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GENETIC PROGNOSIS*

BY

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It is a great honour to be invited to give the Charles West Lecture, and to follow so many distinguished predecessors. The lecture perpetuates the memory of one of the outstanding, perhaps the most outstanding, of the founding fathers of paediatrics. An American, Garrison (1923), writing in a chapter on the history of paediatrics, has this to say: "The greatest English paediatricist of his time, and perhaps the most genial practitioner of the art who ever lived, was Charles West, of London." I trust that that benign spirit would have approved of the subject of this lecture. I think he would, for no aspect of child health and child care was foreign to that fine intelligence.

The essential theoretical basis which makes a rational consideration of genetic prognosis possible did not exist in the lifetime of Charles West, but there is another and very obvious reason why the subject appears to us to-day to possess a relative importance it could not have had until fairly recent times. This is because there were still many other and easier fields to conquer, fields in which rapid, indeed dramatic, advances in prevention and therapy were still possible. During his long lifetime of 81 years West saw great and rewarding progress. But even when he died, in 1898, there was still great scope for advances on traditional lines. To take one important measurement, the infant mortality rate in England and Wales for the quinquennium 1901-5 was still 138 per 1,000 live births (Martin, 1949). During the past 60 years there has been a steady and smooth decline, though necessarily at a decreasing pace. The rate to-day is little over 20 per 1,000 live births.

Two causes of death, however, have not shared in this improvement. One is deaths attributed to injury at birth, a subject outside the scope of this lecture; the other is deaths attributed to congenital malformation. Deaths attributed to this later cause have fluctuated in successive quinquennia during this century, and without any definite trend, between 4 and 6 per 1,000 births, the average being a little less than 5. So, when West died, less than 1 infant death in 30 was due to this cause; to-day it is one in five. This hard core is still with us, assuming an ever-growing relative importance, and notably refractory to prevention, and indeed to treatment, though with some important exceptions.

Congenital malformations are sometimes, though not very often, wholly genetic. Much more often they are partly genetic. A comparison which comes nearer to an assessment of genetic causation has been made by my colleague Dr. Cedric Carter (1956), who classified causes of death among children coming to necropsy at

the Hospital for Sick Children, Great Ormond Street. Table I singles out two years for comparison, 1914 and 1954. In 1914 environmentally determined conditions accounted for two-thirds of all deaths, the main causes being tuberculosis, intestinal infections, and pneumonias. By 1954 the proportion had fallen to one-seventh. In the Table the conditions classified as of unknown origin include certain congenital malformations and the cancers

TABLE I.—*Causes of Death at the Hospital for Sick Children, Great Ormond Street*

Year	Environmental	Unknown	Partly Genetic	Wholly Genetic
1914	68%	15½%	14½%	2%
1954	14½%	48%	25½%	12%

of childhood. The partly genetic group includes such conditions as harelip and cleft-palate, congenital pyloric stenosis, and spina bifida.

One excellent comparison in terms of morbidity has been made by Sorsby (1950). A survey of the causes of blindness in schoolchildren had been made by the Board of Education in 1922. Sorsby carried out a similar survey a quarter of a century later. During the interval the total rate had been halved; but blindness attributed to congenital and hereditary anomalies showed no reduction. Hence, whereas in 1922 37% of blindness in the school population was attributed to these causes the proportion had risen to 68% in 1950. Sorsby makes the pertinent point that in terms of total years of blindness the contribution of congenital and hereditary anomalies is much more marked still. No doubt in many other fields the trend in relative frequencies of morbidity would show the same pattern.

So I think we can feel sure that were he alive to-day Charles West would have fully appreciated the importance of the genetic contribution to childhood disease as we now see it. I like to think that he would have said the same thing as my friend Professor Moncrieff when it was proposed in 1946 that a clinic for genetic advice should be set up at Great Ormond Street—namely, that paediatrics embraces the welfare of the unborn child, and, furthermore, the welfare of the prospective child.

