CIBA FOUNDATION SYMPOSIUM

Jointly with

THE INTERNATIONAL UNION OF BIOLOGICAL SCIENCES

ON

BIOCHEMISTRY OF HUMAN GENETICS

Editors for the Ciba Foundation

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and

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PREFACE

As part of a special programme in the year of the early but significant milestone of its 10th Anniversary, the Ciba Foundation has organized for the first time conferences in places other than its own agreeable and well-equipped premises in London.

The first of three such conferences, on the small scale and in the informal style characteristic of the Foundation, was arranged in Naples, Italy. This volume contains the papers and discussions contributed by the group happily gathered in a place where so many generations of mankind have left their traces and where their living descendants are so humanly helpful and hospitable.

This symposium on human biochemical genetics was initiated by Professor Montalenti on behalf of his own Department at Naples and also of the International Union of Biological Sciences. The Rockefeller Foundation also generously supported the project. Professor Montalenti and Professor Siniscalco made many of the preliminary arrangements in Naples and played vital parts in the successful realization of the meeting.

The young Ciba Foundation was also most fortunate in holding its first overseas conference in the world-famous, almost centenarian Zoological Station, and received every conceivable assistance from Professor R. Dohrn and Dr. Peter Dohrn.

A preface is quite inadequate for acknowledgements where so many are so richly due and warmly felt, but the Editors must mention also their thankfulness to Professor Siniscalco, Dr. Harris and Miss Joan Etherington for detecting the threads of discussion among the simultaneously recorded street sounds of Naples.

List of those participating in or attending the Symposium on "Human Biochemical Genetics in Relation to the Problem of Gene Action"

13th–16th May, 1959

S. Brenner	Medical Research Council Unit, Cavendish Laboratory, Cambridge
Sir Macfarlane Burnet	Walter & Eliza Hall Inst. of Medical Research, Royal Melbourne Hospital, Melbourne
A. A. Buzzati-Traverso	Inst. of Genetics, University of Pavia
L. Califano	Inst. of General Pathology, Naples
L. L. Cavalli-Sforza	Inst. of Genetics, University of Pavia
R. Ceppellini	Dept. of Medical Genetics, University of Turin
B. Childs	The Johns Hopkins Hospital, Baltimore, Md.
H. Eagle	Laboratory of Cell Biology, National Inst. of Allergy and Infectious Diseases, Bethesda, Md.
R. Grubb	Inst. of Bacteriology, University of Lund
H. Harris	Dept. of Biochemistry, The London Hospital Medical College, London
V. M. Ingram	Division of Biochemistry, Massachusetts Inst. of Technology, Cambridge, Mass.
H. A. Itano	Dept. of Health, Education and Welfare, National Insts. of Health, Bethesda, Md.
H. M. Kalckar	McCollum-Pratt Inst., The Johns Hopkins University
H. Kalmus	The Galton Laboratory, University College London
W. Kalow	Dept. of Pharmacology, University of Toronto
J. Lederberg	Dept. of Genetics, Stanford University Medical School, Stanford, Calif.
S. E. Luria	Dept. of Biology, Massachusetts Inst. of Technology, Cambridge, Mass.
A. Monroy	Dept. of Comparative Anatomy, University of Palermo
G. Montalenti	Inst. of Genetics, University of Naples
W. T. J. Morgan	The Lister Inst. of Preventive Medicine, London
J. V. Neel	Dept. of Human Genetics, University of Michigan Medical School, Ann Arbor

L. S. PENROSE . . .	The Galton Laboratory, University College London
G. PONTECORVO . .	Dept. of Genetics, University of Glasgow
ELIZABETH B. ROBSON .	The Galton Laboratory, University College London
A. ROSSI-FANELLI . .	Dept. of Biological Chemistry, University of Rome
M. SINISCALCO . . .	Inst. of Genetics, University of Naples
O. SMITHIES . . .	Connaught Medical Research Laboratories, University of Toronto
WINIFRED M. WATKINS .	The Lister Inst. of Preventive Medicine, London
S. W. WRIGHT . . .	Dept. of Pediatrics, University of California Hospital, Los Angeles

