G. Mendel memorial symposium 1865-1965 : proceedings of a symposium held in Brno on August 4-7, 1965 / edited by Milan Sosna.

Contributors

G. Mendel Memorial Symposium, 1865-1965 (1965 : Brno, Czechoslovakia)
Sosna, Milan.
Československá akademie věd.

Publication/Creation

Prague : Academia, 1966.

Persistent URL

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SYMPOSIA ČSAV

G. Mendel Memorial Symposium 1865 - 1965

Proceedings of a Symposium
held in Brno
in August 4 - 7, 1965

Academia ● Prague

KERATOPLASTY

Proceedings of a Symposium held in Prague, October 19—21, 1960

332 pp. — 21 ill. — in English — hard covers 33,50 Kčs

The Czechoslovak Ophthalmological Society as a section of the Czechoslovak Medical Society of J. E. Purkyně together with the Czechoslovak Academy of Sciences held in Praha-Liblice the Second International Symposium was attended by the most outstanding ophthalmologists from all over the world. The main topic were keratoplastics (transplantation of the cornea) with associated problems of biochemistry, histology, aloplastics (the use of artificial substances in keratoplastics) and heterotransplantations (the use of foreing corneal transplantates in keratoplastics), the conservation of transplantates and questions of operational techniques.

Jaromír Kolář, Arnošt Babický, Radko Vrabec

THE PHYSICAL AGENTS AND BONE

292 pp. — 89 ill. — 55 suppl. — in English — hard covers 50,— Kčs

The authors of THE PHYSICAL AGENTS AND BONE describe the findings gained in their treatment of patients, base their observations on clinical and X-ray pictures, and histological examinations, and offer advice on the treatment and prognostic evaluation of the changes caused by the above mentioned physical agents. Of special importance is the chapter dealing with changes in bones and joints occasioned by burns. The study contains the most ample statistics of such clinical observations to date (taken from almost 1000 patients). Equally great care and thouroughness characterize the chapter dealing with changes in bones following exposure to severe cold (where the authors examined 198 patients). The chapter on the influence of supersonic waves is also of great importance. Parts examining changes in bones after accidents involving electricity and radiation are based on the wide experience gained by the authors.

In its experimental part, the work deals with radioisotopic experiments on animals, which enabled the authors to ascertain the metabolism of bones in cases of physical injury. They found important abnormalities not only in bones directly affected, but also in the entire skeleton and in all classified tissues of the body.

ACADEMIA

Publishing House of the Czechoslovak Academy of Sciences

Vodičkova 40, Praha 1 - Nové Město, Czechoslovakia
Distributors: ARTIA - POB/790, Praha 1 - Czechoslovakia

Tem. skup. 03/14

21-142-66

Cena váz. 55,— Kčs —l

G. MENDEL MEMORIAL SYMPOSIUM

1865—1965

Proceedings of a Symposium held in Brno in August 4—7, 1965

The book contains the collection of papers delivered at the G. Mendel Memorial Symposium of the same name organized by the Czechoslovak Academy of Sciences under the patronage of Genetic section of I.U.B.S., U.N.E.S.C.O., International Atomic Energy Agency (I.A.E.A.) and Council for International Organizations of Medical Sciences (C.I.O.M.S.) in August in Brno. The Symposium was attended by a great number of foremost scientists from all world.

The book has number of themes: The Origin of Mendelism, The Establishment of Genetics, Modern Development of Genetics and Special Application of Genetics. These themes contain twenty official invited lectures — (B. Němec, H. Stubbe, F. A. E. Crew, C. Zirkle, N. W. Timoféef-Ressowsky, B. L. Astaurov, W. Gajewski, N. P. Dubinin, J. H. Lewis, F. Jacob, G. Melchers, M. R. Irwin, C. H. Waddington, Å. Müntzing, Å. Gustafsson, N. V. Tsitsin, A. Tavčar, I. M. Lerner, C. Stern, L. Gedda and M. Milani-Comparetti) and eleven discussion contributions.

The book has a list of full members of the Mendel Memorial Symposium.

G. MENDEL MEMORIAL SYMPOSIUM

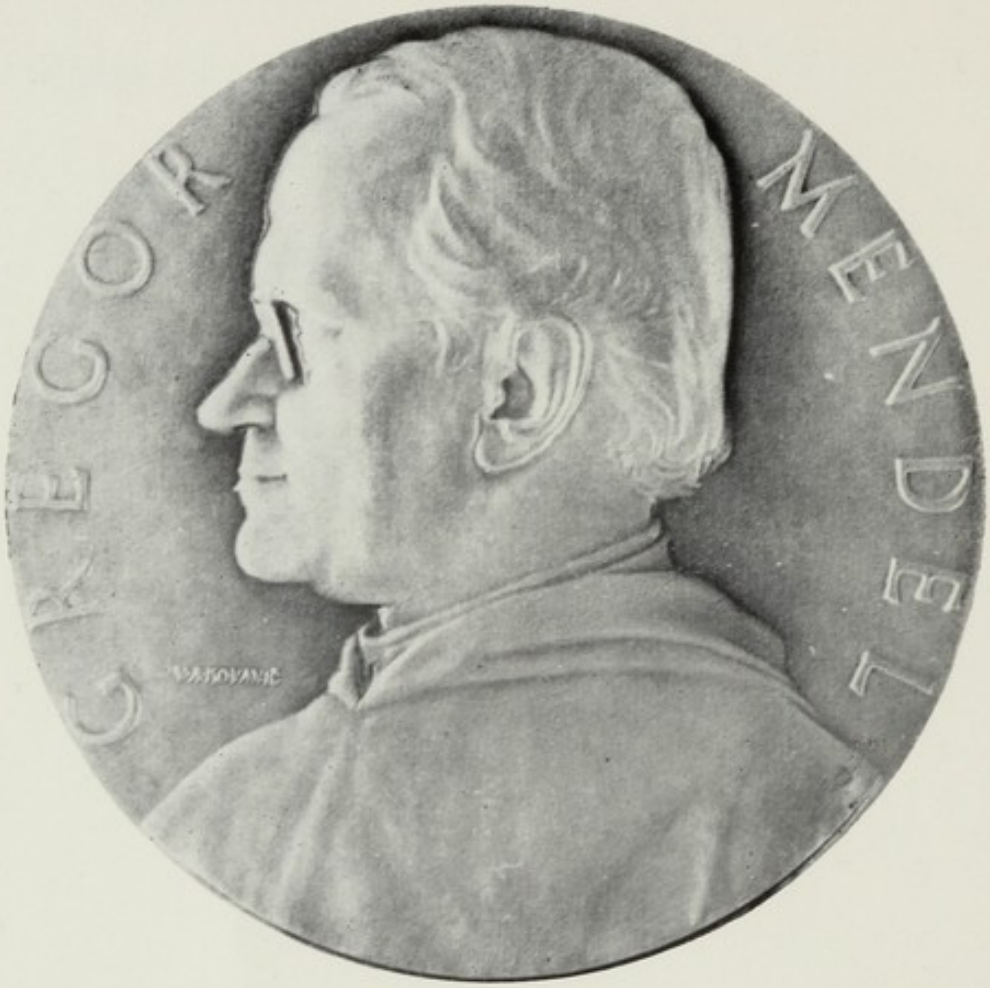
1865—1965

BRNO, AUGUST 4—7, 1965

Scientific Editor: Milan Sosna

Foreign Language Editors: Marta Rauscherová
and Peggy Kalinová

Graphic Design: Josef Prchal



Memorial Medal of Gregor Mendel
edited by Czechoslovak Academy of Sciences

G. MENDEL MEMORIAL SYMPOSIUM 1865 – 1965

Proceedings of a Symposium
held in Brno
in August 4 - 7, 1965

Edited by: Milan Sosna

Kommissions-Verlag:
Verlag Werner Flach
Frankfurt/Main

ACADEMIA
Publishing House of the Czechoslovak Academy of Sciences

Prague 1966

Printed in Czechoslovakia

In closing this edition allow me to remember the sudden death of Professor Dr. B. Němec, chairman of the Organizing Committee, who died after a noble life devoted to outstanding scientific work and public activity on April 7th 1966 at the venerable age of 93.

He concentrated his efforts to the preparation of the celebration of Mendel's Centennial and devoted his scientific and human authority to ensure its success.

M. Sosna

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G. MENDEL MEMORIAL SYMPOSIUM, BRNO

organized by the Czechoslovak Academy of Sciences
under the patronage of
Genetic Section of the I.U.B.S., Czechoslovak National Commission
for U.N.E.S.C.O., I.A.E.A. and C.I.O.M.S.

The Opening Ceremony

The Openning Ceremony was held on August 4, 1965 in the New Theatre-Building in Brno. The agenda was as follows:

Introduction Address

ACADEMICIAN B. NĚMEC
Chairman of the Organizing Committee

Ladies and gentlemen, dear guests,

I was greatly honoured by having been appointed Chairman of the Preparatory Committee of the Celebrations of the Mendel Anniversary 1865—1965.

I decided to undertake the task out of deep respect for the discoverer who has by his work made such a giant contribution to drawing up the theory of heredity which is one of the key problems of biology.

It is our fervent desire that the celebrations and the Symposium should become part of the scientific work in the field of biology demonstrating international cooperation of all cultural nations in solving the fundamental questions of living nature, including mankink and its endeavour to discover the processes of life, and the use of this knowledge for the benefit of mankind's health, prosperity and happy future. We welcome all foreign guests as well as all Czechoslovak biologists in Brno, the town where M e n d e l lived and worked. We shall strive to satisfy all guests and other participants and enable them to attend the lectures and take part in the discussion on all debated questions, to become acquainted with those places in our country which are interesting from the point of wiew of history, its people, its culture and its work for peace and cooperation with all nations. It is my genuine desire that our working assembly should become an impulse and a progressive factor influencing the further progress of genetics and its application.

Opening Address

ACADEMICIAN F. ŠORM
President of the Czechoslovak Academy of Sciences

Ladies and gentlemen,

It is my pleasure and privilege to open this important scientific gathering, devoted to the memory of the great scientist, G r e g o r M e n d e l. This autum one hundred years ago, at a meeting of the National Sciences Society of Brno, M e n d e l first reported on the results of his original investigations

on plant hybrids which laid the experimental foundation for the scientific study of phenomena of heredity.

Allow me, first of all, to welcome you on behalf of the Presidium of the Czechoslovak Academy of Sciences. Czech and Slovak scientists are proud of the outstanding achievements of their great countryman and therefore with great pleasure accepted the suggestion of the Genetics Section of the International Union of Biological Sciences that a Mendelian Conference be organised by our Academy in the Czechoslovak Socialist Republic. The importance of the Conference is underlined by the support is received from UNESCO. I might perhaps also mention that this is not the first occasion that a Mendelian Anniversary is being commemorated on an international scale in this country: as early as 1922, on the occasion of the 100th anniversary of Mendel's birth, a conference was held here and aroused considerable interest.

As you are all very well aware, the science of genetics has, since Mendel's days, undergone many important changes, and at the present time, is in a stage of particularly rapid development, as part of the present almost explosive growth of the life sciences.

The study of living matter is the proper domain of biology but other sciences, mainly chemistry and physics are now joining into the attack. The secrets are beginning to yield to the manysided assault: knowledge of the immensely intricate mechanisms and laws of living matter is rapidly becoming available and is acquiring an exact character. It is, in fact, possible to say that we are standing on the threshold of the greatest of all scientific revolutions — a revolution which — eventually — will enable us to govern living matter and to transform it according to our needs. One of the principal tasks and aims in this area obviously is to clarify and harness the mechanisms of the transfer of biological information as a fundamental genetic phenomenon. We now know that these processes are governed by the specific properties and metabolic interactions in the macromolecular systems forming the proper material basis of living matter, i.e. proteins and nucleic acids. Even in the light of the great advances in the field of genetics, the work of G r e g o r M e n d e l , which brought to light the fundamental laws of genetics and showed that the genetic material proper is laid down in the germ cells of living matter will always be remembered. Even today we admire the creative genius, experimental skill and scientific integrity of Gregor Mendel.

There is no doubt in my mind that your meeting, the first part of which is held in the city in which M e n d e l spent all his active life, will be a fitting tribute to his memory as well as a valuable contribution to further development of genetics.

I wish you every success.

Address

The Symposium was addressed by Professor S. J. Geerts, President of the Genetic Section of the International Union of Biological Sciences,
by Professor C. H. Waddington, President of the International Union of Biological Sciences
and by Dr. B. Keil, Representative of U.N.E.S.C.O.

PROFESSOR T. MARTINEC
Rector Magnificus of the Purkyně University, Brno

Mr. President, ladies and gentlemen,

Allow me to greet you all on behalf of the University in Brno which bears the name of Jan Evangelista Purkyně, one of the great figures of our science.

It is an honour for us that among those who took part in the preparations for this Symposium were also members of our university which, recognizing the significance of genetics for biological sciences, fully endorses its development. This has also been manifested by the establishment of new genetic laboratories at the Faculty of Science and the Faculty of Medecine of our University in Brno. These days we all realize the importance of Mendel's discoveries which have become the basis for a new scientific discipline — genetics. The significance of Mendel is in that he was the first scientist who mathematically proved the laws of heredity and his work thus became the foundation for the development of modern genetics.

The importance of Mendel's discoveries has often been compared with that of Darwin's work. I do not intend to make an evaluation here. However, I would like to point to the fact that both theories have one feature in common — they were extremely important and aroused many discussions and controversies among the scientists. One of them sooner and the other later. Both theories had to go through a period of skepsis and both had to wait for a long time before they were recognized. Mendel himself said: "I have had many bitter experiences in my life, but my investigations brought much satisfaction to me. I am sure that my time will come!" The fact that this time has come can be seen from this Symposium at which scientists from all parts of the world will discuss problems of a science which has developed from the experiments carried out by a modest scientist of genius Father Gregor Mendel, in the small garden of the ancient monastery in Brno. Our nation is proud of the fact that this country was the cradle of genetics which today is one of the most important disciplines of biology.

DR. J. JELÍNEK
Director of the Moravian Museum, Brno

Mr. Chairman, ladies and gentlemen, dear guests,

It's a great honour for me to welcome you on this occasion here in Brno, in Mendel's town, in the name of the Moravian Museum.

This year whole scientific World is celebrating the centenary of the "most important biological discovery that has been made in the last five hundred years", speaking with the words of T. H. Morgan.

It's good alvays to look forward — but it's also good from time to time to look back. Looking back on the whole history of genetics on this occasion it's astonishing to see how fascinating and dramatic the history of this science has been and still is. Mendel's discovery — when he knew very well the difficulty and the danger for the discoverer and for the discovery which is too far ahead of the contemporary Science, of the contemporary level of human knowledge.

Not to be understood for the whole life, then after many years to be rediscovered for all mankind but later to be burried again in his own country and in many others. Many scientists recognized the nature and meaning of Mendelism and offered to this science their life — work. Some did not. For miscomprehension or for insufficient personal courage.

Now, hundred years later. Mendel stands again as one of the greatest man of science and is honoured as a man, whose genius made the discovery which can bring one of the greatest benefits to man. And we know that this story has not ended. Modern Genetics as the fundamental biological science promise for the future unimaginable possibilities, the results of which can be even more revolutionary for human existence than even the greatest discoveries of contemporary science. But these celebrations will be over in five days and we should like to pay our permanent tribute to this great Man.

Just before the second World War there was a proposal to establish here in Brno a special Mendel Institut but the War stopped all efforts. After the War some of the University professors namely Křížecký and Úlehla tried it again. But the events in the fifties stopped it once again. In the following years the Moravian Museum succeeded in collecting and preserving all the existing material and documents connected with Mendel, known here. In 1960 this Institution opened a small one — room — exhibition for experts in the Mendel Monastery. In 1961 and 1962 I tried to establish a special Genetic Department — Mendel genetic department and I asked the late prof. Křížecký, one of the greatest Czech Mendelists to work with and later to lead the new department. With the help of some scientists and some responsible authorities, we succeeded. The Mendel genetic Department in the Moravian Museum was established and we began to work on the Centen-

ary celebrations and on the Mendel Memorial and garden at the Monastery. Many people and institutions helped — not only here in our country but also from other countries without any difference of nationality, race, religion or political ideology. Our deepest thanks to all of them.