Advice to Potential Parents

Genetic prognosis implies an interest in prevention: and how different are the roles of the agencies concerned if we contrast this with prevention in relation to, say, infectious disease. With infectious diseases the main agents of prevention are the medical officer of health, the sanitary engineer, and all those social agencies which

*The Charles West Lecture delivered to the Royal College of Physicians of London on November 28, 1961.

improve the conditions of life. It is true that the co-operation of patients and parents is needed, but they are small even if essential cogs in the machine. In the prevention of genetic disease the sole effective agents are potential parents. True, they can be helped with advice, but the choice is theirs, for I am sure that nearly everyone would agree, and it is certainly my view, that no one has the right to dictate to individuals what children they should have. They may be informed about possible risks, but the choice is theirs alone. Some potential parents, knowing there is a serious risk of a child being abnormal, would doubtless refrain from parenthood, or further parenthood. This might to some extent lessen the burden of genetic disease. My view, however, is that the provision of genetic advice is a service to individuals, though incidentally, as in other spheres, some contribution is automatically made to the well-being of the community as a whole.

I do not want, however, to stress the negative side of genetic advice to patients. It is possible that more harm is done by unfounded fears, that the damage done by having deformed children is outweighed by the damage done through abandoning the hope of parenthood, or further parenthood, when in truth the risk of abnormality in the child is very small or, it may be, for practical purposes negligible.

The proportion of the population which really needs genetic advice is not large. In the great majority of instances the query arises when a defective child has been born and the parents are anxious to know the risk of recurrence in further children. I think we might take the proportion of such births as about one in 40; then with additions and deductions which may perhaps more or less balance each other we get an estimate of about 3,000 potential inquiries a year in Greater London, or about 200 in a city of the size of Bristol. Putting it in another way, the number in the average family practice is rather more than one a year.

Those who do need genetic advice, however, often need it badly. The problems are serious; deep-seated feelings are involved; the choice may be very difficult—whether to have a further child, whether to accept a lifelong deprivation, whether to adopt a child. It seems to me that it is a clear medical duty to provide information about the risks to the extent that knowledge is available. It is not a question of doctor's advice or nothing. If medical advice is not forthcoming, or if the answers are evasive, the parents will get plenty from well-meaning or not so well-meaning sources, and nearly all of it very ill-informed. The whole subject of the welfare of the unborn child or the future child has always gathered around it a rich store of superstitions and old wives' tales, often of a highly alarming and gloomy character. On the other hand, there is a large and growing body of scientific knowledge. Sometimes the risks of malformation in a subsequent child can be specified precisely; sometimes a useful estimate can be made. Often, though the genetics are obscure, in fact because they are obscure, the empirical risk of recurrence is known to be small and of an order which most couples would consider it reasonable to run. In any event, even if the estimate is not very securely based, it is better than nothing, and much better than the old wives' tales.

Since the war I have been associated with a clinic for genetic advice to patients at Great Ormond Street Hospital, and for a rather shorter period with a similar clinic at the Bristol Children's Hospital. The first

figures I want to mention relate to the clinic at Bristol. The records were analysed by my former colleague, Dr. Oppé, and relate to 105 cases (Oppé, 1960). In 16 instances the parents had not asked for genetic advice. They came because of interest on the part of doctors, or sometimes because of their own interest, or because it was thought we would be interested. This leaves 89 cases in which genetic advice was sought. Of the 89 no fewer than 78, or 88%, were couples who had had an abnormal child and wanted to know the risk of recurrence should they have further children. There were only four instances of inquiries before marriage and two from married couples who had not yet had a child. Five queries related to whether normal children might transmit an abnormality when the time came for marriage and children. It is likely that these figures represent quite well the queries likely to come to a genetic clinic when facilities are available, and generally known to be available, for steps had been taken to advise the specialists and family doctors in the area that the clinic was being set up.

Nearly all the inquiries refer to couples who have had an abnormal child. This is as it should be. Usually it is only the birth of an abnormal child which shows that a special risk may exist. Routine premarital genetic counselling could seldom serve a useful purpose. In the great majority of instances there is no indication of anything amiss until an affected child is born. Nor, I think, is it wise to encourage doubts about other conditions in the family group which may have some genetic basis. Few families are free of such things. It may be asthma, or hypertension, or gout, or ischaemic heart disease. If it is not one it will be another; and surely it is better that couples should just go ahead.

