THE GENETIC ASPECTS OF ANAESTHESIOLOGY*

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THE DEVELOPMENT OF genetics from quality to quantity, from descriptive genetics to measured genetics, has interested investigators in the biochemical sphere. Recently geneticists have found a very wide field of research and application in normal metabolism and its many reactions. In this way, biochemical genetics was born, and it is becoming more important daily. The purpose of biochemical genetics is to study man under normal metabolic conditions and under conditions of pathological metabolism, conditioned by heredity.

Between normal and pathological metabolism lies the so-called "provoked" metabolism. We consider the provoked metabolism as a biochemical reaction of the organism to artificial factors, for example, to anaesthetic drugs. If normal and pathological metabolism are under the influence of heredity, as biochemical genetics shows, it would appear that reactions following drug administration may partially depend upon some hereditary factor. We have taken this consideration as a basis for our work, and have thought that it would be advantageous and possible to inquire into such an hypothesis not only from the theoretical but also from the practical point of view.

We have been interested in the experimental and clinical results published by many authors, such as Lehmann, Ryan, and Simmons (1956-58), showing the importance of the heredity factor in the prolonged apnoea caused by succinylcholine. These authors noticed that some families had a deficiency of cholinesterase in the blood and that all the members of the family seemed predisposed to a protracted apnoea following the administration of succinylcholine.

The studies of Van Oye and Charles were quite different, but arrived at the same conclusion, that is, the existence of a hereditary factor which conditions the organic reaction to drugs. Van Oye and Charles, in 1952, showed a different type of hyperglycaemic curve in the white man and in the negro. Walravens (1931) and Pales and Monglong (1934) showed the extraordinary resistance of the negro to hypoglycaemic shock. It is well known that racial differences depend on the genotype, which means that they are hereditary.

This problem could have been developed from many points of view, as, for example, from the point of view of sensitivity to drugs with special regard to tolerance and threshold of biological reaction.

Since we wanted to study this problem in man, we thought that it would be advantageous from the point of view of ethics and practicability to use the operating room cases, which are actually everyday practical experiments with no research purpose. Many factors suggested that we should develop the problem in this way: (1) the satisfactory standard level of anaesthesia; (2) the many

*Read at the Second World Congress of Anaesthesiologists in Toronto, September, 1961.

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surgical operations performed under general anaesthesia on members of the same family; (3) the fact that we were able to use the records of a hospital where the patients belonged to a strongly endogamic zone, which is the population of the islands of the Laguna Veneta.

MATERIAL

The material that we used consisted of about 627 family units (Table I) and of 1,629 persons who had general anaesthesia for different reasons between the 4th October, 1953, and the 31st July, 1960 (about 13,000 general anaesthetics).

TABLE I
GENERAL TABLE

No. of persons in group	No. of groups	No. of individuals	Total no. of anaesthesias
2	427	854	957
3	115	345	370
4	47	188	205
5	17	85	97
6	10	60	67
7	6	42	48
9	3	27	31
11	1	11	11
16	1	16	16
Total	627	1628	1802

The subdivisions of the various groups, depending on the genetic affinities (Table II), gave us the possibility of various approaches. In the material at our disposal, we considered it advisable to observe immediate and delayed reactions, and the difference between them, and to attempt to put in evidence whenever possible the parallelism between relationship in the same family and the reactivity. On the basis of these principles we have chosen as pharmacologically conditioned reactions the following:

1. Modality of rest the night before the operation.
2. Psychological reactions after pre-anaesthetic medication.

TABLE II
TABLE OF GENETICAL AFFINITIES

No. of persons in group	Grand- parents, nephews	Grand- parents, nephews	Parents, sons	Parent, sons	Brethren	Uncles, nephews	Cousins	Consan- guineous	Total
2	13			164	165	48	37		427
3	1	3	7	36	12	30	1	25	115
4	1	2	8	5	3	7		21	47
5			2	4		3		8	17
6						1		9	10
7						1		5	6
9								3	3
11								1	1
16								1	1
Total	15	5	17	209	180	90	38	73	627

3. Reactions of the cardiovascular system.
4. Reactions of the respiratory system.
5. Muscarinic reactions.
6. Various other reactions.
7. Psychological reactions during the awakening period.
8. Post-anaesthetic vomiting.
9. Post-anaesthetic urinary retention.