We feel as our duty to build up the memory of this Great Man, whose work is so important for the whole international science. This is program, this is what we here, in Brno can do and what only we can do. To build up a Mendel memorial and documentary Center for the history of Genetics here in the place where he lived and worked. This is the program for the museum which takes acre of Mendel's material: to concentrate all the documents of the history of genetics, of course not only for us here in Czechoslovakia but for all the scientists all over the world. And only with the help of all of them is the realisation of our program possible. Mendel does not belong any more to us here — he belongs to the whole of mankind.

Much succes to the Mendel Memorial Symposium!

Much succes to your future work in genetics!

MR. V. VAVERKA
Mayor of Brno

Ladies and gentlemen, dear guests,

Allow me, on behalf of the Council of the Municipal National Committee and of all inhabitants of the trade fair town, to welcome you all in the town of one of the greatest biologists of the past centuries, in the town of M e n d e l!

In the recent years, Brno has been undergoing rapid development. It is becoming a centre not only of the traditional branches of industry, mainly engineering trade fairs, but also the centre of various meetings, symposia and scientific congresses.

These celebrations are held to pay tribute to the memory of M e n d e l whose significance has far surpassed the border of our country.

M e n d e l no longer belongs only to Czechoslovakia, and it is my hope that I express also your opinion when I say that M e n d e l belongs to all progressive mankind, regardless of race, nationality, religion or political affiliation.

It is not long ago that while many scientists were coming to understand the significance and impact of Mendel's discoveries that others still doubted — sometimes from lack of conviction, sometimes from lack of personal courage.

We are thus also witness to the victory of scientific truth.

We pay tribute to the memory of a great scientist who was born in this country and who by the foresight of a genius lay the foundations of a science whose practical application has found its way into all branches of modern science, into life and of course into man himself.

You will certainly agree with me when I express my gratitude to the workers of the Moravian Museum for preserving all valuable documents and relics of M e n d e l, which are today, in the newly arranged Genetical Department of the Museum becoming the property of the entire international scientific world.

You are all meeting to pay tribute to the memory of M e n d e l on the occasion of the centenary of his famous discoveries, here in Brno you will review the entire development of genetics from M e n d e l to the present and then in Prague at a special symposium you will devote your attention to contemporary genetics.

We consider the fruitful and creative meeting of scientists of all nations, races, political denominations, as one of the pathways towards peaceful cooperation, so much needed by all mankind.

Therefore we wish you every success in your scientific meetings and discussions, mutual understanding and exchange of views.

Once again cordial welcome to you here in Czechoslovakia, in the trade fair town of Brno for the M e n d e l celebrations.

We shall be very glad if you come back to our town in the future as close friends.

We wish you dear friends and guests much success in your work.

Message of Professor Herman J. Muller to Mendel Memorial Symposium in Brno

PROFESSOR HERMANN J. MULLER
The Institute for Advanced Learning in the Medical Sciences, City of Hope, Duarte, California, U.S.A.

It is a matter of great joy to me that the epochal contribution of G r e g o r M e n d e l will be celebrated on its hundredth anniversary by an international conference held in the town in which he did his work and in the capital of the country containing that town. I rejoice the more because of two special circumstances. One lies in the fact that despite the denial of the truth and value of the principles discovered by M e n d e l, that has been so widespread throughout a considerable part of the world for nearly thirty years, these principles are at last being given their due recognition again. The second special circumstance consists in the enormous development of fundamental knowledge regarding the ultrafine structure and workings of the material basis of Mendelian heredity that has taken place in the last dozen years, and that has united Mendelism with chemistry and physics.

In the earlier years of my life I was privileged to have a rather close-up view of the first resurrection of Mendelism and of the establishment of the

chromosomes as its material basis and as the basis of the alterations that take place in its units. Later, while still following the ramifications of these quests, I was also in a position to see at somewhat closer range than most of my professional colleagues the course taken by both of the series of special events that I have just referred to, that is, the partial eclipse of Mendelism among non-scientists and its second resurrection, and also the underpinning of Mendelism by those who tied it to the physical sciences. And I agree with G a l i l e o that the world does move.

Because of the strategic position that I have occupied for so long in the grandstand, I feel especially drawn toward your celebration. I would like to offer my token of homage at the birthplace of the man who, along with D a r w i n , started us on the road to the deepest understanding of the biological nature of man and of all organisms.

I must, however, rejoice with you at a distance. For circumstances of health have made it inadvisable for me at my age to understake so long a trip, involving such radical changes of the time schedule, and such prolonged stress. Let me however send the following call to you, across ten thousand miles.

The science that we at present term genetics, that had its first clear start in the brilliant work of G r e g o r M e n d e l , contains the main clue to the means by which life acrose out of non-living material, to the nature of the threads that have woven evolution, and to the way that man must follow up when he transcends himself. M e n d e l has been twice resurrected but man will be resurrected repeatedly and even continuously. This rebirth will proceed by way of two reciprocally reenforcing methods: the manipulation and improvement of the physical and cultural environment on the interests of humanity, and the raising of man's inner genetic constitution. In this work of self-creation all of mankind will participate and cooperate. Science is many faceted but unified. In pursuing science and its applications the many faceted family of man also will attain a higher union. In this great adventure genetics, started by M e n d e l , will play a central role.

●

Further, messages of greetings and wishes of success from several scientific and cultural organizations of all over the world are presented.

Session I

ORIGIN OF MENDELISM

CHAIRMAN: H. STUBBE
VICE-CHAIRMAN: M. E. LOBASHEV

Mendel's Discovery and Mendel's Time

B. NĚMEC
Czechoslovak Academy of Sciences, Praha, Czechoslovakia

We commemorate the great work of Gr. Mendel which, published one hundred years ago and almost utterly forgotten, had waited for 35 years for its rediscovery. Competent speakers will speak here on the substance and significance of Mendel's work. I am going to try to explain why the importance of Mendel's discoveries was not appreciated at the time of their publication, and if, had they not been rediscovered, the present wonderful development of modern genetics would have taken place.

Mendel did not make any publicity for his discoveries. He lectured twice on them in a small circle of the Society for natural science in Brno, sent his paper to several well-known biologists, above all to Nägeli with whom he could hope for greatest understanding, to Kerner v. Marilaun, H. Hoffman, W. O. Focke; besidet his, his lecture was given to such societies with which the Society of Brno was in the habit of exchanging their publications. The only man who, up to 1900, appreciated the most important discoveries of Mendel's experiments, was an anonymous reviewer, who had reported on both lectures held in the Brno Society in 1865.

Mendel's paper did not meet with any response, though he himself was convinced that his work in genetics would be recognized and appreciated in the long run. Every investigator runs the risk that his work may be forgotten, yet each hopes that it will be recognized and rediscovered. Mendel may have felt a bitter disappointment when remembering his work. At least it is characteristic of him that, in his last letter, written 17 days before his death, he remembers meteorology, taking leave of it, but not so with genetics and his hybridization work.

His faith that the future would admit he was right, came true. In 1899, at the instigation of the Royal Horticultural Society an International Congress on hybridization was held in London. One of the speakers was W. Bateson who had occupied himself with the problem of mutation and other kinds of variations, the application of statistical methods to cross-breeding, the same as Mendel had claimed and carried out 34 years ago. Bateson, however, did not know Mendel's work. The following year, he lectured to the same Society on his own investigations in which he had obtained the same

results as Mendel. He made his exepriments without being influenced by Mendel, so that he has become a pioneer of genetics just as Mendel himself.

In Holland Hugo de Vries started his investigations on hybrids and their succeeding generations of his own accord; his attention to Mendel's paper had been drawn by Beijerinck, he quoted it and did full justice to its pioneering significance. C. Correns gained great merit by his concrete pioneering works in genetics; he began his experiments probably knowing the paper as we may presume according to a quotation in Focke's book from 1881. In the same way E. v. Tschermak came to know it; he deserves credit for his comprehension of the fact how important Mendelism might be for application in agri- and horticultural practice. W. Haacke in 1893—95 worked at hybridization of two breeds of mice and almost approached some of Mendel's results. Their explanation, however, was not correct. They did not know Mendel's work.

It was excellent that these three investigators stood at the cradle of modern genetics; each of them possessed his own method and working individuality. The fact that three different scientists had rediscovered Mendel's results 35 years old, has contributed to an adoption of Mendel's laws by almost all biologists nearly without any opposition or reservation.

For his experiments Mendel used to choose a perfectly simple material and thus we can explain that his results were comparatively simple, too. Though he himself was convinced of the vast validity of the laws of genetics, he emphasized the necessity of testing further material; since even taxon, differing in a great number of characters, can be cross-bred, he was aware that in such cases the results must necessarily be more complicated, though, in principle, especially in their independence of capacity for various characters, they must be identical.

H. de Vries defended his hypothesis on the hereditary substance and this made him try, to prove it experimentally. The existing hypothesis on heredity, including the Darwin's hypothesis on pangens which were corpuscular in natures required a verification by way of experiment. Darlington believes that even if Darwin had known Mendel's results he would hardly have realized their importance.

Mendel's paper was written in a clear and convincing style. His results were comparatively simple and were conclusions of concrete experiments. They were derived from facts which could not be assumed to have been wrongly observed. It was not a matter of uncertain or intricate facts. What semed to be hypothetical in his conclusions, could easily have been proved. Why then did his work not attract any attention and why did nobody take a good notice of it?

We must realize that even natural sciences are liable to the so-called "fashion-

able problems" which for some time, before being replaced by some new problems, attract most investigators' attention as well as their research. The problems of heredity and hybridization were not among these in the sixties. Amont the mentioned problems were included those of the origin of species and the variations of nature. The problems of evolution almost utterly occupied three quarters of the 19th century. Even Linné turned his attention to the origin of species and, having discovered on the basis of concrete hybridization experiments its influence upon the succeeding generations, he took hybridization for a probable origin of new species. He openly recommended it to botanists if they wanted to produce new species. But essentially he stuck to his opinion on the stability of species. Later, however, after the discovery of Peloria of *Linaria*, he abandoned his statement "nulla species nova". We cannot consider him as a predecessor of Lamarck or Darwin.

Though Buffon had doubted the stability of species, he had to withdraw his view later. Goethe was cautious. He once wrote that if we could not observe the development of any thing directly, then we cannot ascertain it correctly. The most radical evolutionists at the break from the 18th to the 19th century was Erasmus Darwin who, like his grandson Charles, attached utmost importance to the struggle in the nature. In his work "Temple of Nature" (1803) he declared the world to be a furious battle-field; he maintained that plants, too, are always struggling for space, air and light. Geoffroy Saint Hilaire (1772—1844) openly opposed (in 1830) the doctrine of stability of species and drew the scientists' attention to the unfavourable influence of environment on organisms. To Lamarck the nature was rather the mother of organisms and his evolutionary conception he worded as follows: "The nature had begun with the least perfect material and finished with the most intricate. The organization of organisms was getting gradually more and more intricate. Animals and plants have spread all over the habitable parts of globe, and each species has gained, by means of external circumstances, its own habits and metamorphosis."

Ch. Darwin won great admiration by his work "The Origin of Species" from as early as 1859. In this book he quotes 177 of his predecessors and witnesses. His doctrine gained many followers as well as adversaries and critics. In England many disputes arose, sometimes very keen, but soon they calmed down. Darwin's pertinacious follower was T. H. Huxley, in France he was strongly opposed by Flourens, the secretary of the Academy, in Germany by K. Schimper. E. Haeckel agreed with Darwin as early as 1862 in his monography on *Radiolars*, and next year he suggested a discussion on his doctrine at the congress of German physicians and naturalists. He elaborated phylogenetic problems of animals, later even those of plants, returning again and again to the experiments for the reconstruction of their pedigrees. Like Darwin Haeckel did not abandon the problem

of the origin of man. By means of a number of great works and fiery articles he became an enthusiastic apostle of Darwinism, which he included into the philosophy of materialism. He had also provoked the monistic movement whose high priest he became. Darwinism became a popular movement in Germany. Sometimes his statements could not be proved, sometimes he may have exaggerated, but taking all his scientific work into consideration it in no way reduces his merits for the progress in biology and for the motivation of the theory of evolution.

In the struggle for Darwinism in Germany appeared many Catholic and Protestant adversaries of his doctrine, but in the course of time this struggle calmed down, especially after some critics had referred to the fact that even some of the Christian Fathers (Patres) had practically been evolutionists, like A u r e l i u s A u g u s t i n u s and others. The Swiss Benedictine monk G a n d e r reconciled, as far as possible, their views with the theory of evolution, believing, however, like the Christian Fathers in the governing influence of a supernatural force. With us, Prof. A. M r á z e k, the zoologist, drew attention to these facts, though H a e c k e l had found quite a lot of adherents in our country. His work "Die Welträthsel" was translated into Czech, but it did not rouse so much attention as it did in Germany.

In France Darwinism met with a kind of solemn superiority; this is proved by extensive articles published in the Revue des deux Mondes. Maybe it was due to Cuvier's influence.

By the middle of the 19th century the situation in biology was quite different from that when L a m a r c k in 1809 had published his work "Philosophie zoologique". Zoology and botany had made great progress. Experimental physiology, embryology, ecology, phytopaleontology and zoopaleontology had been founded. Comparative morphology and taxonomy had acquired a lot of new facts. The theory of the cell, announced by P u r k y n ě in nuce in 1837 made people understand, from a uniform point of view, the uni- and multicellular organisms.

Darwin's works were remarkably comprehensive. He possessed an all-round curiosity and was attracted by all branches of natural science. Undisturbed, he could devote all his time to his research, he had the inborn English patience, perseverance and gift criticism. In all spheres he achieved remarkable results and everywhere he found evidence for his doctrine. The idea that species have changed and are continuously changing was conceived by him during his trip round the world, particularly in South America. Here he saw how profoundly had changed the fauna of the geological era preceding directly our era. In the Galapagos Islands he ascertained how species, inhabiting various neighbouring islands, separated from one another may differ. In Australia he saw the less resistant races die out as a result of contact, competition and struggle of various races of mankind. He did not consider species to be stable, but

plastic. He considered variation to be an actual property of a living substance. He admitted, however, the influence of external factors and the inheritance of acquired characters. He supposed the organisms to be absolutely changeable and giving rise to varieties with new characteristic creatures, either advantageous or disadvantageous. He also admitted the importance of bastardation and of abrupt changes. Organism produce so many descendants which, in a few years, might invade all dry land and most of them would perish in the struggle for space and food. Only individuals, best equipped for this competitive struggle will be left. This phenomenon was called by Darwin "natural selection". It is not a new idea. Linné's pupil Daniel Wilcke mentioned it, in Plato's dialogue Gorgias Kallikles says: "Nature itself distinctly determines that it is only just if a better individual is preferred to a worse one, and a stronger to a weaker. This fact is proved by examples of animals as well as of states and people. The supremacy of the strong over the weak is determined by nature, but hardly by our own laws." We might quote many authors. None of them, however, has used this struggle for existence as a driving force of evolution.

The theory of evolution has infiltrated all branches of natural and social sciences (philosophy, history, sociology, aesthetics etc.). There were, of course, biologists who had reservations as regards Darwinism, or such who took up a critical, even negative, altitude towards it. Our botanist, L. Čelakovský said in 1875 that the theory of evolution would suffer no detriment if it were ascertained that Darwin's doctrine, based on natural selection was not adequate for the explanation of the development of organisms.

Until 1890 very few Darwinists were keen to investigate the laws of hybridization. Naturally, botanists described various hybrids, mostly those they had found finished in the nature.