Simply Inherited Conditions

Table II shows a breakdown of the 89 cases in which patients had sought genetic advice. It will be seen that more than half are simply inherited conditions. The dominant cases included such conditions as Huntington's

TABLE II.—*Breakdown of 89 References to the Genetic Clinic*

	No.	%
Simply inherited conditions (dominant, 16; recessive, 18; sex-linked, 12)	46	52
Partly genetic conditions	33	37
Conditions thought to be non-genetic	10	11

chorea, craniofacial dysostosis, muscular dystrophy of the peroneal and facio-scapulo-humeral type, and achondroplasia. The recessive cases included fibrocystic disease of the pancreas, Werdnig-Hoffmann's disease, phenylketonuria, and gargoylism. Most of the sex-linked cases were haemophilia, Christmas disease, or muscular dystrophy of the Duchenne type.

In the group of simply inherited disorders inheritance, as we know from previous studies, is either uncomplicated or with a minimum of complication. The risks are in general bad: one in two for any child of a parent suffering from a dominant defect; one in four for any further child of a couple who have had a child suffering from a recessive defect; one in two that a further child of a couple who have had a child with haemophilia will be affected if a boy, or a carrier if a girl; or one in four for the sister of such a boy. Evidence of a recent mutation may transform the outlook with dominant defects, but does not greatly improve the chances with sex-linked defects. Recent mutation is irrelevant with recessive conditions. It is just as well that with these bad risks the observer usually knows just where he is and can give exact chances.

Partly Genetic Conditions

The partly inherited cases include such conditions as the major malformations of the central nervous system, low-grade mental deficiency of no particular type, harelip and cleft palate, and epilepsy. In this group the outlook for further children is in general good. The risk of recurrence for subsequent children following the birth of a child with anencephaly or spina bifida is about 1 in 25; it is about the same when a normal couple have had a child with harelip. It is perhaps about 1 in 30 after the birth of a child with low-grade mental deficiency of the ordinary undifferentiated type. It is probably not more than 1 in 40 for epilepsy, provided it is not an instance of the rare kind of family in which major epilepsy of late onset behaves as though determined by a more or less regularly transmitted dominant gene. The risk of recurrence of congenital heart disease is also very low. The cause of mongolism has now been elucidated—a trisomy of chromosome 21. This is, of course, a genetic mechanism, but, barring a translocation, the risk of recurrence is very low—in fact, little if at all greater than for any other woman of the same age. In the light of present knowledge it would seem that translocation, carrying high risks of recurrence, is a very rare occurrence in the fairly elderly mothers of mongols, but may be not very infrequent in the young mothers. Chromosome studies should soon provide more precise data and will show to what extent routine chromosome counts are needed for separating the much less frequent high risk from the ordinary very low risk.

Sometimes, though not often, the risk is bad in this group also. For example, after the birth of two children with a major central nervous defect the risk of recurrence, according to the results of a survey we have carried out, is about one in seven. If parent and child have harelip the risk for a subsequent child is about 1 in 10. With central cleft palate the risk following the birth of an affected child is good if there is no similarly affected relative; but if there is an affected relative the risk is about one in eight.

The risk that any random pregnancy will end with some serious congenital malformation or other, or that some serious error of development will manifest itself in early life, is probably of the order of 1 in 40. This gives us, and our patients too, I think, a yardstick against which to measure the risk of recurrence of a particular condition. If a risk exceeds 1 in 10 then I think we can call it a bad risk; and probably most prospective parents would agree. If, on the other hand, the particular risk does not exceed, say, 1 in 20, we may call it a relatively good risk. Now it seems to be a fact that the great majority of risks do group themselves into these two regions, either higher than 1 in 10, or not greater than 1 in 20. It is rarely that our estimates lead to a figure in the intermediate region. This is fortunate, I think, from the point of view of the inquirers.

The cases seen at Bristol run at about 40 a year, or, adopting the figure we started with, perhaps one reference out of five potential inquiries. This seems reasonable. Some parents will not seek or want advice. Others will already have been reassured by the family doctor or the specialist. Reverting to Table II, the proportion of simply inherited conditions carrying the bad risks is very high, for, of course, partly inherited conditions are much more numerous. It would seem

that a high proportion of the simply inherited defects are reaching the clinic, but only a minority of the others.

This raises the point of who should give genetic advice. It may be the family doctor, or the specialist, or reference can be made to a genetic clinic. Doubtless as time goes on and a knowledge of genetics becomes more widely disseminated the proportion of cases referred to the clinic will decline. Increasingly, the family doctor and the specialist will give the advice themselves.