There are somatic, psychic, and psychosomatic reactions. The somatic reactions are functional, as are the psychic and the psychosomatic reactions. All these reactions are objects of research studies in genetics but they are not measurable or totally quantitative entities. We tried to define the value of these factors in the best possible way and then to determine the degree of relation that the factors themselves showed in patients who were related by blood and in controls who were not related.

The greater, lesser, or equal coincidence of reactions in the two groups of related and unrelated patients subjected to general surgical anaesthesia represents the principle on which research becomes possible upon the material at our disposal in the operating theatres.

We shall now consider the data that we have collected, but before proceeding, we wish to point out the characteristics of the general surgical anaesthesia used, which actually has been the same in all the material, so that it is possible to make a comparison between the results. These are summarized in Table III. The technique that we used was based on these requisites.

TABLE III
PREMEDICATION AND ANAESTHESIA

Drugs administered	No. of cases	%
Premedication		
Atropine	37	2.05
Atropine + Morphine	480	26.66
Opium + Scopolamine	1242	68.86
Cocktail	44	2.44
Anaesthesia		
N ₂ O + O ₂	20	1.10
Ether + O ₂	22	1.22
Thiobarbiturate	1760	97.67
Muscle relaxant	1690	93.69
Analgesic	236	13.09
Fluothane	23	1.22
Ether	3	0.15
Ganglionic blocker	1	0.06

COLLECTION OF THE MATERIAL

The collection of the observed reactions of psychological and physiological nature was done in a systematic manner, and the data were entered on a special form prepared for the purpose. We found the persons who had relatives operated upon and anaesthetized in one of our surgical departments in the Ospedale Al Mare in the following way:

- (1) Commencing January 1, 1958, we asked all patients who were to have

general surgical anaesthesia if they ever had any relative operated on in one of our surgical departments. If the answer was positive, that patient was a candidate for our study, and we reported all data of that patient on the special form; at the same time enquiry about his relative was made in our anaesthesiology records. Once we found the relative's chart, we reported all reactions that he had had on the special form and then made a genealogical tree, so that it was possible to see the blood relationship between the individuals examined.

(2) At the same time about 5,500 letters were mailed, containing a special questionnaire for the purpose of finding out whether some other relative had had surgical anaesthesia in our hospital performed by the same anaesthetic staff. We considered only the patients who came to our hospital after October 5, 1953, because at that time one of us (Rizzi) organized the new anaesthesia department. All the information that we collected was reported on a special octagonal form designed to make the elaboration of the data easier.

METHOD

The concept of concordance (i.e., uniform effect) has been defined in such a way to consider as concordant only those couples who have the same reactions with the same modality, while we considered discordant (i.e., not uniform) those having reactions of different intensity. Therefore, to arrive at the concept of concordance, we had to define the possible modality of reaction for each single sector.

Having once defined the concept of concordance for the single sectors in this way, we tabulated the material collected in such a way as to realize, in the comparison with the controls, the proper hypothesis for the factors: sex, age, type of tranquilizer used, type of pre-anaesthetic medication, type of anaesthetic used, type of surgical procedure, anti-emetic drugs used, and type of awakening. In this study, the patients examined, i.e., the couple on which the authors wished to check the probable influence of the hereditary factor, were near-consanguineous and were represented by couples of parents and sons, or couples of brothers.