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ADDRESS OF WELCOME

L. Califano

Il Consiglio delle Ricerche vede con la più viva simpatia questo Symposio della Fondazione Ciba, che si svolge a breve distanza dall'altro affine tenuto presso l'Accademia del Lincei, sotto gli auspici dello stesso Consiglio. Il fatto che il Simposio di Genetica Biochimica si svolga presso la Stazione Zoologica è assai significativo. Questo Istituto fu fondato da Anton Dohrn per la ricerca zoologica sistematica ed ecologica, per la citologia, istologia ed embriologia e fisiologia delle forme viventi del mare, ma il fine reale supremo che animò l'impeto creativo del suo fondatore è quello della ricerca della evoluzione e della azione di dette forme. La lapide apposta sulla facciata dell'Istituto esprime nelle armoniose frasi scritte dal Croce tale destino: "quanta luce di verità promettesse l'indagine della vita nei mari". La Stazione Zoologica nella sua lunga vita ha potentemente contribuito a tale indagine ed ha così ben meritato nella sua vita. Il grande spirito di Anton Dohrn aleggia qui in questa sala dove è anche ritratta l'effigie della persona e si coglie volentieri anche questa occasione per rendere omaggio e rispetto alla sua memoria con grato animo, come gratitudine e rispetto si esprime al paziente ed umano continuatore dell'opera paterna, il caro Rinaldo, che ha tenacemente retto le sorti dell'Istituto per oltre trenta anni, ed augurio ed incoraggiamento si rivolge a Pietro, erede di sì nobili tradizioni, che imprime all'Istituto con sovrumana fatica un nuovo corso, quale è richiesto dal progresso e dalla specializzazione della biologia. Per molti anni è sembrato che la Stazione Zoologica poco potesse contribuire allo sviluppo della genetica, e solo potesse in tal campo portare contributi collaterali. Quando invece dalla genetica formale si è sviluppata la genetica biochimica, l'ufficio della Stazione Zoologica è apparso di nuovo importante. Dallo studio delle forme e delle strutture e dei meccanismi che li determinano, ha avuto qui

una sua culla la indagine biochimica della vita dei mari che riserba grandi possibilità di scoperte, e poichè ogni fatto biochimico, cioè ogni funzione metabolica, energetica e plastica è di dipendenza genica, lo studio comparativo e biochimico sarà di grande significato per la genetica chimica e per quella che si dice l'evoluzione biochimica, e certamente per la evoluzione delle forme, che è strettamente connessa. Perciò l'odierno Simposio di Genetica Biochimica per la Stazione Zoologica ha lieto auspicio per il fervore dell'opera futura. Il Consiglio delle Ricerche e la Stazione Zoologica sono così molto grati al caro illustre amico Prof. Montalenti, che ha con saggezza lungimirante promosso questo Simposio, egli che alla sapienza ed al fervore di ricercatore unisce passione sincera per il progresso degli studi, e perciò anche grande amore per la Stazione Zoologica. E ciò lo testimonia anche la attuale premura a che il Simposio della Fondazione Ciba di Genetica Biochimica si svolgesse in questo Istituto.

CHAIRMAN'S OPENING REMARKS

G. MONTALENTI

BEFORE the work of the symposium begins, I should like to explain its meaning and how it originated. This I shall do especially for the benefit of the invited audience present at this opening session, and I hope that the members of the symposium will forgive me if I go into some details which may seem quite trivial and obvious to them.

In 1949 a symposium was held in Milan at the Istituto Sieroterapico Milanese on "The Recent Contribution of Human Genetics to Medicine". In my opening address I stated something which was quite obvious at that time, i.e. that Man, who had formerly been considered as the least suitable animal for genetical research, had gradually proved to be one of the best subjects for at least some kinds of genetical investigation.