A Statement of Odds

At a genetic clinic advice is given in terms of odds. It is no part of the task to advise parents whether or not to have children. This presupposes that patients understand the meaning of chances and odds. My experience is that they do. We have something to thank racing and the football pools for here. Not infrequently one hears the remark: "Well, we know the chances now and it's up to us to go home and think about it." Of course, the family doctor can go a good deal further. Knowing the couple and the family circumstances, he can take into account factors other than the purely genetic, and may indeed give valuable additional guidance in helping the couple to come to a decision.

But even during a single interview at a genetic clinic it quickly becomes obvious that psychological considerations are of the first importance. Professor Kallmann, of Columbia University, told me recently that he regards giving genetic advice as the first step in a course of psychotherapy. He, of course, deals predominantly with mental disease, a field in which I have practically no experience; it must, I think, be left to the psychiatrists. But even with conditions other than mental diseases psychological factors are of prime importance, and one's hope is that quite an amount of help may be given even in a single interview. Feelings of guilt, overt or hidden, are common. The parents of a deformed child often feel a sense of loneliness and apartness. Why should this thing have happened to them when relatives and friends have numbers of normal children? Did something go wrong during pregnancy? Was some precaution omitted? Is it the husband or wife who is to blame? Or is it one side of the family or the other?

Some of the genetic and other points may be illustrated by considering in some little detail the couple who have had one or more children suffering from a recessively determined defect, say fibrocystic disease of the pancreas or Werdnig-Hoffmann's disease. The genetics are known and simple. The chance that any subsequent child will be similarly affected is one in four, a risk that most couples are disinclined to face. Some persevere, however. One couple had a child suffering from Werdnig-Hoffmann's disease and were told the risk of recurrence. Nevertheless they decided to go ahead, but their second child too was affected. Again they attended the clinic and were told the odds were still the same. However, they still persevered, though they were simultaneously put in touch with an adoption agency. Unfortunately the one-in-four chance came up yet again, and they adopted a baby. In a somewhat similar instance, also of Werdnig-Hoffmann's disease, the outcome was happier. A couple had had a normal child, followed by three affected children. They were told the chances, but with great courage they decided to make one more attempt to provide their first boy

with a much-longed-for brother or sister. Fortunately this child was normal. For most couples, however, the risk seems too formidable to contemplate.

There is much more to add, however, to this simple statement of odds. It can be explained to the couple that they are in no way peculiar or different from other people; how we all of us, without exception, carry at least one, and probably more, seriously harmful recessive genes. Actually, the usual estimate is about three to eight such genes per person, or their equivalents. Most of us, however, have the luck to marry someone who carries not our own brands of harmful gene but others instead. Thus the harmful genes cannot come together in double dose, so producing the abnormality. Furthermore, even if the couple do chance to carry the same harmful gene, the one-in-four chance will often not come up.

Carriers of Recessive Gene

Table III shows the proportion of families of different sizes which will include normal children only, even though the parents are heterozygous for the same gene. There must be many of us who did in fact share the

TABLE III.—*Proportion of Matings of Two Carriers of a Recessive Gene Which Will Yield Normal Children Only*

Size of Family	Proportion	Percentage
1	$\frac{3}{4}$	75
2	$\frac{9}{16}$	56
3	$\frac{27}{64}$	42
4	$\frac{81}{256}$	32
5	$\frac{243}{1,024}$	24
n	$(\frac{3}{4})^n$	

same harmful gene with our wife, or husband, but have had only normal children, and can never know the peril we so narrowly escaped. Among those who are unlucky there are of course degrees of bad luck. The luckier couples are those who have had one, or two, or more normal children before the birth of the affected one. They already have normal children, for whom nothing is to be feared. The very unlucky couples are those who have had a first child who is affected, or perhaps a first and second, and who then dare not take the chance their rather luckier counterparts have successfully taken before knowing the risk was there. It is just sheer bad luck that the couple happened to carry the same gene and that the one-in-four chance came up. Then the point can be made that the harmful gene comes from both sides, for it is clear that family arguments are apt to go on: another disturbing circumstance for the couple.