Hybridization experiments were mostly carried out in agriculture, horticulture and pomology, even with domestic animals. Gärtner's consuming effort for hybridization that had not led to any generally valid law may have dissuaded biologists from experimenting rather than attracted them to do so.

In the 19th century agriculture, pomology and horticulture made great progress the investigators having begun to base their work on scientific facts and several breeders reached the same results as Mendel. Above all it was A. Knight who ascertained individual cases of dominance and splitting. W. Herbert has recognized the uniformity of the first generation of hybrids and the splitting in further generations. Goss, Seton, Laxton and especially Vilmorin and Hope achieved similar results. Darwin, Nägeli, H. de Vries, Weismann, Haeckel propounded several hypotheses on heredity of a corpuscular and static rather than dynamic character. Breeding by individual selection prevailed.

In the second half of the 19th century there prevailed in biology an interest

in the theory of evolution, its motivation and research into its causes. The evolutionary doctrine was a great power with which Mendel's results could not cope. By works in the sphere of the evolutionary theory they completely fell into oblivion. By stating this I do not want in any way to depreciate the theory of evolution, but it is a fact that between 1859 to 1900 the problems of evolution prevailed in biology, while others attracted much less attention.

Were it not for Focke's mention of Mendel's publication, maybe we sould not know anything about Mendel's ingenious discovery.

There is no doubt that we would know the facts about hybridization and its laws, because four biologists, at the same time just before 1900, working with the same material as M e n d e l had worked, achieved the same results.

In Sharp's "Hymn on Nucleus" from 1932, the rediscovery of Mendel's work from 1900 is justly celebrated as an appearance of a star after a long eclipse; this star will be a guiding light for the travellers to find the right pathway.

In the decades after the publication of Mendel's paper anatomy, histology, embryology, most of all, however, cytology made great progress. As early as 1833 R o b e r t B r o w n declared the nucleus to be a widely spread cell organ. L . W . S h a r p in his Hymn on Nucleus declared it to be an all-powerful part of the cell. This is the opening of the Hymn:

"I am the nucleus ! In toads and toadstools, cycade, cabbages and kings I play my myriad roles . . . " It was with difficulties that the correct information on the genesis of cells by division was gaining ground, though their genesis by division with some algae had been ascertained by M o h l , with higher plants by M i r b e l and U n g e r , with ova of mammals by B i s c h o f (in 1842), with *cephalopods* by K ö l l i k e r (in 1841). It was impossible to determine the process of fertilization in *Phanerogams* without application of the latest cytological methods. With animals it is a much simpler process; O . H e r t w i g in 1875 studied the fertilization of Echinoid *Toxopneustes lividus* and summed up his observations as follows: "The fertilization consists in a fusion of two nuclei of different sexes." This knowledge was nompleted by F . V e j d o v s k ý ' s work "The ripening, fertilization and division of the ova of the worm *Rhynchelmis litorella*". In this work the author has proved that the spermatozoon carries his centrosome into the ovum which causes a division of the same, while the female centrosome disappears. In 1873 A . S c h n e i d e r recognized the mitotic division of the nucleus in some *Plathelmits*, whose general occurrence with plants was then described by S t r a s b u r g e r in 1875. W . F l e m m i n g discovered chromosomes, their longitudinal splitting was discovered by G u i g n a r d in 1883, R a b l formulated the law of individuality, continuity and constant number of chromosomes. The periodical reductions of chromosomes was described by O . H e r t w i g and E . S t r a s b u r g e r who declared them to be the actual material bearers of heredity.

The knowledge about the nature of fertilization, the individuality of chromosomes and the periodical reduction of their number necessarily led the scientists to believe that the cytological results of hybridization might help in the explanation of inheritence. That may have induced Bateson, W. Haacke and others to undertake hybridization experiments which led to identical results which Gr. Mendel had obtained as early as 1865.

Three scientists began to carry out hybridization works without knowing at first Mendel's experiments. They were induced to do so by the existing state of biology by the end of the last century. They were joined by Bateson who, in 1895 explained what methods were to be used when experimenting, both as regards the parents of the hybrids and the elaboration of the obtained results i.e. the statistics of all the obtained material and the individual exploration of each alternative trait. He gave an account of his own experiments in 1900 at the Royal Horticultural Society, and in 1909 he published his classical work: Mendel's principles of Heredity. Though until 1900 Mendel had been unknown to him he ranks as equal with the rediscoveres of his work, since quite independently he had attained Mendel's laws.

It has been my duty to determine why the great importance of Mendel's discoveries was not understood at the time of their publication, and if, even without their rediscovery, the astonishing development of modern genetics would have taken place.

Mendel did not do any publicity for his discoveries. His second work on *Hieracium pilosella* rather impaired the substance of the first paper. At that time the interests of the biologists were fully absorbed in Darwin and his work on evolution. The latter was thought the essential problem of biology. Mendel applied to several biologists with his work. Kerner's doctrine was that new species arose by hybridization and that bastards were constant from the very beginning. The splitting and variations of hybrids did not fit into his hypothesis. He may not even have read Mendel's paper. Nägeli had his own opinion as regards idioplasma and he could not accept the hypothesis of independent genetic factors. Besides, he was too deeply absorbed in experiments on evolution and the study of *Hieracium*. H. Hoffman observed the variation of plants and he used his results against Darwin. He simply did not understand Mendel's experiments. Focke did not believe in a uniform lawfulness of the process during bastardation. Up to the end of the 19th century only these three authors knew and referred to Mendel, though only quite superficially, while other great men in botany and university professors did not take him seriously enough.

The fact that he was rediscovered and his doctrine recognized by three scientists at the same time had a favourable influence on the development of genetics. It caused Mendel's discoveries to be accepted instantly as well as to make them spread quickly. We must pay to credit Bateson for having

discovered Mendel's laws independently, though, to him, Mendel at once became his great model. The remarkable report of an anonymous reviewer in a Brno daily, so full of understanding for the scientific value of Mendel's discoveries, met with no response, but we do remember him with gratitude, as well as his recent discoverer Dr. J. Sajner.

Carl Erich Correns 1864—1933

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"The more we look back, the further one can look forward." We may think of these words of a statesman when remembering the life-work of Carl Correns who was one of the great heads of genetics in the first three decades of our century.

At that time Germany took an active and directive part in the development of this science and the research centre in Berlin-Dahlem where Erwin Baur, Richard Goldschmidt, Max Hartmann, Paula Hertwig, Hans Nachtsheim, Elisabeth Schiemann, Curt Stern, Fritz v. Wettstein and many others were working, had become known all over the world.

Also in the present epoch of molecular genetics glory and fame of those decades will endure since they have laid the foundations of our science and have enriched and settled the classical period of genetics by a wealth of new basic knowledge.

The unrivalled leader of this team was Correns who, by means of his experimental skill along with a careful selection of his objects, by means of his unfailing understanding of the consequences and by means of his indefatigable energy, was gradually led to the solution of the fundamental problems, problems that, in his time, often have only been presaged by many others.

His way, ending in the position of the director of the newly founded Kaiser-Wilhelm-Institut für Biologie in Berlin—Dahlem, was not easy. After careful botanical studies he took his doctor's degree with Nägeli in München, went to Graz, Berlin and Leipzig, to Tübingen as an unsalaried private-lecturer in 1892, 10 years later he was appointed assistant professor in Leipzig. In 1909, finally, at the age of 45, he was offered a chair at the University of Münster and from there, in 1914, he accepted the invitation of the Kaiser-Wilhelm-Gesellschaft.

In his years of travel he made experiments on the structure of the cell membrane with Nägeli in München, pursued anatomical-physiological studies with Haberlandt and worked on problems concerning the physiology of stimulation with Pfeffer in Leipzig. During those years he may have looked out for a field, that would fully engage him.

His youth already and later his student days were filled with the struggle for Darwin's revolutionary ideas on the origin and evolution of species, and probably the excellent studies on the fertilization process by Bütschli, Hertwig, Boveri, Strasburger and many others will have fascinated young Correns. For to him, as a well-trained botanist, the efforts of many colleagues were well known to discover by means of hybridization experiments the nature of the species and so to produce new species. Till then they had had no satisfactory results and time had become ripe to look out for new ways to the end to use the biology of fertilization and the research in the nature of bastards as the decisive means for the elucidation of the hereditary process. The key to the desired result was the hybridization of varieties and not of species because as a result of the great number of "segregating" characters following species hybridization no chance was given to find out the laws for the inheritance of individual characters.

At this point, almost simultaneously, De Vries and Correns started their work. In his idea of an "intracellular pangenesis" De Vries had postulated individual molecules, pangenes, for any heritable character and a decomposition of the species characters in exactly separated components. Emphasis of his work, however, was in the theory of descent and in his "mutation theory". Correns, on the other hand, having investigated the fertilization of maize and peas, analyzed the hereditary process proceeding from the particular problem of the so-called xenia of maize and studied it on various other objects.

Like De Vries and soon there after also Tschermak, Correns found in 1900 the laws of segregation in the hybrids and at the same time their precursor Gregor Mendel was discovered who, $3^1/^2$ decades before, had found the laws of segregation now named after him.

Much has been written about the details of this rediscovery and not all the questions that appeared in this context could be unambiguously answered. As a matter of fact, the rediscovery was the signal for the genesis of a new science that, starting from the analysis of the hereditary material of plants, animals and man, has advanced at present to the molecular basis of the life-process and has developed into the central discipline of life sciences as no other branch of biology. It was, in particular, Correns who by means of systematic experiments paved the way for the development of the new science and who advanced it — a great and unique merit that found acknowledgement in Correns' nomination for the Nobel prize, together with DeVries, in the first decade after the Nobel Foundation had been established.

In all directions the laws found were verified by the rediscoverers and an ever increasing number of scientists. Not only the distribution of the genetic material was uppermost in the research at that time, but also the problems of its action and interrelationship of its components were studied. By means of

his investigations in the xenia of maize, the analyses of the inheritance of flower colours in flax, his experiments on linkage in *Matthiola* and the studies on lethal factors C o r r e n s contributed decisively to the explanation of a number of exceptional cases and — and this is the essential part — put them in their relation to the great general problems.

During the last years allegations have often been made that in classical genetics there has been to great an insistance on the monopoly of the cell nucleus, whereas the co-operation of the extranuclear material and the environmental factors have been overlooked. C o r r e n s himself demonstrated already in 1900 the contrary by his studies which gave evidence for a non-Mendelian plastid inheritance in *Mirabilis*. More striking results could soon be adduced by other research workers.

The greatest of his achievements may however be seen in the elucidation of sex inheritance, the millenial problem of the reasons for sex determination and the mode of sex inheritance. In no other field of biology more fantastic and mystical conceptions have been developped than regarding sex formation and sex determination. Generations of naturalists did not succeed, C o r r e n s , however, made the fundamentals clear and consolidated his findings which in many variations were confirmed with animals and plants by other research-workers.

C o r r e n s started with the experience that normally both sexes are produced with equal frequency and looked for exmaples showing equal segregation numbers for various characters. He found them in back-crossing a bastard heterozygous for one gene pair with the homozygous recessive parent from which the heterozygous and the homozygous recessive type segregated in equal numbers. In comparison with the inheritance of sex, the phenotypically dominant hybrid would be analogous to the male sex giving two types of germ cells — male and female determining ones — and the homozygous recessive parent of the back-cross would be analogous to the female sex producing only one type of germ-cells.

C o r r e n s proved the correctness of this simple model using *Bryonia* as his experimental material. He crossed males and females of the dioecious *Bryonia dioica* with *Bryonia alba*, which is a hermaphrodite. He found that the male of *B. dioica* produced two types of germ-cells in equal parts, the female only one. This is in accordance with expectation. The same situation was true in case of *Melandrium* and thereafter C o r r e n s started his first experiments with the aim to influence the relative proportions of the two sexes by means of so-called "competition experiments". After pollination with pollen amounts equalling the number of egg-cells a clear 1 : 1 ratio of both sexes was found. When the amount of pollen was increased, female determining pollen grains had a higher chance for fertilization than male determining ones. Furthermore, aging of pollen grains was connected with advantages for the male-determining

pollen. These experiments laid the foundations of all later efforts to change sex-ratios artificially.

The proficiency of Carl Erich Correns will always be remembered with admiration. Looking back I see his tall figure with the imposing head in the nursery of the Dahlem institute, indefatigably observing, registering, working. Nobody dared disturb him. We, Erwin Baur's young pupils at the institute, looked at him with awe, admiring the precision of his thinking and the breadth of his mind. Looking back I see by the side of Correns at the Dahlem institute the other outstanding biologists Richard Goldschmidt, Max Hartmann, Hans Spemann, Otto Warburg and the men of the younger generation who, altogether possessed by the idea to be servants of science, made the fame of the institute known all over the world.

The more we, looking back, reflect upon the work by Correns and his co-workers the further we shall look forward and understand what will have to be done to attain further success in the wide field of biology. In those days in the Kaiser-Wilhelm-Gesellschaft zur Förderung der Wissenschaften the idea of a union of research institutes came true. At the institutes of this society the élite assembled to live for their studies, free from other duties and best equipped. The steadiness of concentrated research, the standing exchange of views with like-minded colleagues of all biological disciplines, the world-wide union of the large family of scientists — all this gave the basis where successful work could be done.

We know very well that world has changed since then. In addition to the necessity to continue the own investigations, to study the ever increasing literature, to care for the education of the coming generation of scientists and of many other duties, the obligation is on us to take general responsibility and to help that world will change to what is good.

However, let us never forget that the principal task of a scientist is to struggle for a realization of the so far unknown to the end that, one day, it may be profitable for the welfare of man. Those responsible must make all efforts to improve more and more the prerequisites to a performance of this great task. The trust left to us by Carl Correns will then be realized.

Mendelism Comes to England

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Even if Mendel's paper, giving an account of his hybridization experiments with the pea and presenting his interpretation of the results he had obtained, had been widely circulated among the biologists of Britain in the year of its publication, it is most improbable that any of them would have appreciated its significance. At that time and for long afterwards their interests were absorbed in problems that sprang from Darwin's The Origin of Species by means of Natural Selection and they were eagerly occupied in establishing the phylogenetic relatiosnhips of different forms of animals and plants through studies in the fields of embryology and comparative anatomy. They accepted the teaching of Darwin that the evolutionary movement had taken the form of small and even almost imperceptible continuous steps that had yielded gradual and improving changes in characterization. It was agreed that these continuous variations were heritable but concerning the mechanism of organic inheritance nothing was known.

Darwin himself had accepted the prevailing view that when the new variant and the older form were crossed blending inheritance occurred, the differing properties of the two parental forms becoming amalgamated in the offspring. In his "The Variation of Animals and Plants under Domestication", 1868, he adopted the doctrine of the inheritance of acquired characters promulgated by Lamarck in 1809 and developed a new version of the very ancient theory of pangenesis, calling upon the physiological units of Herbert Spencer *(*Principles of Biology, 1863*)*. Mendel remained unknow to Darwin and when the former visited London in 1862 the two did not meet.

Darwin's conclusion that continuous variations constituted the bulk of the heritable novelties upon which natural selection operated gained strong support from the statistical studies of Francis Galton on stature, intelligence and susceptibility to disease in man, studies which led directly to the formulation of his law of ancestral inheritance in 1897. It is of interest to note that Galton and Mendel were born in the same year, that both became interested in problems of heredity and that, being possessed of a high grade of mathematical competence, both employed statistical methods in the study

of biological phenomena. Galton's Hereditary Genius, 1869, was a truly remarkable study but its importance could not possibly be recognized until the science that was to develop out of Mendel's discoveries had grown large. By 1875 Galton had come to appreciate the unique value of twins for the detection of the relative roles of mature and nurture in the control of the development of the characterization of the individual, a discovery of fundamental importance which was further elaborated in his Inquiries into Human Faculty, 1883.