It was long thought also that human genetics was merely an applied branch of biology. Fundamental problems, it was said, have to be studied in animals, in plants, in micro-organisms, if the general principles are to be worked out; as soon as these are discovered, one can try to see whether they hold true in Man, and how they can be applied to explain hereditary or evolutionary patterns in this particular organism. As investigation on human genetics proceeded, however, it was realized that this was not true, or at least it was only a part of the picture. Human genetics is no longer a mere applied science; on the contrary, human beings are a very good subject for the investigation of some primary basic genetical or evolutionary problems. For instance, as Haldane pointed out at the 1949 symposium in Milan, human populations are perhaps more suitable than any others for the investigation of problems of variation of gene frequencies, whether due to selection or to other causes. The selective value of some genes—such as those responsible for sickle-cell

anaemia and thalassaemia—and some blood groups have been demonstrated or are under investigation and appear to offer a promising field of study.

Only a decade has elapsed since that meeting, and the situation has since changed quite considerably. Another kind of fundamental problem has been focused by human genetics and has led already to fine results, i.e. the problem of how genes act, which is clearly an essentially biochemical one.

It is often said that biologists are now busily rewriting all their knowledge in terms of biochemistry. It must be added, however, that just as there are two ways of dealing with biological phenomena, namely pure description and interpretation of the causal relationships, the same is true of the chemical presentation of biological events: it may be merely descriptive, or it may try to penetrate more thoroughly and intimately into the processes, i.e. to discover the elementary molecular reactions and the basic principles whereby a chemical fact is transformed or amplified giving rise to a biological event perceptible at the phenotypic level.

Genetics has greatly contributed to the chemical interpretation of basic biological phenomena. Indeed it is mainly thanks to the genetical outlook that we have a deeper insight into, and are perhaps approaching the solution of some of the most fundamental biological problems, such as specificity, reproduction—which implies transmission of information—and *quod est in votis* the origin of living matter.

Taking into consideration only biochemical genetics as such, it is well known that the first work which had a considerable impact by arousing a lively interest among geneticists was that of Ephrussi and Beadle, in the nineteen-thirties, on substances controlling eye colour in *Drosophila*. Then came Beadle and Tatum's work in *Neurospora*, which established the fact that a gene may control a single step in a given biochemical reaction, thus providing a clue for the investigation of the mode of action of genes. However, it is now generally recognized that this very fact had been discovered as early as 1902 in Man. At that time, in the infancy of genetics, Garrod

found in Man a beautiful instance of what he very properly called "inborn errors of metabolism": namely, alcaptonuria. Garrod demonstrated that this anomaly, characterized by excretion of alcapton in the urine, is the result of a block in the chain of reactions by which the amino acids, phenylalanine and tyrosine, are metabolized. Many other instances were described and elaborated in subsequent years in a masterly way by the same author with the help of Bateson's advice on genetical aspects. Each instance seemed to be due to a single Mendelian factor—a gene. Garrod saw clearly that the normal gene controls the very step of the reaction which in the presence of the mutated allele is stopped or altered. Garrod is undoubtedly to be considered as the founder of the one gene–one enzyme theory, and he also had a clear idea of the biochemical polymorphism in human populations. Garrod's discovery and theoretical outlook have been fully understood and appreciated only with a delay of some decades.

It may be said, therefore, that the first important step in the understanding of gene action was made in human genetics. Later came the beautiful work on *Neurospora* and other micro-organisms which led, as is well known, to most brilliant results, and provided further evidence in support of the one gene–one enzyme hypothesis which has played an important rôle in genetics.

The next achievement along this line was the discovery by Pauling, Itano, Singer and Wells in 1949, that in sickle cell anaemia the red cells have an aberrant haemoglobin called haemoglobin S, which has an electrophoretically different behaviour from normal haemoglobin A. According to the finding of Neel, sickle-cell anaemia depends on a gene pair. Pauling and co-workers were able to show that homozygous individuals have homogeneous haemoglobin of an aberrant nature; heterozygotes, showing the so-called sickle-cell trait, have a mixture of normal and aberrant haemoglobin: about 60 per cent of the former and 40 per cent of the latter. Normals have only haemoglobin A. In this particular case it appears that the action of the gene is not to build an enzyme. It gives