Of course, should the parents chance to be blood relatives a little more must be said, for they are very likely to wonder whether this had anything to do with it. Here it can be explained that the cousin marriage did somewhat increase the risk of a recessive defect turning up; but in the absence of any indication in the family history—and there practically never is—it does not seem in retrospect a foolish risk to have run. Before the event it was a relatively small risk—smaller, for example, than the risk of haemolytic disease of the newborn in the marriage of a rhesus-positive man to a rhesus-negative woman, which is one marriage in seven in our population.

One of the most important considerations with recessive defects is reassurance about normal children and other normal relatives. Couples are often concerned about the chances of marriage and parenthood for their

normal children, even though they may still be very young. It can be explained that, though they have a chance to carry the gene, we all carry some harmful genes or other, and provided they do not marry a blood relative there is a very small chance of marrying someone carrying the very same gene. They have in fact nothing at all to worry about. The same thing can be said for the brothers and sisters of the husband and wife.

It might be added here that the same argument applies to the person suffering from a recessive condition provided, as with, say, retinitis pigmentosa, it is compatible with life and reproduction. There is no genetic reason why such people should not marry and have children if they want to. Provided they do not marry a blood relative the chance of marrying a carrier is remote and the likelihood of having a similarly affected child is much less than the general random risk of a deformed child of one kind or another which is inescapable in any pregnancy.

I will not go into any detail about genetic advice in respect of conditions inherited in other ways or in which there is merely some indication of partial genetic causation, but for which approximate empirical chances have been reasonably established. Nor will I mention the complications due, for example, to alternative modes of inheritance or non-inheritance. I have attempted elsewhere to cover these more detailed and technical aspects (Roberts, 1959). Genetic prognosis depends on three things: diagnosis, the individual family history, and the background of the literature. The last is, of course, very important, and the probable accuracy of our estimates depends on the size and scope and quality of systematic surveys on the particular condition in question. Such surveys are constantly being made, with ever-increasing gain in the basic knowledge on which genetic prognosis can reasonably be attempted.

Detection of Heterozygotes

Before turning to the results of an inquiry we are at present carrying out at Great Ormond Street I should like to mention briefly one other topic. This is the detection of heterozygotes, with the hope it offers that carriers of the same gene may be warned in time of the danger of marrying each other. The most notable example at the present time is provided by Cooley's anaemia, thalassaemia major, the gene for which occurs with such extremely high frequency in some areas, notably parts of the Mediterranean basin. In some parts of Italy the gene frequency is very high (Bianco *et al.*, 1952). In the province of Ferrara 1 person in 10 carries the gene, and in certain townships no less than one in five. This means that in those townships, given random mating, one child in every 100 suffers from Cooley's anaemia. The heterozygotes, who exhibit thalassaemia minor, microcythaemia, can almost invariably, if not invariably, be detected by haematological tests. In the areas where the gene is common facilities for testing are available and registers are being built up, so that heterozygotes can be made aware of the danger of marrying each other. Of course, it is a little late when the banns have been published and the wedding arrangements made, but this knowledge may well prevent those early approaches which ultimately lead to courtship and marriage.

Doubtless when other and more urgent problems are tackled in Africa the same thing will happen with the

very common sickle-cell gene, which in double dose produces sickle-cell anaemia. No harmful genes reach universal frequencies like these; we have none of very high frequency in our own population. The commonest is fibrocystic disease of the pancreas, with a frequency of perhaps 1 in 1,600 births, which means that about 1 person in 20 carries the gene, provided, that is, that the disease is always due to the same gene. If methods for detecting heterozygotes were available routine testing might be worth while, and this may in the rather distant future apply to a number of recessively determined conditions. It is a long-distance objective, however, for present indications are that with conditions ordinarily regarded as recessive it is nearly always found that only a proportion of the heterozygotes can be detected given the methods currently available. Nevertheless, when the time comes there may well be an extension of genetic prognosis to something more than the calculation of odds after the first disaster has happened.

Systematic Follow-up

Patients at a genetic clinic are usually seen once only. One does not know what happens afterwards. Yet it is highly desirable to find out. One would like to know whether further children were in fact born and whether they were normal or not. One would like to know the reaction of the patients to the advice given. If the outlook was bad did they nevertheless persevere, or did they deliberately refrain from having children? If the outlook was good did they really accept the reassurance? For several reasons it is impracticable to ask patients to let one know the result. One consequence might well be to sow doubts again after a good prognosis had been given. Then one could never rely on all patients sending in information about further children; some would and some would not, and the replies might well provide a biased sample. It seemed to us that the only way of finding out what happens to be carry out a systematic follow-up.