The influence of Darwin and of Galton was all-pervading in the 1890s in Britain. The creed of the younger biologists of those days was proclaimed in 1895 by one of them who was to figure prominently in the disputation that was to follow upon the rediscovery of Mendelism in 1900, Raphael Weldon, a Cambridge zoologist who had moved to University College London; 'The questions raised by the Darwinian hypothesis are purely statistical and the statistical method is the only one at present obvious by which that hypothesis can be experimentally checked'.

At that time there was only one academic zoologist in Britain who was investigating, by means of experimentation, such phenomena as atavism, reversion and telegony, phenomena that had puzzled Darwin during the development of his evolution theory. This was Cossar Ewart of Edinburgh (The Penicuik Experiments, 1899) and only one man, who not knowing of Mendel's existence, was carrying out hybridization experiments, though for different reasons and with different aims, essentially similar to Mendel's own, William Bateson, like Weldon a Cambridge zoologist and a friend of his. It was a chance meeting with Weldon that had decided Bateson to become a zoologist and from Weldon Bateson had received much encouragement when the two of them were members of the staff of the zoology department in Cambridge.

In 1894 Bateson's book, Materials for the Study of Variation with special regard to Discontinuity in the Origin of Species had appeared. It was the outcome of seven years spent in collecting patiently, after the manner of Darwin, from a very wide variety of sources facts relating to the kind and frequency of variation in animals and plants. As his store of information enlarged he had become more and more persuaded that discontinuous variation was far more common that had been thought and that it had played a far greater role in evolution that had been supposed. He had become a saltationist and was seeking a saltationist interpretation of evolution. He was quite unable to accept the teaching of the biometricians whose interest was in the continuous form of variation and was totally unimpressed by their mathematical inventions. To Weldon, Bateson's book constituted a challenge that could not be disregarded and to it he reacted violently. The close friendship that had existed between these two men, always ready to defend strenuously their own views and to attack equally strenuously such as contra-

dicted them, was to become dissolved in bitterness during the next nine years that were to witness much passionate argument.

The first clash between them was in 1895 over the question of the origin of the cultivated *Cinereria*. W e l d o n maintained that the different varieties had been produced from an ancestral wild species by the systematic and long-continued selection the horticulturalist of small continuous variations as these appeared, always working towards a predetermined end and getting nearer to his step by step. B a t e s o n , on the other hand, insisted that many of these varieties had arisen quite abruptly as the result of hybridization between different recognized species and in support of his contention was able to call upon the results obtained in carefully designed experiments undertaken by the curator of the Cambridge Botanic Garden. These conflicting views and the language in which they were couched did much to enliven the columns of Nature.

The conflicting opinions of these two men illustrate clearly the differences that distinguished the early Mendelians and the Darwinian selectionists. The former rejected natural selection for the reason that the large discontinuous variations with which they dealt appeared to arise quite abruptly and fully fashioned without any help from selection. The latter, on the other hand, maintained that these wide discontinuities of characterization could not possibly be reconciled with the gradual and gentle way in which evolution had occured and that moreover they were for the most part less in harmony with the conditions of the habitat than were the forms from which they sprang.

In 1894 the Royal Socity, at the instigation of G a l t o n , had set up a committee for conducting statistical enquiries into the measurable characteristics of animals and plants. W e l d o n became a member. B a t e s o n was invited to join in 1897 but, although at that time it seemed likely that an experimental station in connexion with the committee in Darwin's old home, Down House, would be stablished, he declined for the reason that the methods of investigation employed by the members of the committee did not appeal to him. Later this committee was reorganized and the scope of its enquiries widened. W e l d o n resigned and B a t e s o n joined, later to serve as its secretary. W e l d o n , together with K a r l P e a r s o n , who had succeeded G a l t o n as leader of the biometrical school in England, launched the journal Biometrika.

B a t e s o n , because of his consuming interest in variation and of his many contacts with horticulturalists in his search for examples thereof, took an active part in the affairs of the Royal Horticultural Society of London. It was this body, that had done much to encourage the English plant hybridizers who had preceded M e n d e l , which had organized the first international conference on hybridization in London, in July 1899. B a t e s o n presented a paper Hybridization and cross-breeding as a method of scientific investiga-

tion to this conference. In it he inveted his audience to enquire into the ways in which new varieties of cultivated plants arose and suggested that the problem of the origin of species could best be tackled by studying the origin of varieties within a species. He himself was doing exactly this, investigating the relationships of the different forms of comb in the domestic fowl. He pointed out that in such studies it was necessary to carry out large scale experiments which could give figures that could be subjected to statistical treatment.

On 8th May, 1900 Bateson was in the train en route for London where he was to address the Royal Horticultural Society on Problems of heredity as a subject for horticultural investigation when he happened to read Correns' paper in which an account of Mendel's discoveries was given. (Gregor Mendel's Regel über das Verhalten der Nachkommenschaften der Rassenbastarde.) He immediately saw that Mendelism provided the strongest possible support for his own views concerning the role of discontinuous variation in the creation of new forms and therefore altered his notes so as to include the news of the re-discovery and an assessment of its significance. He described the seven pairs of characters studied by Mendel and called attention to the percentages of dominants and recessives in the second hybrid generation and to the 3 : 1 ratio. He did not refer to Mendel's "elements that determined" characterizations but spoke of "pollen grains and ovules each of which bears only one of the alternative varietal characters but not both" and of each ovule and pollen grain being pure in respect of each character to which the law of segregation applied.

The Royal Horticultural Society published an English translation of Mendel's paper.

It was in this year, 1900, that two papers by Karl Pearson appeared, On the inheritance of coat-colour in horses and On the inheritance of eye-colour in man, both of considerable interest and dealing with the mode of inheritance of characters not capable of oxact quantitative mearurement. It was unfortunate, therefore, that Pearson thereafter turned aside to indulge in a fruitless debate with Bateson on a variety of biological concepts, e.g. On the principles of homotyposis and its relation to heredity, to the variability of the individual and to that of the race; Note on Mr. Bateson's paper Heredity differentiation and other conceptions of biology; and On the fundamental conceptions of biology. Bateson's contributions to this particular disputation were Heredity, differentiation and other conceptions of biology, a consideration of Professor Karl Pearson's paper on The Principles of homotyposis etc., and Variation and differentiation in parts and brethren, the latter being privately printed for the reason that the columns of Nature were closed to Bateson. In retrospect it is clear that these matters were of but ephemeral interest and that much of the argument was a display of personal antagonism.

In 1902 there appeared, to be completely unnoticed apparently, a paper by Udney Yule, Mendel's laws and their probable relations to interracial heredity, in which the author maintained that the Mendelian scheme could accommodate both the typical Mendelian characters and the kind of characters that engaged the attention of the biometricians. Had the message of this paper been noted and understood by the hybridizers and the biometricians at the time a great deal of misspent energy might have been employed to better purpose and the development of the science of genetics might have been speeded. It was not until much later that it came to be accepted that blending inheritance was essentially Mendelian and that it was controlled by multiple factors which individually lacked dominance. Towards this understanding of the genetic basis of quantitative characters Fisher and Mather, in England, were later to make their notable contributions. Fisher* it was who in 1918 showed that far from the observations on continuously distributed metrical characters being inconsistent with Mendelian theory they could not be explained in any other way. It is said that when this paper was submitted to the Royal Society of London the two referees, one a Darvinian selectionist and the other a Mendelian, both recommended that it should not be accepted for publication. The paper was then submitted to the Royal Society of Edinburgh and was published in its Transactions.

When Mendel's work and ideas became known to Weldon it seemed to him that they constituted a serious threat to the biometrical school and so he set out deliberately to belittle them in his paper Mendel's law of alternative (sic) inheritance in peas. In his reply to this Bateson produced a small book, Mendel's principles of heredity; a defence, with a translation of Mendel's original paper on hybridization. The defence was certainly robust, even fierce. Weldon promptly retorted with two papers, On the ambiguity of Mendel's categories and Mr. Bateson's revisions of Mendel's theory of heredity. In his turn Bateson responded by sending in a communication to the editor of Nature but the latter declined to accept it.

Bateson, at this time, greatly aided by his wife and by Miss Saunders, lecturer in botany, Newnham College, was carrying out fairly extensive hybridization work with poultry and sweet peas. Looking back over the years it is impossible not to be astonished at the quantity as well as at the quality of the experimental work that was undertaken by Bateson during the period 1897—1902 when it is remembered that the amount of money available for its support was utterly trifling. In 1897, aided by a grant from the Royal Society he was able to rent an allotment belonging to the Cambridge Botanic Garden and to begin breeding experiments with his poultry and plants.

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*) The correlation between relatives on the supposition of Mendelian inheritance. Trans. Roy. Soc. Edin. 52, 309.

In 1899 he rented an adjoining alotment and expanded his work. Still further expansion became possible when he moved his family to Merton House Granchester. In one of his "cheap" years his receipts were — from the Royal Society £ 36, from sales of produce £ 30; and his outgoings totalled £ 90, leaving him with a deficit (which he himself had to make good) of £ 24. At all times difficulties of various kinds threatened to bring everything to a halt but somehow or other, with the aid of these small Royal Society grants and others received from the British Association for the Advancement of Science, they were overcome. Never have these bodies dispensed their moneys to better advantage. In 1903, a friend who wished to remain anonymous, offered Bateson £ 150 a year for two years. He at once invited R. C. Punnett, then a junior demonstrator in the zoology department, to join him and so a partnership that was to make lasting and very notable contributions to developing Mendelism came into being. It was Punnett who included the rabbit among the experimental animals used by the Batesonian group in Cambridge. He happened to notice an old disused shed fitted with wire cages standing on a piece of waste ground near the university laboratories. He found on enquiry that it had been used by Walter Heape in his experimental work on reproductive physiology. Heape handed the shed over to Punnett who promptly began hybridizing experiments with a number of rabbit varieties. Among other discoveries that he made was the dominant black coat colour which contradicted the conclusions reached by Woods. Punnett did not publish his results until 1913. (Inheritance of coat colour in rabbits. J. Genet. 2.)

From this time of the Bateson group progressively enlarged, as his missionary zeal enthused such people as Miss Durham, his sister-in-law, (who worked with mice), Miss Killby (goats), Miss Marryat, *(Mirabilis jalapa)* Miss Sollas (guinea-pigs), Mis Wheldale *(Antirrhinum)*, L. Doncaster *(Lepidoptera)*, R. P. Gregory (sweet pea and *Primula*) R. Staples-Browne (pigeons) and C. C. Hurst (poultry and rabbits) and as the experimental work expanded, the universality of the Mendelian principles was demonstrated.

Following his example, Weldon turned to experimentation, using moths, mice and poppies. He enlisted the help of a young zoologist named Darbishire, who later was to become the first lecturer in genetics in the University of Edinburgh. A cross was made between the agouti and the albino varieties of the house-mouse and in the second hybrid generation a ratio of 3 agoutis to 1 albino in every 4 was obtained. The albinos were discarded in this and in every succeeding generation and the agoutis interbred generation after generation. It was observed that the proportion of albinos thrown by these agoutis in successive generations progressively diminished until eventually none appeared. Weldon maintained that this result completely destroyed the Mendelian

doctrine. Bateson vigorously disputed this and for a time the columns of Nature were enriched by communications from these two antagonists. The public dispute was brought to an abrupt end when the editor once again declined to accept anything more from Bateson concerning either Mendelism or Weldon. Bateson was right and Weldon wrong for in the experiment no distinction had been made between the homozygous and the heterozygous agoutis.

In the same year, 1904, Bateson was president of section D (zoology) of the British Association for the Advancement of Science meeting in Cambridge. In his address on Heredity and variation to the section he forcefully presented his ideas concerning these matters, being well aware that very few in his audience shared his views concerning the significance of Mendel's discovery. "Had" he said, "a discovery comparable in magnitude with that of Mendel been announced in physics or chemistry, it would at once have been repeated and extended in every great scientific shool throughout the world". But the academic biologists were so much engrossed in their surveys of terrestrial types that most of them were not even conversant with Mendelism and had failed to assimilate this new knowlege. He urged those who talked so glibly of heredity, variation and selection to look to the collecting box, the seed-bed and the poultry-yard where these could be seen in operation and their properties tested. He referred to the "unfixable heterozygote" introducing the terms homo- and heterozygous and F. 1. and F. 2. and although he spoke of the synthetic production of walnut-comb in the fowl by the mating of pea-comb and rose-comb he still talked of unit-characters and of characters being carried in the gametes. He showed that dominance as not an essential feature of the Mendelian scheme and gave examples of irregular dominance and of intermediacy in the F. 1. He gave several examples of the "entanglement between sex and gametically segregable characters" and referred to coupling and repulsion. Having asserted that "the problem of heredity is the problem of the manner of distribution of characters among germ-cells he ended by asking what was the cause of variation.

Bateson's thesis was supported by contributions from Punnett and Hurst dealing with their own experiments with poultry and from Miss Saunders on stocks.

In 1905 Weldon and Bateson clashed once more. The latter had submitted to the Royal Society of London a paper by Hurst on the inheritance of coat-colour in the horse in which it was stated that chestnut was recessive to both bay and brown. Weldon, who read the paper as a referee, advised against its acceptance for the reason that he had found in the records instances in which chestnut x chestnut had thrown bays or browns. Hurst maintained that these were errors in recording. Bateson withdrew the paper, examined the studbooks, satisfied himself that Hurst was right and

resubmitted the paper which was read at the meeting of the Society on 18th January, 1906, when a very lively discussion took place.

Shortly after this W e l d o n died, suddenly and unexpectedly and with his death the biometricians' attack upon Mendelism came to an end and the further development of the science was no longer impeded by purely destructive criticism and unprofitable disputation. The work of the Cambridge group flourished and the academic opposition to B a t e s o n himself weakened. In 1908 he was elected to the newly created but impermanent chair of biology in Cambridge but resigned this in 1910, largely because of its impermanence, to become director of the John Innes Horticultural Institute. In 1912 the Cambridge chair was permanently endowed and its title was changed from biology to genetics. But B a t e s o n , when invited to return to Cambridge to occupy it, decided to remain where he was and so P u n n e t t was appointed to the first chair of its kind in Britain.

It is reasonable to end the story of the coming of Mendelism to Britain at this point, for by this time M o r g a n and his colleagues in Columbia University, New York, working with *Drosophila melanogaster*, were about to formulate the chromosome theory of heredity which was to transfer the leadership in genetics from Cambridge to Columbia.

The attitude of the senior and more influential naturalists towards Mendelism and the Mendelians during this period is clearly revealed in J . A r t h u r T h o m s o n ' s Heredity which appeared in 1908, in an article in the August, 1908, number of the Contemporary Review by A . R . W a l l a c e and in E . B . P o u l t o n ' s Essays on Evolution, 1908, all of which are considered in a review article by P u n n e t t in the October 1908 number of The New Quarterly.

T h o m s o n devotes but little space to Mendelism and makes it perfectly clear that he thought little of it and understood it not at all. In a special section on Non-Mendelian Results he cites T s c h e r m a k's 9 : 3 : 4 ratio in the F. 2. of a white x redflowered *Pisum sativum* cross which he states "cannot be called Mendelian" and also records that "the progeny of a white x black (skin colour in man) is a mulatto, and mulattos intermarrying breed true, neither white nor black reappearing. It is a clear case of blending inheritance remaining stable. And this applies to hair as well as to colour . . . There is not the least hint of Mendelian inheritance". P u n n e t t , in his review, suggests than "it is unlikely that any one again will undertake a serious work upon heredity without the knowledge which actual contact with the facts can only supply".

W a l l a c e was, of course, a dedicated Darwinian and maintained that the variation that was of importance in evolution was the continuous kind. To him "the only intelligent clue to the mighty labyrinth of nature" was to be found in the Darwinian theory. His attitude towards Mendelism was scornful.

". . . the claims of the Mutationists and the Mendelians, as made by many of their ill-informed supporters are ludicrous in their exaggeration and total misapprehension of the problem they profess to have solved." Punnett pointed out that the Mendelians did not claim to have solved the problem of the origin of species but had merely suggested that the orthodox theory should be reconsidered in the light of the facts concerning discontinuous variation and Mendelian segregation that had recently been disclosed.

