations of internal genitalia in females	8
G. Miscellaneous	55
Consanguineous marriages	11
Offspring of incestuous unions	4
Children being adopted, assessments of unfavourable family histories	6
Assessment for proposed sterilizations, etc.	18
Drug sensitivities	3
Zygosity of twins (mostly discordant for an anomaly)	7
Assessment for parental radiation exposures where one parent had been treated with cytotoxic drugs	4

* In a majority of cases (92) the children tested had trisomy 21. In others the child was dead and only one or both parents' cells were examined and found to be normal, but the clinical diagnosis of mongolism was unequivocal and the children are presumed to have been trisomy 21.

TABLE II.—Reasons Why Families Were Referred for Advice

Reasons for Referral	No. of Families
As unusual and interesting cases	274
For estimation of risks to subsequent conceptions	319
Primarily for cytological diagnosis	402
„ „ other investigations	69
Total	1,064

TABLE III.—Doctors Who Referred Cases

Referrals by	No. of Families
Paediatricians	458
Obstetricians and gynaecologists	189
Consultants in other specialties	279
General practitioners	94
Local authority staff	44
Total	1,064

As is well known, risk estimation may be very simple or it may be extremely difficult. The necessary prerequisites are as accurate a clinical diagnosis as possible and as precise a definition as can be made of the genetic mechanisms involved. The main problems arise because conditions not differentiable clinically can have diverse environmental and genetical determinants, and because the genetic contribution to the commoner conditions with familial concentration of cases is usually complex and ill-understood. It follows that only in a minority of cases can risk estimates be calculated from simple Mendelian segregation ratios, while the majority have to be empirical, based on our own accumulated experience or published data.

Where the risk estimates are straightforward, as in most instances where clear-cut single gene trait problems are involved, it is most satisfactory for the paediatrician or other clinicians to advise. However, paediatricians or others may not have the time or the facilities for the assembly of accurate information about families. On the whole, in the more difficult cases, clinicians seem to arrive at more pessimistic estimates than ourselves, though in a few cases risks considered low by those referring cases have seemed very much higher to us. We prefer to ask the referring specialist or the family doctor to explain risks to patients, but we are often asked to do this ourselves, but are not always successful. The parents of a child with Werdnig-Hoffmann's disease were seen on four occasions, and it was explained to them that if they had another baby there was a one-in-four chance that it would be affected. About a year later they brought a fine healthy baby to see us and told us triumphantly that, as we could see, we had been wrong.

The amount of work involved in assembling the information on which adequate advice can be based varies greatly in different families. It may involve extensive family visiting by a medical or a nursing-staff member, examinations of several relatives, and writing for copies of clinical and necropsy notes to different hospitals.

The problem of meeting demands for chromosomal investigations in this country is becoming increasingly acute. Almost

all the facilities for investigations are provided in university departments, teaching hospitals, or research units, but the demand cannot continue to be met unless arrangements are made for such examinations as part of routine hospital laboratory services. At present we try to limit the families accepted for cytological diagnosis to about three per week, as otherwise the entire work of this laboratory would be occupied with so-called "routine" cases. There is little doubt that if the service was fully available there would be over 1,000 referrals per year.

Down's syndrome probably occurs in about one in 500 live births, and the requests for chromosomal investigations are very numerous. Here, as elsewhere, it is impracticable to meet requirements for investigation of all families, but priority is given to those where the mother is young or the affected child is the first-born and another is wanted. This is because the frequency of the translocate carrier state is higher in the younger than in the older mothers of children with Down's syndrome, and it is in these translocate parents or in those who are mosaic for a 47-chromosome cell line that the risk to subsequent conceptions is so high. Though the majority of mothers examined were under 30 years of age only one mosaic mother and two who were balanced translocates have been found in families investigated.

Chromosomal investigations of intersex states, infertility, and amenorrhoea are always justifiable, as they may provide a definitive explanation of the clinical situation and help in determining how far treatment should be pursued. At present, at

least, almost all other investigations are of value to patients and their families only in so far as the presence or absence of transmitted chromosomal abnormalities can be established. In short, we are faced with an ever-recurring problem in medicine, where expensive and time-consuming investigations should be undertaken in many patients, even though the majority of the findings will be negative, as the exclusion of high risks of transmission of abnormalities is important to all and the identification of a high risk extremely important to the few.