We are now in course of doing this for a sample of couples seen at Great Ormond Street during a period which ranges from two years ago to six and a half years ago. All the couples were seen either by Dr. Cedric Carter or by myself. I should say that our attitude to the giving of genetic advice is closely similar. Quite often we see patients together and we consult each other about difficult cases. The families have been visited by our colleague Miss A. R. Buck, who records details about subsequent children, and in particular has questioned the parents about their attitude to the advice given, both at the time and subsequently. The total number so far investigated is 81. There has been only one refusal to co-operate. This was a difficult case; a father consulted us without the knowledge of his wife. There are some inevitable losses due to failure to trace couples after a change of address. Otherwise the sample is complete as far as we have gone.

The cases are divided into the bad risks and the good risks. The bad risks are taken to be those where the chance of recurrence is greater than 1 in 20, though, as explained previously, nearly all are in fact greater than 1 in 10. In this sample only 2 out of the 28 bad risks were estimated to be between 1 in 10 and 1 in 20. Table IV shows 77 couples altogether. This is because three inquiries were about the chances for normal children too young for marriage as yet. The 28 couples for whom the risk was bad have had 14 subsequent

children. Of the 11 who are old enough to be classified as normal or affected seven are normal and four affected.

The good risks range from 1 in 20 to lower, sometimes much lower, frequencies. These 49 couples have had 36 subsequent children, and of the 34 old enough to classify 33 have been normal and one affected. Incidentally, the one affected child had a small meningocele, which was remedied by operation.

Needless to say it is not the purpose of this investigation to see whether our forecasts were correct or not. A sample of 10 times the size, including as it must a wide variety of conditions, would not be nearly sufficient

TABLE IV.—*Subsequent Children of 77 Couples so far Investigated*

	No.	Normal	Affected	Too Young
Bad risks	28	7	4	3
Good „	49	33	1	2

for that purpose. If the results did look peculiar it would probably be due to chance and would be no reason for preferring our own small numbers to the mass of systematic surveys and investigations on large numbers upon which the calculation of chances must be based. In fact, however, there is nothing peculiar about these pooled results and we have certainly not been over-optimistic about what we regarded as the good risks.

Attitude to Advice Given

The real purpose of the inquiry is to find out what the attitude of the parents was to the advice given and how this was reflected in the number of subsequent children they actually had. Incidentally, the numbers in Table V are two fewer than those in Table IV. This is because with two couples we know the results in terms of children but the parents have not yet been interviewed

TABLE V.—*Subsequent Children in Relation to Attitude to Advice Given*

	Parents		Subsequent Children		
	No.	%	No. of Couples Having Children	No. of Children	No. per Couple (All Couples)
Bad risks:	28				
Decided to go ahead ..	6	21	4	8	1.33
Doubtful	4	14	1	1	0.25
Against	18	64	5	5	0.28
Good risks	47				
Reassured	23	49	21	26	1.13
Doubtful	14	30	6	7	0.50
Not reassured	10	21	2	2	0.20

about their attitude to the advice given. Six out of the 28 bad risks either decided to go ahead or to accept the future without bothering too much about it. Four of them had eight subsequent children between them. Of the few who were doubtful and the 18 who definitely thought they should avoid further parenthood only six couples had subsequent children, resulting in an average of about a quarter of a child per couple. Five couples adopted children and one couple adopted twins; this seems a useful result.

Just half of the good risks said they were definitely reassured and all except 2 of the 23 did have one or more subsequent children, an average of 1.13 children per couple for all 23 couples. Those who were doubtful include some who were partially reassured but were left with niggling doubts. Sometimes the wife was reassured but not the husband, or vice versa. Of these 14 couples,

6 had a subsequent child, giving an average of half a child per couple. In 10 instances the couples were not reassured at all. They either thought even a small risk too great to run, or else said they did not believe what they were told. Only 2 of the 10 had a subsequent child. It should be added that a few couples were clearly anxious to find additional reasons to reinforce their reluctance to have further children, a reluctance based on reasons other than the genetic outlook.