The analysis was done by making a direct comparison between the percentage of candidates and controls with concordant reactions and noting the significance of the difference with the χ^2 test (Table IV). The comparison by the χ^2 test

TABLE IV
PERCENTAGE FREQUENCY OF CONCORDANT REACTIONS

Reactions		Genetical affinity						
		Father, son	Father, daughter	Mother, son	Mother, daughter	Brothers	Brother, sister	Sisters
Nocturnal rest	Propositi	43	56	61	35	52	50	51
	Controls	32	28	39	35	33	46	44
Psychology after premedication	Propositi	91	93	89	64	78	75	74
	Controls	54	53	78	57	52	65	51
Muscarinic	Propositi	79	91	93	95	79	88	98
	Controls	58	74	80	84	64	76	89

gave us a very remarkable difference. We know that the "test" between the theoretical frequencies series and an experimental one has to be applied. We have treated the controls as a theoretical series and we believe we are correct in stating that the casual variations have no sensible influence on the experimental values we obtained.

Groups were determined in the following way:

(1) Character of sleep during night preceding the operation. It is customary

FIGURE 1. Frequency of concordant reactions in nocturnal psychology.

in our anaesthesia department to give the patient a drug which helps him to sleep and relieves his anxiety the night before surgery. On the following morning the patient was asked how his sleep had been during the night—worse, the same, or better than usual? The patient always answered this question very easily. We could analyse the results obtained for 272 couples. For the control couples we kept the same variants constant—i.e., treatment at night, sex, age, etc. (Fig. 1).

FIGURE 2. Frequency of concordant reactions in psychology after premedication.

(2) In the morning, after premedication and before starting anaesthesia, while the patient was in the anaesthetic room, we inquired into his feelings towards general anaesthesia—alarmed, worried, or tranquil? We analysed the results obtained for 138 couples. For the control couples, we kept the variants constant—i.e., pre-anaesthetic medication, procedure, sex, age (Fig. 2).

(3) Cardiovascular reactions to general anaesthesia. In this section we considered the following reactions: (a) pulse rate, (b) heart rate, (c) blood pressure—systolic, diastolic, and differential. We considered a reaction as tachy-

FIGURE 3. Frequency of concordance in muscarinic effects.

cardiac when there was an increase in the pulse rate of 20 per minute, and as bradycardic when there was a decrease in the pulse rate to 60 or less per minute. We considered a reaction as hypertensive or hypotensive when there was an increase or decrease in blood pressure of 20 mm. of Hg. We always kept in mind what happened after the anaesthetic premedication. The increase or decrease of the differential blood pressure has been underlined only when the difference was at least 20 mm. of Hg. We analysed the results obtained for 52 couples. For the control couples we kept the same variants constant (i.e., pre-anaesthesia, anaesthesia, anaesthesiologist, surgical procedure, sex, age).

(4) Respiratory reactions to general anaesthesia. The reactions that we considered are: (a) laryngospasm-bronchospasm, (b) tachypnoea or bradypnoea. For the last two values we considered also the age of the anaesthetized patient. We analysed 58 couples and for the controls kept the same variants constant, as for the cardiovascular system.

(5) Muscarinic reactions. Under this heading we considered (a) salivation and bronchorrhoea, (b) lacrimation, (c) sweating. We analysed the results obtained for 203 couples, and for the control couples we kept the same variants constant (i.e., premedication, anaesthesia, sex, age) (Fig. 3).

(6) Various reactions were considered under this heading: vomiting, hic-coughing, coughing. We analysed 96 couples; for the control couples we kept the same variants constant.

(7) Psychological reactions during the awakening period. Among the many reactions which occurred during the awakening phase, we considered the following: (a) convulsions, (b) psychomotor reactions, (c) affective reactions, (d) rational reactions, (e) end of physical lacunae. We are now doing a systematic study in which the awakening period is followed chronometrically and this will be the subject of a future report. We were unable to analyse these reactions because we did not have a satisfactory number of control couples with the same variants.

(8) Post-anaesthetic vomiting. We considered only vomiting that occurred within the first 24 hours after the end of the surgical procedures. We analysed the results obtained for 42 couples and kept the same variants constant.