Poulton expressed the view that Mendelism was "injurious to Biological Science and a hindrance in the attempt to solve the problem of evolution". He thought that it would lead to "the contemptuous depreciation of other lines of investigation directly inspired by the work and teaching of Darwin and Wallace" and to "a widespread belief among the ill-informed that the teachings of the founders of modern biology was abandoned".

In Punnett's 3rd edition of Mendelism, 1910, he argued for a mutational basis in connexion with mimetic resemblance. Poulton took exception to this and started a controversy in the journal Bedrock. Punnett took up the challenge and a fierce but nevertheless friendly disputation began.

Bateson was largely responsible for an ever enlarging appreciation of the significance of Mendel's principles of heredity among the biologists of Britain during the first two decades of the present century. Slowly it came to be accepted that Mendelism destroyed the doctrines concerning pangenesis, blending inheritance and the inheritance of acquired characters and offered new and more reasonable explanations for atavism, reversion, prepotency and telegony, phenomena that had puzzled Darwin and his followers. Its impact was such that an increasing number of the younger biologists turned from purely descriptive to experimental biology.

It was Bateson who gave to the developing science the fitting name genetics. He first made the suggestion that it should be so called on 18th May 1905 in a letter dealing with the title of a new professorship that was about to be created in Cambridge. A year later in his inaugural address to the Third International Conference on Hybridization in London he repeated the suggestion publicly — "I suggest for the consideration of this congress the term genetics, which sufficiently indicates that our labours are devoted to the elucidation of the phenomena of heredity and variation; in other words to the physiology of descent, with implied bearing on the theoretical problems of the evolutionist and systematist, and application to the practical problems of breeders, whether of animals or plants. After more or less indirect wanderings, we have thus a definite aim in view."

It was Bateson who gave much clarity to Mendelian theory by introducing terms such as homo- and heterozygous and the idea of gametic purity. It was Punnett who introduced the useful checkerboard scheme for displaying, simply and clearly, the genetic constitutions of gametes elaborated

by a mated pair. In 1908, when lecturing to the Royal Society of Medicine in London, Punnett was asked why it was that brown-eye colour, a dominant character, did not become increasingly common in the population. He pointed out that among the brown-eyed there were always very many who were heterozygotes and that these contributed their quota of blue-eyed. On his return to Cambridge he discussed the question with his friend G. H. Hardy the mathematician whose reply was later to become embodied in the Hardy-Weinberg equilibrium. It was not realized at the time that the answer had already been supplied by Pearson in his paper On a generalised theory of alternative inheritance with special reference to Mendel's law.

Bateson, Saunders, Punnett and their colleagues discovered and described the phenomena of linkage, sex-linkage and factor interaction. To explain dominance the Presence and Absence hypothesis was invented, very useful in its simplicity at the time but doomed to be jettisoned when reverse mutation was observed and its significance understood. To accommodate the observed facts concerning linkage, the idea of coupling and repulsion was devised, very adequate at the time but due for replacement when the chromosome theory of heredity came to be accepted. The discovery of factor interaction necessarily meant that the notion of the unit character had to be discarded and meant also that the attention was attracted to the nature of the material entities which Mendel had referred to as factors or elements which determined characters. (From his notebooks it is probable that Mendel himself had observed this interaction of factors in his experiments with the bean but that he had disregarded it for the reason that it was outwith his immediate interests.) Bateson himself adopted Mendel's term "factor" for the reason that it implied no hypothesis concerning its actual nature.

Bateson was the first to show that Mendel's principles applied to animals as well as to plants and he and his colleagues did much to demonstrate the universality of the Mendelian theory.

During the period 1895—1906 Bateson encountered fierce opposition that surely would have exhausted a less determined and less combative man. But he withstood it and so was able to render to science in Britain a service of the very greatest importance. A memorial to him and to his colleagues of those early years (and therefore to Mendel himself) is to be found in every university and research institution in Britain where the science of genetics now flourishes.

Looking back, it can be seen that to Bateson the essential feature of Mendelism and the discovery of prime importance seemed to be what Correns called the law of segregation. He was interested in variations in respect of characters and in the hereditary transmission of these; he was therefore intensely interested in the ratios that were obtained among the progeny of different matings. He certainly was not interested in what lay behind the

character. He paid little attention, therefore, to Mendel's two major conclusions concerning the meaning of the results he had obtained: —(i) that the development of the fertilized egg "followed a constant law wich is founded on the material composition and arrangement of the elements which meet in the cell to give a vivifying union", referring to "elements of both (germ-) cells which determine opposite characters" and (ii) that it is only possible for the differentiating elements to liberate themselves from the enforced union when the fertilizing cells are developed". Mendel was postulating the existence of an element-distributing mechanism exactly like that which was to be built into the chromosome theory of heredity and also the existence of a reduction division during gametogenesis. He thus forestalled Weismann who was to arrive at the same general conclusions by an entirely different route 22 years later.

Bateson was not attracted by Weismann's ideas concerning the nature of the hereditary material and desplayed a stubborn reluctance to pay much attention to the results being obtained by the Morgan group in Columbia University, granting that they were interesting but maintaining that they were of little importance to the student of evolution. However, en route for Toronto where he was to address the American Association for the Advancement of Science in 1922, he spent some time with Morgan and his colleagues and was shown in detail what they were doing. For the first time he encountered "cytology as a living method of enquiry" and was greatly impressed. In a letter home he wrote "cytology here is such a commonplace that everyone is familiar with it. I wish it were so with us" and "The details of the linkage theory strike me still as improbable. Cytology, however, is the real thing . . . we must try to get a cytologist". In his address in Toronto he went so far as to declare that "the chromosomes are definitely associated with the transferable characters" but even in 1922 this is as far as he was prepared to go.

To the expansion of Mendelism through breeding experimentation alone there was a limit and it was inevitable that the leadership in the field of genetics would pass from the Batesonian group in England to the Morganian group in America, because there the search for ratios came to be closely and intimately associated with enquiries concerning Mendel's "elements that determine" and into the manner in which these elements produced their effects, where the development of cyto-genetics came to be actively encouraged despite Morgan's initial opposition. It was not until Bateson, then at the John Innes Institution, got his cytologist, C. D. Darlington, that the American leadership was challenged.

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Some Anomalies in the History of Mendelism

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Any historian of science, who investigates the pre-Mendelian descriptions of heredity, can discover with very little effort that every single discovery of Mendel's had been made earlier and that some of them had been made many times. No one before M e n d e l , however, ever put the discoveries together and no one ever saw their significance. Indeed, M e n d e l stood alone for, even after he had published what was, perhaps, the most important paper in all of genetics, no one understood what he had done. It was not until sixteen years after his death that the biologists appreciated his work. The biologists of the world were not ready for M e n d e l and his discoveries until the dawn of the twentieth century.

There are many oddities in this delay in the appreciation of Mendelian genetics. The first is to be found in the history of our notions concerning heredity itself. We know that our ancestors have been interested in heredity long before history started. In fact, all of our domestic animals and cultivated plants (except coffee) were domesticated in prehistoric times. Our ancestors not only domesticated them but also bred, selected and improved them greatly. The individual characteristics of both animals and plants were known to be inherited and, for some thousands of years, the operation of heredity was the subject of much speculation. Many of the speculations concerning heredity were published. But the speculations, which interpreted heredity were without any factual foundations, and the explanations of heredity exposed little but the all pervading ignorance of the times. It seems almost as if those who were interested in heredity suffered from some psychological block that effectively obscured its machinery. Even after Mendel's paper was discovered and appreciated, there remained a number of biologists, who did not understand it, who refused to accept its validity, and who continued to adhere to their pre-Mendelian concepts.

Some of the "mere facts" of Mendelian inheritance could not have escaped observation, and some were even recorded in classical times. L u c r e t i u s, for example, stated that children often resemble a grandfather or a great grandfather because parents carry in their bodies primordia that they themselves do not show, and here we have an observation of the transmission of

recessive Mendelian factors. A century later, Columella recorded the fact thatthis uncle had crossed Spanish sheep with Moroccan and had succeeded in combining the fine wool of the Spanish breed with the various colors of the Moroccan. Here we have an instance of the recombination of discrete Mendelian factors. But Columella's observation led nowhere. Some fifteen hundred years later, Leeuwenhoek described the dominance of the wild type coat color over the albino factor in rabbit crosses, but no one seemingly developed these experiments any further.

Many of the raw facts on which Mendelism is founded were also observed in the vegetable kingdom even before the sexual reproduction of the flowering plants was recognized. In 1588, Tabernaemontanus described the occurrence of different colored grains on ears of Indian corn *(Zea mays)*, and in doing so he listed numerous examples of the Mendelian segregation of different unit factors but, of course, Tabernaemontanus did not know this. About one hundred descriptions of these varicolored ears were published before 1716, when Cotton Mather ascribed their occurrence to cross pollination, but it was not until 1900, over three hundred years after they had first been observed, that their inheritance was recognized as Mendelian. Mendelian segregation had even been recorded several times in Mendel's own genus — in *Pisum*. But no numerical ratio was ever recorded in any of these segregations.

In 1799, Sir Andrew Knight crossed different varieties of peas, and discovered different types appearing among his hybrids. However, he had mixed and thoroughly contaminated his pollen and he thought he was finding evidence for superfetation. In 1822 — the year in which Mendel was born — two English experimenters, John Goss and Alexander Seton, working independently, crossed different varieties of peas. They reported dominance in the first hybrid generation and the reappearance of both dominants and recessives in the second. The recessives bred true but there were two kinds of dominants, one of which bred true but the other continued to segregate. Knight verified these results in 1824, and in 1826 Sagaret described the independent inheritance of unit characters.

We know that this earlier work on the genetics of peas was known to Mendel. It was included by Gärtner in his comprehensive work (Bastarderzeugung im Pflanzenreich (1848) and this was a book that was cited by Mendel. However, none of the pre-Mendelian plant hybridizers counted their progeny. To the best of my knowledge there is but one pre--Mendelian record of a genetic ratio. Johann Dzierzon had shown in 1845 that drone bees are hatched from unfertilized eggs. In 1856, the year before Mendel began his experiments Dzierzon reported that hybrid queens produced two kinds of drones and produced them in equal numbers — just what a Mendelian vould have expected. And Mendel must have known of this

work because Mendel also hybridized bees. Moreover, Mendel seems to have been the only nineteenth century investigator who hybridized both plants and bees.

Thus we see that Mendel had a certain number of hints as to what to look for in his crosses. We can show that he was preceded by certain adumbrations of Mendelism. He was unique, however, in that he alone saw the basic principles behind the raw data and he designed quantitative experiments to secure more pertinent facts. It does not require great genius to observe and record bare facts, but genius is needed to recognize their interrelationship and to organize them into a fundamental scientific theory. Mendel, of course, was a genius, and he seems to have been the only one before the last year of the nineteenth century who understood the implication and the importance of his work. Thirty-five years elapsed between the publication of his paper and its recognition by the biologists of the world. The question that arises at this point is: why were the facts of Mendelism disregarded for so long a time, and why were they ignored even after Mendel had organized them into a logical and consistent theory? This brings us to an important principle in the growth and in the history of science.

Facts, of course, have no meaning in themselves. They acquire meaning only when they are organized. And we have no choice but to organize the facts at our disposal in some sort of a framework. We need the organization if only as a mnemonic device. Our knowledge, however, is rarely adequate and almost never complete and, as a consequence, our organization of facts is almost never permanent. The provisional hypotheses that we construct, however, may be both aesthetically and intellectually satisfying and may incorporate all the data. Such hypotheses often have long lives and some may persist for thousands of years. Their mortality, however, is demonstrated whenever some newly discovered and acknowledged facts refuse to fit into the ancient and honorable framework. But to abandon an historically useful and well loved hypothesis is never easy, and our universal intellectual inertia often keeps us from doing so until the last possible moment. Some scientists find the desertion of an hypothesis impossible. The acceptance of Mendelism thus was not easy as it involved the discarding of an hypothesis that had been accepted almost universally since about 400 B. C.

The history of science is replete with the tragedy of beautiful hypotheses being killed by obdurate facts. For example, the increased accuracy of astronomical measurement caused the elegant Ptolomaic explanation of planetary motion to become obese with cycles and epicycles. It was replaced by the still more elegant Copernican explanation which, reshaped by Kepler, explained by Newton and modified by Einstein, still meets the needs of astronomers. Biologists also build hypotheses, some of which persist longer than the Ptolomaic. When Mendel published, he challenged a theory of

heredity that had been enunciated precisely by Hippocrates, Democritos and Aristotle. It was even current in pre-historic times as is shown by the myth of Phaethon.

When Mendel published, the few recorded instances of Mendelian heredity had been either ignored or dismissed as exceptional instances of only peripheral importance. At the time, the biologists were interested primarily in the inheritance of quantitative characteristics, such as the milk production and size of cattle, the weight of hogs and the yield per acre of the crop plants. In all such instances, polygenes are involved, and these genes as a rule lack dominance, and the variations they produce fit routinely into a normal distribution curve. Here the Mendelian ratios are not at all evident. The interpretations of heredity, current in the nineteenth century were in harmony with the data that existed, but a Mendelian explanation would have only complicated matters.

When Mendel published, belief in the inheritance of acquired characters was held almost universally. In 1859, Darwin himself incorporated it in his explanation of evolution, where it served as an important ancillary factor to the basic concept of natural selection. Later in the nineteenth century the heritability of acquired characters had to be abandoned but it was abandoned with great reluctance. A belief that had lasted 2500 years does not die easily. It was not until the 1880's that Weismann challenged the belief, and not until 1900 that the majority of biologists rejected it. But this was long after the time of Mendel! Three years after Mendel's paper, Darwin described his provisional hypothesis of pangenesis, an hypothesis to explain how acquired characters could be inherited, and here Darwin gave a name to an explanation that had been current since the time of Anaxagoras.

It was not until the biologists accepted Weismann's discovery that the soma was separated from the germ plasm and that only the germ plasm gave rise to future generations that a basic doubt arose as to the inheritance of acquired characters. The discovery of a continuous germ plasm giving rise to the successive generations provided a possible mechanism for the transmission of Mendelian factors.

Perhaps no erroneous notion in all of biology lasted longer or had more influence than the doctrine of the inheritance of acquired characters. The doctrine, throughout its entire life, had but one explanation — but one postulated material basis — the one that Darwin named pangenesis. And pangenesis had been described well over a hundred times. We shall cite but two passages written over 2200 years apart to illustrate this startling example of the lack of progress in a science.

The first is a short excerpt from On generation, ascribed to Hippocrates and written ca. 400 B. C.

1. Law governs everything. The sperm of man comes from all the humors

which are in the body, and it is the most active part which separates off. Here is the proof: after coition, the evacuation of such a small quantity of semen renders us feeble. The disposal is thus: veins and nerves run from the whole body to the genital parts; rubbed, warmed, and full, a longing occurs which gives pleasure and warmth to the whole body. The humors grow warm in the body with the friction of the genitals and their movement. They dilate and are stirred by the movement, and become frothy just as all liquids become frothy when agitated. In this manner, in man, the sperm separates itself, the humor becomes frothy, the most active and most corpulent part collects in the dorsal marrow; in effect it collects there from the whole body, the brain particularly discharges into the loins, and into the marrow, which, in its turn, is supplied with efferent veins in order that the humor may both flow there, and later leave. The sperm, once it has arrived in the marrow, passes along the kidney; for that is where the channel is through the veins; and in case of ulceration of the kidneys, evacuated with the semen. From the kidneys, the semen proceeds to the thousands of parts of the testicles and to the genital member, not by the urinal tract but by another particular tract (ejaculatory ducts) which is close by. 2. I say that the sperm comes from the whole body, from the solid parts as well as from the soft parts and from all the humors which are in the body.

The second passage is from Variation of Animals and Plants under Domestication, published by Charles Darwin in 1868.