It is, I am afraid, a measure of failure that we succeeded in fully convincing only half these couples that the risk was in fact very small and not unreasonably out of proportion to the risk run by any random couple any time they have a child. When the study is complete we may perhaps strengthen our letters to family doctors, mentioning that experience shows that some couples are not fully reassured and that further talks by him reinforcing the advice given might be a good plan.

Conclusion

It is interesting to note how clearly the attitude to the advice given is reflected in the action taken and in the number of subsequent children the couples did in fact have. It may be hoped that as time goes on and genetic prognosis becomes increasingly the concern of the specialist, and above all of the family doctor, in addition to the specialized clinic, we shall get better results. Those who have to recognize that the risk is bad will be helped to reconcile themselves to their bad luck, and helped too in the matter of adoption. Those for whom the outlook is good may increasingly be encouraged by repeated assurances that in fact they have little to worry about, and so a higher proportion of those who do indeed want further children will be given the confidence to go ahead.

REFERENCES

- Bianco, I., Montalenti, G., Silvestroni, E., and Siniscalco, M. (1952). *Ann. Eugen. (Lond.)*, **16**, 299.
Carter, C. O. (1956). *Gt Ormond Str. J.*, **11**, 65.
Garrison, F. H. (1923). In *Abt's Pediatrics*, **1**, 89. Saunders, Philadelphia.
Martin, W. J. (1949). *Brit. med. J.*, **1**, 438.
Onpé, T. E. (1960). *Med. J. S.-W.*, **75** (iv), 77.
Roberts, J. A. F. (1959). *An Introduction to Medical Genetics*, 2nd ed., chapter 11. Oxford Univ. Press, London.
Sorsby, A. (1950). *The Causes of Blindness in England and Wales*. M.R.C. Memo. No. 24. H.M.S.O., London.

"All of them [on these advisory committees] serve in a voluntary capacity and it is therefore of the greatest importance to stress this voluntary element because it carries with it a very grave hazard. You can only maintain this voluntary structure of the National Health Service if there are people willing to come forward and carry the burden of this service. It is becoming more and more difficult to recruit from younger members of our communities those who are willing to undertake service on committees of this kind. That is not surprising. They have other responsibilities. Their time is otherwise occupied. But I warn you, and I warn you in the strongest terms which I can command, that unless voluntary service is continued we can look forward to the National Health Service being completely under the control (I do not want to use this word in a pejorative sense) of bureaucracy in which the human element, which we are all endeavouring to ensure shall permeate the spirit of our health services, will have disappeared. That is why I would stress the great importance of this voluntary endeavour within the Health Service in its administration, its planning and in the advice which it gives to the Minister on general and on specialist topics." (Lord Cohen of Birkenhead addressing the conference of the British Hospitals Contributory Schemes Association.)

CLINICAL USE OF HYPOTHERMIA COMBINED WITH CARDIO-PULMONARY BYPASS*

BY

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In Perth during the past two years various modifications of techniques of cardio-pulmonary bypass have been tried to obtain more satisfactory conditions for carrying out open heart surgery. Previously, bypass at normal temperatures had been attempted in the animal laboratory, using a modified bubble oxygenator (DeWall *et al.*, 1956; Cooley *et al.*, 1958), with disappointing results. When Drew *et al.* (1959) described their technique of achieving profound hypothermia by means of a low-flow bi-ventricular bypass and using the patient's own lungs to oxygenate the blood, it was decided to develop this method.

However, this technique seemed unsuitable for certain types of clinical case (Simpson *et al.*, 1960), and to avoid the disadvantages of bi-ventricular bypass and yet retain the advantages of deep hypothermia animal experiments were carried out using deep hypothermia induced by means of a heat exchanger (Brown *et al.*, 1958) combined with a bubble oxygenator (Fig. 1). In

FIG. 1.—Diagram of the extracorporeal circulation using a bubble oxygenator and heat exchanger to induce profound hypothermia.

this technique cooling by means of a partial bypass was begun; then as cooling took place and the heart as a result began to fail the bypass automatically became complete. When the pharyngeal temperature reached 15° C. the circulation was discontinued while the intracardiac procedure was carried out.

Experimental cardiac surgery using profound hypothermia in this way was followed by a much higher survival rate than when bypass without hypothermia was employed. The occasional incidence of pulmonary

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