Summary

An account is given of the conditions for which 1,064 families have been referred to genetic clinics, by whom they were referred, and the main reasons why advice was sought. It is noted that, in Oxford as elsewhere, the problem of complying with requests for chromosomal studies cannot at present be met. In the text and tables some indication is given of the proportions of those presenting members of families suspected of having various types of chromosomal anomalies who proved to have abnormal karyotypes.

It is emphasized that to arrive at adequate risk estimations is often difficult, and that the facilities required, the amount of work involved, and the necessary experience are often considerable.

We are indebted to our colleagues for their permission to include families seen by them in their series.

CONFERENCES AND MEETINGS

International Congress of Clinical Pathology

[FROM A SPECIAL CORRESPONDENT]

The Sixth International Congress of Clinical Pathology was held in Rome between 3 and 8 October.

In a discussion on antibiotic therapy the importance of the site of infection was stressed by Professor Y. A. CHABBERT (Paris). He pointed out that simple antibiotic sensitivity testing was inadequate in the assessment of the choice of antibiotic. The site of infection was equally important—for example, in cholecystitis the antibiotic was expected to act under special conditions, which could well alter the pharmacology of the drug. Furthermore, the distribution of antibiotic in an abscess was very irregular and might be greater in the centre than in the periphery. In the tonsil the concentration as a whole was about one-tenth of the blood level, but tonsillar fragments showed as little as one-twentieth or one-thirtieth of blood levels. The concentration of antibiotic in heart valves rarely reached one-third of blood levels, but this was achieved even in calcified valves. Sometimes, too, lymph and lymph nodes showed higher levels than blood. Finally, he stressed that speed in the removal of bacteria from the tissue was the most important factor in the effectiveness of any antibiotic. He described the newer techniques for the assessment of the latter by the use of labelled antibiotics—which had been employed for some time—and the use of autoradiography for determining sites of concentration of antibiotics.

Discussing the newer antibiotics, Professor E. P. ABRAHAM (Oxford) pointed out that, though antibiotics with widely different structures were known, since 1956 there had only been variations on the known structures—either obtained from new strains of bacteria or by chemical modifications. Nevertheless, the development of bacterial resistance was a continual stimulus to developing new antibiotics. More specifically, the resistant staphylococci showed that the production of β -lactamase was responsible for the resistance of some strains to methicillin and cephalosporin; the relative importance of this β -lactamase production, compared with the inherent resistance of the cells to these antibiotics, was not clear. Occasionally a combination of antibiotics was essential, some having high affinity for this enzyme while others being readily hydrolysed by it. Knowledge of the behaviour of staphylococcal β -lactamase did not help in the understanding of other bacterial β -lactamases, as they might behave differently.

Professor G. GIUNCHI (Perugia) advocated single-disc testing to assess minimum bacteriostatic and bactericidal activity. He said that, though an antibiogram was used, the clinical assessment of the patient was paramount and could be very different. He advocated high-dosage therapy, and used as much as 2 billion units of penicillin intravenously. He recommended continuous penicillin therapy combined with other antibiotics, and recalled the gradual increase in dosage

needed to treat meningococcal and gonococcal infections successfully.

Plasma-cell Dyscrasias

Dr. E. F. OSSERMAN (New York) preferred the term "plasma-cell dyscrasias" to dysproteinemia. He described a very wide range of possibilities when plasma cells proliferated, from the malignant proliferation in multiple myeloma to the benign forms, which perhaps were recognized only by the presence of a gammaglobulin abnormality. Plasma cells could be elaborated as immunologically competent cells, or cells which were recognizable as plasma cells in the absence of antigenic stimuli. The four major classes of immunoglobulins so far recognized were designated as γ G (7S), γ A (7S and 9S), γ D (7S), and γ M (19S), and they all contained a number of structurally and functionally specific molecules with a wide range of electrophoretic mobilities. The molecular weights of the first three groups were all 160,000, while γ M had a molecular weight of about 1 million, and all these molecules were synthesized by special clones of plasma cells. The clinical pattern of abnormalities of gammaglobulin synthesis could be recognized as overt multiple myeloma, primary amyloidosis, heavy-chain disease, and Waldenström's macroglobulinaemia. The clinically occult pattern included the other plasma-cell dyscrasias (though some of these might