(9) Post-anaesthetic urinary retention. We considered only the inability to void during the first 12 hours after operation. We analysed 68 couples, and kept the same variants constant for the control couples. As a subexperiment we considered the following factors: (a) surgeon, (b) patient's cultural and social conditions, (c) weather conditions at the moment of the test.

There is a possibility that other factors may exist, besides those that we have considered; factors able to influence the results. Therefore our conclusions are approximate. Nevertheless our hypothesis, at least in certain sections, would appear to be sufficiently proved.

DISCUSSION

At the present moment we cannot attribute a specific significance to the differences that we found (Table V) in the reactions of the cardiovascular

TABLE V
SUMMARIZING PICTURE*

	Father, son		Father, daughter		Mother, son		Mother, daughter		Brother, brother		Brother, sister		Sister, sister																
	P	C	P	C	P	C	P	C	P	C	P	C	P	C															
Nocturnal rest	12	16	9	19	14	11	7	18	17	11	11	17	24	28	28	26	30	35	33	30	38								
Psychology after premed.	10	1	6	5	14	1	8	7	8	1	7	2	9	5	8	6	18	5	12	11	47	16	41	21	46	16	32	30	
Circulation	1	0	1	0	4	1	3	2	0	0	0	0	0	0	0	0	0	0	1	1	0	5	4	5	4	7	3	3	
Respiration	1	3	1	3	0	0	0	0	0	0	0	0	0	1	0	1	3	0	0	0	3	6	6	7	3	9	2	5	6
Muscarinic effects	15	4	11	8	21	2	17	6	14	1	12	3	18	1	16	3	11	3	9	5	59	6	51	16	45	1	41	5	
Postoperative vomiting	2	0	1	1	0	0	0	0	0	0	0	0	1	0	1	0	2	0	2	0	5	0	4	1	5	6	8	3	
Retention of urine	2	0	2	0	5	0	2	3	0	0	0	0	0	0	0	0	3	0	3	0	9	3	10	2	12	0	10	2	
Various	3	0	3	0	3	2	5	0	1	0	1	0	5	0	5	0	6	0	6	0	11	3	14	0	14	0	14	0	

*Note: P = propositi; C = controls. The number of concordances is printed in italics; the other numbers are discordances.

system, of the respiratory system, of post-anaesthetic vomiting, and of urinary retention. We will only say that the difference between the percentage of concordances of candidates and of controls, in the above-mentioned reactions, cannot be considered significant, because of the limited number of couples satisfying the requirements of the large number of variables that we wanted to make constant. In the psychological reactions, after tranquillizer and after anaesthesia premedication, and in the muscarinic reactions, the difference in the percentage of uniform response (concordance) between candidates and controls assumes such a high value that we can say that, in this section, the genotype reaction is a reality.

The authors will eventually subdivide (subclassify) the sections mentioned above into subsections, so that it will be easier to find the relation between cause and effect.

CONCLUSIONS

It is certain that the various reactions noted, even those that show most clearly a hereditary factor, are not pure, which means that they contain an element of exogenous variability. We shall broaden the study, in order to find all the possible endogenous variants and in order to isolate the specific element of the genotype susceptible to the anaesthetic drugs. However, the value of the psychological response of the patients to general anaesthesia is satisfactory from the genetic point of view, because the method that we used seems to be the best for isolating the reactions and for finding the family element, in this case hereditary. From the anaesthetic point of view, we would like to say that the method that we used to analyse the psychosomatic reactions to general anaesthesia is quite similar to the method used to test the anaesthetic drugs. This genetic interpretation of anaesthesia would be of practical help to anaesthesia itself. From the data obtained from our research, a practical anaesthesia problem came to our mind: "Will the anaesthesiologist be able to make the right choice of anaesthesia and to avoid anaesthetic complications in an anaesthetized patient? Will he be able to do so when he knows the problems that the patient's relatives have had previously during anaesthesia?" We cannot answer these questions yet, but we are undertaking another research project in which we are trying to find the true cause of the various reactions, keeping in our mind the value of all the possible variants.

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