"... But besides this means of increase I assume that cells before the conversion into completely passive or 'form-material', throw off minute granules or atoms, which circulate freely throughout the system, and when supplied with proper nutriment multiply by self-division, subsequently becoming developed into cells like those from which they were derived. These granules for the sake of distinctness may be called cell-granules or, as the cellular theory is not fully established, simply gemmules. They are supposed to be transmitted from the parents to the offspring and are generally developed in the generation which immediately succeeds, but often transmitted in a dormant state during many generations and are then developed. Their development is supposed to depend on their union with other partially developed cells or gemmules which precede them in the regular course of growth. Why I use the term union will be seen when we discuss the direct action of pollen on the tissues of the mother plant. Gemmules are supposed to be thrown off by every cell or unit, not only during the adult state, but during all the stages of development. Lastly, I assume that the gemmules in their dormant state have a mutual affinity for each other, leading to aggregation either into buds or into sexual elements. Hence, strictly, it is not the reproductive elements, nor the buds, which generate new organisms, but the cells themselves throughout the body. These assumptions constitute the provisional hypothesis which I have called Pangenesis."

This mechanism of heredity that Darwin labeled pangenesis had been de-

scribed by practically all who wrote on heredity between the period of Anaxogoras and Hippocrates and the time when Darwin coined the word pangenesis. Darwin's clear statement of the hypothesis, however, called attention to the fact that it had no observable factual basis. Paradoxically, Darwin succeeded in stimulating the growth of a certain amount of skepticism, and later, after the germ plasm was recognized as a separate entity, apart from the soma, the skepticism grew. The great advances in anatomy, embryology and cytology, that occurred during the last quarter of the century, brought to light the chromosomes, the way they reproduced themselves and their overall behavior. In 1892, Weismann even stated that the chromosomes constituted the material of heredity. If this were so, the transmission of heredity factors should follow the same path as the transmission of chromosomes. The rediscovery of Mendel's work in 1900, showed that his hereditary factors and the chromosomes behaved alike and in 1902, Sutton stated definitely that the Mendelian factors were carried in the chromosomes. Mendelism at last had found a material basis.

We now have some clues as to why Mendel was not appreciated when he published. At the time there was no known mechanism for the transmission of the hereditary factors he described. But more important, perhaps, was the fact that the accepted hypotheses as to the machinery of heredity were incompatible with his discoveries. Those of us, whose teachers matured before 1900, can remember what difficulties they had in reorienting themselves and how much they had to unlearn before they could accept Mendelism. Some never could! Even today a very few anti-Mendelians still exist but they have little influence in the world of science. The Mendel Memorial Symposium is striking evidence that Mendel has come into his own.

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Discussion Contributions

An Early Account of G. Mendel's Work in Russia (I. F. Shmalhausen, 1874)

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It is a well-known fact that G. Mendel's work published in 1866 was not understood and was forgotten for a period of over 30 years. And yet, it is ascertained that it ought to have been known to a number of eminent biologists of the time. In the literature in Mendel published abroad there are two cases in which his work had been cited by his contemporaries-botanists H. Hoffmann (1869) and W. O. Focke (1881). Mendel's work attracted their interest merely from the viewpoint of a possibility for species and subspecies cross-breeding and they paid no attention to the general laws of heredity formulated by the investigator.

Against this background it is of great interest to examine the hith ex to unknown account of Mendel's explorations not mentioned by any foreign historian of Mendelism during Mendel's life. I have in mind the Russian botanist Ivan Fedorovitch Smalhausen (1849—1894), the father of Academician I. I. Shmalhausen who recently passed away.

I. F. Shmalhausen was a graduate of St. Petersburg University (1867—1871) where he specialized in botany under the guidance of Prof. A. N. Beketov. In 1874 he took his master's degree with the dissertation "On Plant Hybrids" and in this study he reviewed Mendel's work which is a matter of our concern in this communication. In his "Outline of literature on cross polination in plant species and the basic results pertaining to these experiments", which precedes the description of wild-growing transitional interspecies forms of flora discovered by I. F. Smalhausen in the area of St. Petersburg, one finds an excellent review of papers on this matter. However, I. F. Smalhausen came across Mendel's work after having completed the manuscript of his dissertation when it was ready for printing. He devotes an extensive exposition to Mendel's paper of 1866 and in its footnote he writtes:

"I had a chance of getting acquainted with Mendel's paper (Verhandl. der Naturforschenden Vereines in Brünn IV. Bd., 1866) only after having handed in my study to the printers. I find it, however, appropriate to mention this paper, for the method of the author and his way of expressing his achievements

in formulas wins one's attention and calls for further development (for totally fertile hybrids). The author's task is to estimate with mathematical accuracy the number of forme having originated from hybrid pollination and the numerical correlation of individuals amid these forms. M e n d e l select for crossing those particular plant form which are distinguished by constant and easily notable characters; the hybrids of the latter reveal adequate fertility in subsequent generations. The pea races fully satisfy these demands. For the sake of comparison one choses definite characters which in our particular case are such that in the produced hybrid they fail to mix and in all cases one character is absorbed in 3/4 of the individuals' number, i.e. are fully unobserved because of the predominance of the arbitrary character and 1/4 of the hybrid individuals inherent in this character shift to a type of another form. The latter group of individuals in the subsequent generation remains constant. The first group in its turn is subdivided into two groups: I/4 of it remains constant, I/2 — similar according to the selected character with the first fourth maintains to be of hybrid nature and the last I/4 individual shifts to the opposite type. M e n d e l arrives at the conclusion that of the hybrid seeds of the two distinguished characters one-half reproduces hybrids, whereas the other half reproduces plants which remain constant and reproduce in halves the predominant and the disappearing character. M e n d e l produces a comples seriex in regard to the progeny of hybrids which incorporate a number of characters; and one can imagine that the members of a complex series had originated from the combination (multiplication) of several series and each of the latter is made up of three members produced in the course of crossing of two opposite characters. Amid of and in accordance with Mendel's observations and also in agreement with his mathematical considerations, one invariably arrives at constant members with a new combination of characters. Hix experiments and mathematical considerations in the second part of his work (Befruchtungszellen der Hybriden) lead him to conclusions which are basically similar to the theoretical considerations of N a u d i n . (Nouv. Arch. du Mus. I .)"

This quotation shows with evidence that I . F . S m a l h a u s e n was the first who really understood the outstanding importance of Mendel's investigations. Unfortunately, Smalhausen's exposition of Mendel's work had not attracted the attention of Russian scientists and remained totally unknown in foreign countries. Though in 1875 Smalhausen's dissertation was issued also in German and appeared in the "Botanische Zeitung", the chapter with the historical and literary review however was omitted and hence, the exposition of Mendel's work fell out.

Opening of the Mendel Memorial attached in the Moravian Museum

Openning Address

Gregor Mendel Memorial in Brno

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I have the honour to announce to the participants of the Mendel Memorial Symposium in Brno that the Moravian Museum has opened a Mendel Memorial in Old Brno adjoing the experimental garden where the Father of Genetics Gregor Mendel carried out his famous hybridization experiments with peas. This Memorial has been set up at the instigation of our late Professor Kříženecký, the former head of our G. Mendel Department of Genetics, for the centenial anniversary of the publication of Mendel's classical paper.

Professor Kříženecký, our greatest expert on Mendel, who passed away last December worked up to the very last moment and fought against suffering to concentrate on his work of setting up this Memorial. His death prevented him from seeing the completion of his ideal — this great Celebration of the Centenary of genetics, the science to which he devoted his whole life.

On this occasion we would also like to remember the merits of those to whom we are indebted in Brno for the collection of documents and manuscripts relating to Gregor Mendel. First of all, we have to express our thanks to the late P. Anselm Matoušek who arranged a small Museum Mendelianum in the former Augustinian Monastery and to Dr. Hugo Iltis — the autobiographer of Gregor Mendel who took care of the memory of Gregor Mendel in Brno, gave impulse to setting up a committee for erecting a Mendel monument in Brno, discovered the manuscript of Mendel's classical paper "Versuche über Planzenhybriden" and wrote a biography on Gregor Mendel issued by the J. Springer Publishing House under the title "Gregor Johann Mendel — Leben, Werk und Wirkung" in 1924.

In the refectory of the former Monastery a permanent exhibition has been arranged providing a picture of Mendel's life and his various activities, by means of selected documents, photos, instruments and relics left by him. This exhibition is intended to inform visitors about the personality of this modest investigator, the great man who laid the foundations of genetics.

In the adjacent documentation room there are photocopies of documents kept in the archives of our Department which are at the disposal of those

visitors who are interested in studying them. Although most of the documents from the Monastery archives are quite well-known already, we have been lucky enough to find some new and highly interesting documents during the last few months.

We are searching for further new documents from Mendel's life and activities, especially those which would enable us to throw light on the genesis of Mendel's Idea of Elements, the basis of the hereditary factors discovered by him.

In Mendel's copy of "Verhandlungen des Naturforschenden Vereines" from the year 1866 preserved in our archives, we can see on page 42 that Mendel only underlined in his characteristic way the following sentence: "Since in the habit of the plant no changes are perceptible during the whole period of vegetation, we must further assume that it is only possible for the differentiating elements to liberate themselves from the enforced union when the fertilising cells are developed". We are of the opinion that this fact Mendel's concept also sheds some light on the core of particulate inheritance that pairs of elements in the parents segregate during the production of germ-cells. From his notes it is evident that M e n d e l studied Darwin's work in detail and a number of passages in his paper prove that Darwin's work was very much in his mind when he wrote it.

He especially found much of interest to him in "The Origin of Species" as well as in "The Variation of Animals and Plants under Domestication". In the german translation of "The Origin of Species", issued in Stuttgart in 1863 he marked some passages by lines in the margin and underlined others. For instance: on the first page of the Introduction in the upper corner, we can find in Mendel's own handwriting the note "pag 302". On this page we can see the following text margined by two lines: "The slight variability of hybrids in the first generation, in contrast with that in the succeeding generations, is a curious fact and deserves attention".

The "curious fact" of the slight variability in the first generation and the great variability in the succeeding ones were quite clear to M e n d e l and this is why he margined it. Here is the evidence of Mendel's opinion of particulate inheritance and segregation of elements in contrast to the theory of blending inheritance. From these notes we can see that M e n d e l considered that something was still lacking in Darwin's theory and in his paper he only wanted to give a new and better explanation of how evolution took place.

We can now also testify to the fact that M e n d e l even conducted crossing experiments with bees. His aim was the attainment of cultivated races of bees by crossing geographically different breeds, which is still the subject of precise investigations. In the beehive built by M e n d e l in the Monastery garden in 1871 we have tried in cooperation with the Czechoslovak Beekeepers'

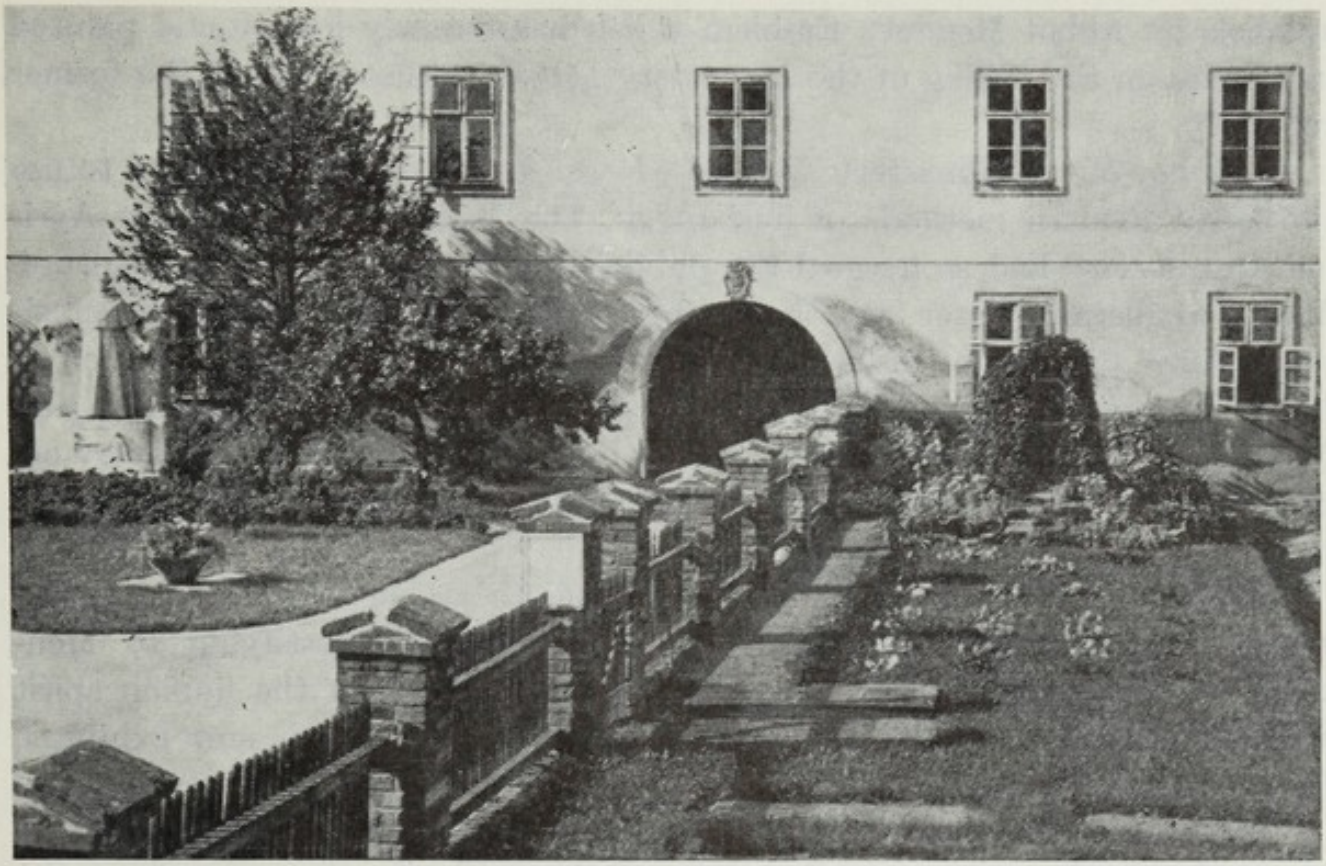

Fig. 1. The garden of the convent at Brno, where M e n d e l performed his experiments.

Union to demonstrate his beekeeping activities by means of a small exhibition.

We have also found conclusive evidence that M e n d e l was also carrying out hybridization experiments with different fruit trees. The most interesting documents deal with a programme of hybridization of apple-trees and pear--trees prepared by M e n d e l and written in his own handwriting in the 1859 copy of the Illustriertes Handbuch der Obstkunde. There are also notes dated 1881, it is only two years before his death. The aim of this hybridization programme was to develop new varieties of fruit trees. These notes testify to the fact that M e n d e l, right up to the close of his life never lost interest for hybridization and pomiculture, the interest which had already been awakened during his boyhood in the native house at Hynčice (Heizendorf) and which led him to carry out his famous experiments.

M e n d e l as an active member of the Horticultural Section of the Moravian--Silesian Agricultural Society contributed significantly to the development of pomiculture in Moravia and his merits were highly appreciated by the Moravian horticulturists at that time. We have also found evidence that it was only these horticulturists who remembered Mendel's hybridization experiments in an obituary notice issued shortly after his death in the following words: . . . his experiments with plant hybrids have in fact opened a new epoch and what he has done will never be forgotten. Great interest will surely be aroused by the

symbols on Abbot Mendel's Emblem which has recently been found painted in colours on the ceiling of the Monastery Library situated above the former refectory.

As Abbot of the Monastery M e n d e l was a good farmer and tried to use the latest modern methods of husbandry. The Moravian and Silesian Agricultural Society had as its goal the publicity of new methods in agriculture. M e n d e l became later also a member of its committee and its vicepresident. After his death this society wrote in their short obituary notice of him: "The studies of the departed have been put to practical use. G r e g o r M e n d e l did not use only lifeless words, but actively intervened on every occasion in the agricultural matters of Moravia and always paid great attention to them.

Admirers of M e n d e l will also be anxious to see the newly found manuscript of a poem written in Mendel's own handwriting testifying to Mendel's enthusiasm for science and the creative power of the human spirit already during his student days. A copy of this manuscript is now exhibited in the Mendel Memorial Hall.

According to the proposal of our late Professor K ř í ž e n e c k ý we are also gathering documents and literature relating to the development of genetics as a science and in this way to form a documentation centre of genetics in the town of its birth.

Remembering the fact that genetics was born in Brno another exhibition in the newly renovated rooms of the Moravian Museum has been installed which is intended for general educational purposes. This is the first step towards the fulfillment of our intention to build up a permanent exhibition of the historical development and the present state of genetics and in this way to acquaint visitors to Brno with the great significance of this branch of science.

Already geneticists from several countries have assisted in the initial work of forming our documentary centre and arranging our exhibition — and in this way setting up a nucleus of memorials to G r e g o r M e n d e l. We would like to realize our great plans and with the support of geneticists from other countries to build up a Mendel Memorial in Brno dedicated not only to the memory of the founder of genetics, but also to the science, the foundations of which were laid here by G r e g o r M e n d e l a hundread years ago.

Session II

ESTABLISHMENT OF GENETICS

CHAIRMAN: J. W. BOYES
VICE-CHAIRMAN: C. ZIRKLE

Gregor Mendel

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I

Gregor Mendel was a classic in the field natural sciences. This is generally accepted, and it is well expressed by the fact that his remarkable paper "Versuche über Pflanzen-Hybriden" was included by W. Ostwald in his famous series "Klassiker der exakten Naturwissenschaften", and may also be found in all similar editions, which appeared in different countries during the first decades of this century. I think, however, that Mendel is to be included in a still narrower circle of the greatest naturalists of the World — his name is worthy of being placed among the "Eternal guides" of human mind apprehending Nature.

It is not uncommon to the history of science, and especially to its popular representation, that a great scientist (with whose name heyday of some special discipline is associated) is honoured not for his principal scientific merit resulting from his profound scientific foresight, but rather for certain "discoveries" which were supposed to be made by him or for the field of knowledge which has become connected with his name. Such injustice befell for example, Charles Darwin: in popular scientific literature he is honoured as the creator of the idea of evolution, and sometimes the science of evolution is called "Darwinism", but Darwin's chief merit is not in the proposition of the evolutional idea which had been proposed long before him, but in the brilliant perceiving in Nature of a unique strictly biological general principle — the principle of natural selection, which has been laid by him in the foundation of his scientific theory of evolution. I think that Mendel underwent a similar fate: his name has been appropriated to experimental genetics which has been developed only in our century, and he is honoured mainly for the famous Mendelian laws, or rules of heredity — "dominance", "segregation", "free recombination". Moreover, Mendel's investigations, just as Darwin's work, are often seen upon as something "new", "breaking all the traditions" and "entirely neglecting" the previous advances of science. But, actually, Darwin's work (as is well-known now) and Mendel's work (as I shall try to show in this paper) comprise broad generalizations, as probably, any great scientific advance does, of all the former positive knowledge in the given field; a generalization which is based on new theoretical principles

developed by them. It is characteristic for both Ch. Darwin and G. Mendel that they created, for the first time, the possibility of true scientific theorizing, free of teleological philosophy, in the two main fields of biology — evolution and heredity.

I shall try to show how Mendel's works were connected with a continuous series of preceding experimental research, and the significance of his two brilliant ideas (one concerning his methods and the other proposed as a working hypothesis), with the aid of which he was able to develop the scientific theory of heredity, and which made him, as I believe, one of the "Eternal Guides" of scientific investigation.

II

The formation and development of modern genetics followed two different paths which were quite independent of one another for a long period of time and were united only at the beginning of this century when Mendel was already dead. These two different paths were the elaboration of the method of hybridization in plant breeding and the development of the cellular theory; the latter leading at the end of the nineteenth century to the initiation of cytology. The second of the two branches was formed only in the middle of the past century, and its advances, especially important for genetics, date to the margin of the nineteenth and twentieth centuries. Thus, his second, cytological, path had not and could not have any relation to Mendel's work. But, secular development of the method of hybridization up to Mendel's famous work exerted the most immediate influence upon the latter, and Mendel's experiments represented the glorious completion of the first large period in this branch of biology. For this reason I will summarize briefly the principal steps in the development of the method of hybridization before Mendel.

In the middle of the eighteenth century due to a significant progress in microscopy, on the one hand, and an echo of the old arguments between "ovulists" and "animalculists", on the other, the final solution of the problem of fertilization and the role of macro- and micro-gametes in this process became an immediate task. Although, up to that time much more scientific observations had been made concerning the fertilization in animals, the exact experimental solution of the problem was first achieved in plant research by the famous scientist — member of the Russian Academy of Sciences J. G. Kölreuter, whose outstanding works on fertilization in plants appeared in 1761—66, i.e. twenty years earlier than the well-known experiments carried out by L. Spallanzani on fertilization in animals. J. G. Kölreuter was to be honoured as the creator of the scientific method of hybridization of plants. In order to prove the role of pollen cells as microgametes in plant fertilization, Kölreuter resorted to heritable differences in the

characters of flowering plants (mainly corolla colour) as markers in his experiments on cross-pollination. To avoid possible errors, owing to spontaneous self-pollination, K ö l r e u t e r elaborated hitherto used techniques of emasculation of flowers (removal of stamens with ripening anthers). It is interesting to mention that although Kölreuter's experiments were presice and the results obtained by him were quite unequivocal, the discussion in biology, generally not strengthened by experimentation, concerning the matter and the nature of fertilization in plants lasted up to the past century. But in plant breeding studies Kölreuter's works were widespread, and his precise method of hybridization has since the been used in the practical selection for raising new varieties of cultivated plants. It is to be emphasized, however, that K ö l r e u t e r himself did not pay special attention to either the selection or the investigation of inheritance of single characters; the heritable plant characters, of which he was aware due to his horticultural practice, served him only as markers for the pollen-or egg-cells of the plants used in his experiments on crossbreeding. At the same time, he introduced the methods of back-crosses to one of the parental forms, and showed, by means of such crosses, that heritable plant characters did not disappear in hybrids, and that the pollen- and egg-cells are equivalent in the transmission of the heritable characters. His exact method of hybridization played an outstanding role in the further development of plant selection. Some main steps of this development we shall mention here.

The method of artificial selection has been applied long since in raising new varieties and in the selection of cultivated plants; it consisted of crosses between different already existing forms in order to get new combinations of characters as material for further selection. In these crosses the precise method introduced by Kölreuter was found to be especially useful. As the first fundamental achievement in the selection of cultivated plants we have to mention the data obtained by the outstanding English plant breeder T . A . K n i g h t , whose works date from the end of the eighteenth to the beginning of the nineteenth century. T . A . K n i g h t , who was aware of and appreciated K ö l r e u t e r ' s work and applied his method of hybridization, carried out a large number of crosses between different forms and varieties of a number of species of cultivated plants with the subsequent raising of further generations, searching for the new combinations of characters and selecting the new varieties. T . A . K n i g h t , who was a keen observer and a precise investigator, had noticed that varieties and forms of any plant species may differ from one another to an unequal degree, and that in generations following the hybridization these differences "scatter" to a number of small separate characters, and the more remote were the crossed forms, the greater is the number of these characters specific to initial varieties. But the most important in Knight's observations is that he found further "indivisibility" of

these small character differences in any crosses; Knight was, thus, the first who came upon the concept of the "unit characters". This result of his observations, experiments, and reflection is to be regarded as one of the most fundamental discoveries upon which modern genetics is based. And our present concept of discrete nature of the code of hereditary information and of the units of hereditary variability is also based in this discovery, which was made one and a half centuries ago (1799—1824).

One of the most significant steps in the further development of the method of hybridization in plant breeding was represented by the works of the remarkable French plant breeders A. Sageret and Ch. Naudin, both of whom knew and appreciated the works carried out by Kölreuter and Knight. Their experiments on hybridization of different forms and varieties of vegetables, *Cucurbitaceae*, in particular, are especially interesting. In these crosses Sageret (1825—1835) obtained clear evidence for the phenomena of dominance and of non-disappearance of Knight's unit characters in the progeny if hybrids. Even in the middle twenties of the past century A. Sageret had do stand up for the results of Kölreuter's work against the attacks of some German botanists (Schelver, Henschel and others), who claimed that Kölreuter's experiments had been unsubstantiated an contended that the plants are sexless, and for that reason cannot be crossed (!). Ch. Naudin, who was also aware of and appreciated the works of his predecessors — Kölreuter, Knight and Sageret, found in his experiments on hybridization of different varieties of vegetables (just as Knight and Sageret did) that unit hereditary characters did not disappear (after hidden stage in the first generation), but showed recombination in succeeding generations. Furthermore, he confirmed, by means of plentiful back-crosses, that hybrids revert gradually to that of the initial parental forms, to which they have been crossed. Naudin made also an attempt, as well, to introduce quantitative methods in the estimation of his data, however, but he failed, to obtain, a clear picture of quantitative interrelations of segregating characters, since he tried to embrace a large complex of the latter among the descendents of hybridization of rather remote varieties and forms. It is also noteworthy that Naudin observed in his crosses some newly arisen unit characters (mutations in our present terms) and mentioned their possible significance for the selection and raising of new varieties.

Only four names were mentioned in preceding paragraphs with which the most important steps in the development of the method of hybridization in plant breeding are associated. But, actually, a lot of good plant breeders, English and French in particular, worked in the nineteenth century, especially from the 'twenties to the sixties', and contributed very much to the development of the method of hybridization and of the scientific basis of plant selection.

On the other hand, the official "academic" biology up to the middle of the past century could not rid inseff of plenty of teleological and metaphysical principles, so that, as we have already seen, in the 'thirties of that century armchair discussions were possible on either the sex and the hybridization that actually exist in plants. In plant breeding, however, exact scientific basis of selection and of inheritance of characters was logically and consistently laid, guided by discoveries made with the aid of hybridological experiments. The whole of this cycle of research was known to Mendel. Thus, his experiments and interpretation of the data obtained were a further logical development of the works of his predecessors and are not to be regarded as something entirely isolated from the latter. These circumstances, as we shall see below, neither lower his merit nor reduce the significance of his extremely profound analysis of original data obtained in his experiments, which are wonderfully simple and correct in their design.

III

It is known that Gregor Mendel (1822—1884) was not a scientifist by profession; he was firstly a novice, then a monk and from 1868 the prelate of St. Augustine Abbey in Brno. However, after he had graduated from the abbey school and studied for two years at Vienna University, Mendel amost all his life combined his clerical service with teaching natural history and physics at the technical high school in Brno, and only during his last years, being overloaded with his service in the abbey and numerous public duties, left his teaching activities. Furthermore, G. Mendel was an active member and, apparently, one of the founders of the Society of Naturalists of Brno, the "Proceedings" of which date from 1862. The Society united about three hundred members — teachers, physicians, agriculturists, engineers, and nature-lovers (botanists, zoologists, and mineralogists) of Brno and its environs. Mendel's early experiments in plant breeding and hybridization, carried out by him in the abbey garden, apparently date from the 'fifties; at the same time, he began his correspondence with a number of botanists and plant breeders. His famous experiments on the hybridization of peas (judging from his letters to K. Nägeli) were carried out in 1856—1863. His main work "Versuche über Pflanzen-Hybriden" was reported to the two sessions of the Society on the 8th of February and the 8th of March, 1865, and published in "Verhandlungen des naturforschenden Vereines in Brünn", Band IV, 1865, Abhandlungen (Brünn, 1866). The first reedition was made by E. Tschermak in Istwald's "Klassiker der exakten Naturwissenschaften" No. 121, 1901.

I shall not describe in detail the well-known data of the famous Mendel's experiments on the hybridization of peas. But the two brilliant features of

these experiments are to be emphasized, due to which M e n d e l ' s work became the foundation of modern genetics, and for which Mendel is to be honoured as a classic of exact science.

The first of these outstanding peculiarities concerns the material and the methods of his experiments. The very beginning of Mendel's "Versuche über Pflanzen-Hybriden" is a wonderful example of the strict and accurate choise of the object (peas), best meeting the demands of his exact experiments. Furthermore, M e n d e l , unlike all his predecessors, did not examine the whole complex of differences between the crossed varieties, but, quite conciously, restricted his attention to the single alternative unit characters suitable for quantitative analysis. At last, he (perhaps the first and the only one among the biologists of his time) applied the mathematical (in the true sense of the word) method, both in design of his experiments and analysis of the obtained data. Therefore, instead of hopeless examination of the confused complex of a large number of alternative and quantitative characters, segregating and recombining in the succession of generations following hybridization, M e n d e l , in his analysis, preferred another and quite correct way — from simple phenomena to complex ones, and that is the reason why he became able to reveal the general principles of heredity. Furthermore, the exactness of his method allowed him to carry out, quite consciously and keeping to the chosen analytical way, the required further experiments, more and more complicated, but checking and confirming his principal idea. Another thing is also striking in Mendel's remarkable work, even in comparison with modern studies in experimental biology, that is the exactness and "clear brevity of representation" (L o m o n o s o v) of his style, free of unnecessary arguments which only make the meaning of the work more obscure. These peculiarities of Mendel's methods, which were quite unusual to biology of that time and which should be the honour of any outstanding physicist, a representative of exact science, comprise, I believe, the first of the two brilliant features of his work. Owing to gracious lucidity of his mind and consistent application of materialistic methodology, this "amateur" was far ahead of contemporary biologists excepting such great scientists as C h . D a r w i n .

I have already mentioned the exceptional merits of Mendel's methods. The first prerequisite of his succes was the restriction of his attention to a comprehensive quantitative analysis of single pairs of alternative characters transmitted from one generation to another. The other advantage of Mendel's methods consisted in wonderful concordance of the thoroughness of his experiments and raising the sufficient number of plants under similar conditions to the accuracy of his mind and consistent application of statistical considerations both to the design of his experiments and, especially, to the interpretation of the data. It is noteworthy, also, that M e n d e l prepared his material for hybridization very carefully. He received from seed-growers

more than twenty different varieties of peas, and, prior to using the material for the hybridization experiments, he checked every stock for purity by means of two to three years inbreeding, and discarded any stock showing segragation of characters. The first findings which M e n d e l achieved in his main crosses were the establishment of dominant and recessive characters for a number of alternative pairs (by the way, the terms "dominant" and "recessive" were introduced by him) and of uniformity of hybrids, all on which expressed dominant characters. In the second generation, which M e n d e l named the first after the hybrid generation, he proved the segregation of the recessive characters in all the examined cases. Then, computing his numerous data on segregation in the second generation, M e n d e l found that in any case statistically variable 3 : 1 ratio of dominants to recessives was obtained, and that deviations from this ratio decreased with the increase in the amount of examined material. The data on segregation in the second generation served him as a basis for the keen logical inference that the second generation is comprised of pure dominants, pure recessives, and of hybrids similar to those of the first generation, and in the progeny of which further segregation was to be found M e n d e l tested his hypothesis on a large number of self-pollinated plants of the second generation and found that all the recessives were actually pure, while among the dominant forms only 1/3 showed to be pure, the rest 2/3 being hybrid. Thus, M e n d e l found that in the second generation a segregation of hereditary factors takes place in the ratio 1 pure dominant: 2 hybrid (usually undistinguished from the dominant): 1 pure recessive. The correctness of this hypothesis on the distribution of hereditary factors was, also, checked and confirmed by M e n d e l in a number of back-crosses to each of the parental forms. Then, in further experiments he revealed that segregation data for any tested pair of alternative characters ascertained the correctness of this statistical law. At last, M e n d e l subjected to similar experimental analysis (involving the segregation data in the second generation, the data of back-crosses, and the further examination of segregating hybrids by means of inbreeding) the results of crosses between the pure varieties of peas differing from one another in two, three, and four pairs of alternative characters. This analysis revealed that in the second generation of such more complex crosses a simple statistical combination of dominant and recessive factors of different pairs of alternative characters is alway observed. Summarizing the data on segregation M e n d e l deduced the general formula for calculating the number of different combinations of characters and their numerical ratios in the second generation for crosses involving any number of pairs of alternative characters.

Applying simple and exact logical and statistical methods to the interpretation of results of his experiments M e n d e l proposed his famous hypothesis of the hereditary factors and the purity of gametes. This hypothesis is the

second and the chief brilliant peculiarity of his work. It contains not only the basis for our contemporary concept of genotype as a complex of discrete units of heredity — the genes, but, also, the exact prediction of behaviour of their material bearers — the chromosomes in meiosis, of which, as well as of the cell fine structure and division, and the gamete production, Mendel was not, and could not be, aware. Remarkable, but not at all astonishing, is the well-known fact that the great cytologists, E. B. Wilson, just after the rediscovery of Mendel's principles published a special paper in which he showed that the behaviour of the chromosomes in meiosis and fertilization exactly follows Mendel's hypothesis; this was the first exact and most solid basis of the chromosome theory of heredity. It is not surprising, therefore, that the further progress in experimental and theoretical genetics up to the remarkable recent works, which throw light on the physical and chemical structure of the genotype and the biochemical mechanisms of its action, is the logical development of Mendel's main hypothesis, universal applicability of which to all the living was proved by extensive experimental research already in the first decades of our century after the "rediscovery" of Mendel's work.

IV

Summarizing our brief considerations we may emphasize again the following points. It was not Mendel to whom the single "discoveries", often associated with his name, really belonged. Naturally, the exact methods of hybridization Kölreuter the unit characters Knight, the dominance Sageret, and the segregation and recombination of characters in the offspring of hybrids (Sageret, Naudin) were discovered before Mendel. But Mendel, being a great naturalist, and being aware of all these discoveries, not yet exactly analysed, took them into account and performed with the aid of brilliant design and interpretation of his experiments the exact quantitative analysis of the inheritance and the recombination of unit characters in the succession of generations. From the data of this analysis he keenly deduced the statistical and combinatorial regularities of heredity and built up his famous hypothesis of the hereditary factors and the purity of gametes. In this respect Mendel passed ahead of his time, he became the pioneer in introducing strict mathematical thought in biology and founded the basis for the fast and gracious development of genetics in our century; and we may state now that genetics together with the evolution theory, grounded on the principle of selection, is the basis upon which the "biological thought" is to be founded, and which imparts the powerful stimulus to the development of all the field of modern biology. For this reason, among the rather numerous classics of exact science only Char-

les Darwin and Gregor Mendel of the outstanding biologists of the past deserve to be included into the selected circle of "Eternal Guides" of human mind apprehending Nature.

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Mendel's Laws of Heredity and Some Selected Pages from the Establishment of Genetics

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The grandeur of Gregor Mendel's contributions consists in that they forestalled his own time by several decades.

Because of the level of sciences at that time, Mendel could not even suspect that he gave an insight into the kingdom of the most important organic macromolecules.

He judged the existence, properties and fate of discret hereditary "factors" not directly, not by the physical and chemical processes running in this submicroscopic world, but only by their remote reflected effects on definitive morphological characters of living beings.

Nevertheless, he succeded in anticipating some properties of this hidden world. He revealed not only the existence of discrete units of heredity, but demonstrated their striking stability and discovered some very important regularities of their hereditary transmission.

Morever, he elaborated some new experimental methods, the only ones suitable for the investigation of heredity: simple methods of analysis by cross-breeding and inter-breeding of analysis by crossbreeding and interbreeding of varieties, conditional alphabetic symbols which are being used up to the present almost unmodified, and quantitative statistical approach for the estimation of the obtained results.

It sems to me that the real penetration into the very essence of the phenomena discovered by Mendel required such a radical change of biological thinking which can be compared with the transition from the classical concepts of Newtonian mechanics to the ideas of modern quantum physics.

It is just that leap from the organic and superorganic levels — the only ones known to the biologists of Mendel's time — to the molecular stratum of life which was, I think, one of the main causes of the hard fate of Mendel's discovery.

What a striking contrast can be seen, for instance, in the fate of the two greatest and almost simultaneous biological events of the XIX-th century — I mean the appearance of the first concise presentation of the "Origin of Species by means of Natural Selection" in 1858 and the appearance of "The Experiments on Plant Hybridization" in 1865.

D a r w i n - W a l l a c e ' s theory shed light on a huge mass of previously accumulated data concerning the life at the organic and higher levels, — the organic Macroworld. This theory gave a clear and simple explanation by natural causes to the innumerable facts that have been often given an absurd artificial, mythological or teleological interpretation. That is why the new evolutionary concepts almost instantly conquered the minds and almost immediately becam the cornerstone of scientific biology, despite the fierce counterattacks of anti-Darwinism, some examples of which surprisingly happen even nowadays.

On the contrary, Mendel's classic investigations despite their intrinsic integrity and lucid clarity did not at first axplain almost anything. As a matter of fact they set tasks and raised problems to be answered during the following century, some of them have remaining unsolved till today. They but lifted the veil from the quite unknown sphere of the biological Microworld. They only touched the deepest Macromolecular level — the very core of life having passed several strata surrounding this core, — lacking completely any information of the level of cellular structures and cells themselves, knowing almost nothing of the processes of their reproduction, on the essence of the processes of sexual propagation, gametogenesis, fertilization, individual development etc.

Thus, in his work M e n d e l broke into the scope of the biology of the future. Now, we regard it as the stroke of genius, but just this foreshadow of the future made his work remain unnoticed.

During 35 years of obscurity there were but three biologists, all of them botanists, who briefly quoted Mendel's work. I should like to stress that of these three botanists I . F . S c h m a l h a u s e n — the father of our well-known zoologist I . I . S c h m a l h a u s e n — expanded the essence of Mendel's work in his thesis "On Plant Hybrids" in 1874 most thoroughly.

By 1900 — the year of the rediscovery of Mendel's law of heredity — the state of affairs in biology changed greatly. A rapid progress transformed biology from a science unprepared to understand Mendel's work to a science that badly needed just the knowledge of Mendelian discoveries.

To become complet, Darwin's theory of evolution was in need of an insight into the material with which natural and artificial selection operated, i.e. into the nature of hereditary variations and the regularities of their hereditary transmission.

On the other hand, a rapid accumulation of the knowledge of the cell, the nucleus, the chromosomes, their division, distribution and recombination during gametogenesis and fertilization almost completed our concepts concerning the pattern of structures and processes underlying Mendel's law of heredity.

But even now the attitude to Mendelism is far from unanimous. While some biologists correctly estimated the broad prospects of Mendelian scientific

contribution, others underestimated its value and not seldom there was prejudice against its seemingly oversimplified mathematical or nonbiological approach to the most complex phenomena of life.

Now, Mendel's name and his contribution to biology appear in an aureola of glory. Certainly the credit for this goes not only to Gregor-Mendel himself, however great this credit is, but it goes also to the whole army of his followers, sometimes not less remarkable than Mendel himself. That is why when speaking of the fate of Mendelism one cannot help speaking of the contributions of his famous followers.

Let us remember, for instance, only such epoch-making stages in the development of Mendelian genetics as the appearane of Sutton-Boveri-Wilson's hypothesis marking the birthday of cytogenetics; the brilliant decades of the elaboration of chromosome theory of heredity in Drosophila-investigations of T. H. Morgan's school and, last but not least, the discovery of the role and fine structure of the DNA marking the beginning of the modern era of molecular genetics.

Of course, the spreading of Mendelian genetics and the progress of science in general are international processes. But it is only natural when speaking of the history of genetics that every contributer prefers to speak about the most interesting pages in this history concerning his native country.

That is the reason why when paying tribute to the great and innumerable contributions made by geneticists all over the world to the development of Mendelian genetics I would like only to touch upon some landmarks associated with the spreading of Mendelian genetics in the country I have the honour to represent here.

The well-known contrast in the fate of Mendelism and Darwinism, as well as the striking difference in the very mode of thinking in the fields of experimental and descriptive biology, resulted after the rediscovery of Mendel's law in a lingering controversy between the adherents of Mendelism and Darwinism. Now, it is quite evident that Mendelism and Darwinism are actually complementary and we must not forget a classical theoretical investigation which stands as the landmark on the way to their organic synthesis — I mean the appearance in 1926 of S. S. Chetverikov's paper entitled "Certain Aspects of the Evolutionary Process from the Standpoint of Modern Genetics".

Chetverikov's ideas concerning the regularities and forms of the participation of Mendelian discrete hereditary factors in the processes of natural selection and speciation were promptly verified by experimental data obtained by his co-workers. It seems to me that his ideas represent the starting point of modern population or evolutionary genetics. Together with the papers of R. Fisher (1930) and S. Wright (1931), Chetverikov's paper of 1926 laid the foundation of the genetic theory of microevolution and speciation.

The next remarkable word in the domain of general biology and genetics was spoken in our country almost at the same time, at the first plenary session of the III.rd Congress of Zoologists held in Leningrad in 1927. This new word entitled "Physical and Chemical Bases of Morphology" was spoken by Prof. N. K. Koltzoff, one of the most prominent founders of experimental biology and genetics in our country.

By that time the concepts of the almost completed chromosome theory of heredity were enriched by physical, chemical and biochemical approaches. It was well-known already that complexes of gigantic molecules of nucleic acids and proteins represented the most important constituents of chromosomes. However, many years earlier, as a matter of fact as early as in 1893, at a congress of naturalists and physicians held in Moscow Koltzoff said, (I quote nov Koltzoff's own words): "Professor Kollie, a chemist, when comparing, estimated by himself, the size of protein molecules with that of the head of spermatozoon through which the whole paternal hereditary material is transmitted to the offspring, came to the conclusion that all hereditary characters were transmitted through a very small number of molecules", which is of the same order of magnitude as the number of chromosomes. Realling this old statement and taking under analysis vast data accumulated since that time in cytology, genetics and experimental morphology, N. K. Koltzoff proposed a well-founded concept, according to which the Mendelian factors of genes corresponded to the links of chains of gigantic "hereditary molecules" representing the genetical material of chromosomes. Koltzoff imagined these "hereditary molecules" as reproducing in the course of mitotic divisions by the same template principle as matrices are reproduced from original type set in typography. Being transmitted through the germ cells from generation to generation, the exact copies of "hereditary molecules" pass to the descendants the hereditary information which determines their morpohological pecularities.

Koltzoff elaborated this hypothesis almost 40 years ago. However a long period comprising the origin, development and flourishing of biochemical and microbial genetics was needed before the validity of his concepts could be checked by direct experimental analysis. When at last the true nature of hereditary molecules was revealed, the interrelationships of nucleic acids and proteins understood and the secret code of hereditary informations deciphered, we became aware of the fact that the concrete suppositions of N. K. Koltzoff concerinng the hereditary molecules were correct only partially. N. K. Koltzoff considered the carriers of hereditary information to be represented by highly polymerized protein molecules of the nucleoprotein complex. Rather surprisingly it turned out later that the determining role here was played by far simpler compounds, the code of hereditary information being written in that part of nucleoprotein complex which is represented not

by proteins but by DNA. In principle, however, the ideas of N. K. Koltzoff were prophetic.

N. K. Koltzoff died 25 years ago, just before the Second World War, which for a long time retarded the progress of biology in our country. Now, it is clear that Koltzoff's concepts must be regarded as a brilliant scientific foresight which represented an outstanding landmark on the straight way leading from the great discoveries of Gregor Mendel to the modern molecular biology.

This more than brief mention of only two pages from the long history of Mendelian genetics in our country certainly does not exhaust the list of names of remarkable Russian geneticists and their contributions to the development of the science of heredity.

On the occasion of the Mendel Memorial Symposium I would like to mention in the first place the famous name of N. I. Vavilov whose unprecedented activity toward the application of Mendelian genetics in the domain of plant breeding is widely known all over the world.

Not less known are his ideas aspiring this activity, which concern the mountainous "centres of diversity of cultivated plants" an "the law of homologous series of hereditary variability".

Nobody could say better than Vavilov himself what a great role for the practice of agriculture he ascribed to Mendel's scientific heritage. Quoting his own words: "Mendelism penetrates the practice of a plant breeder widening the prospects of plant and animal improvement and making selection an exact science. The little booklet of Mendel is undoubtedly one of the most remarkable biological papers that every biologist, every investigator and plantbreeder has to study most attentively. This booklet is highly valuable to us, as a brilliant example of the application of new exact methods to the investigation of one of the most important attributes of life — the heredity.

The penetration of Mendelism into plant breeding brings biologists ever closer to the conscious control of the plant and animal organization. Mendel's concepts started a new era of the deliberate experimental control of the heredity of living beings."

It would also be appropriate to pay our tribute to professors A. S. Serebrovsky, Yu. A. Filippchenko, G. D. Karpechenko, N. G. Levitsky, A. S. Sapegin, Mrs. S. L. Frolova, N. K. Belyaev and many, many others.

Due to the lack of time it is possible only to mention a very incomplete list of names but I cherish hope that many participants of this Symposium will associate these names with the results of their widely known scientific works.

Bearing in mind the memorial character of my paper I intentionally mention only the names of deceased scientists. However, the development of the science of genetics based on Mendelian principles belongs not only to the past but

even more to the present, and to the future. Many of my Russian fellows--geneticists still participate in the search for solutions of the problems put 100 years ago by the discovery of M e n d e l . Many of their contributions, for instance, those concerning the fine structure of the gene, the experimental mutagenesis, especially chemical mutagenesis, the population genetics, the phenogenetics, the analysis of nucleo-cytoplasmic interrelationships by means of experimental androgenesis nad parthenogenesis, the experimental polyploidy in plants and animals, etc. deserve in my opinoin your attention as really impressive evidences of the universality of Mendel's laws of heredity. But some of these actively working geneticists have the honour of participating in this Memorial Symposium and I shall not touch upon their contributions to the development of Mendelian genetics as they can do it themselves much better.

During the years that have elapsed since the time when M e n d e l worked genetics transformed into a vast region of biology divided into many branches and contacting with diverse fields of biology, as well as with other sciences such as mathematics, physics and chemistry. During this time filial branches, of genetics have developed: cytogenetics, evolutionary genetics, physiological genetics, developmental genetics, radiation genetics, biochemical genetics, microbial genetics, genetics of cancer, genetics of behaviour, molecular genetics etc. etc.

Particular subdivisions of genetics concerning the heredity of certain species of microorganisms, plants and animals, and among them human genetics on the first place, acquired self-sufficing importance.

There are ample grounds to believe that the period of the development of genetics during which the nature of discrete Mendelian factors and the mechanisms of their hereditary transmission have been elucidated approaches its completion. During this period we have been answering the questions put by M e n d e l , descending step by step organization levels of living beings to the knowledge of the intimate nature of the genes, whose existence and role had been so clearly shown in Mendel's classical work.

Now, our chief and probably much more complicated task would be to ascend step by step the levels of life to get an insight into the place and role of Mendelian hereditary units in most complex and mysterious processes of hereditary realization, of the biological synthesis and individual development.

However, the task of my paper is not to foresee the future of genetics but to glance back on its development during a century. During this whole very fruitful period the basic work of J o h a n n G r e g o r M e n d e l has been the cornerstone underlying the whole edifice of modern genetics, and even of the whole edifice of modern genetics, and even of the whole general biology. It is beyond any doubt that Mendel's work will retain its significance for a long time to come.

Development of Cytogenetics

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The cytogenetics, as an integral part of modern genetics, owes its inspiration to Gregor Mendel's genial experiments the centennial of which we celebrate with the whole world here in Brno, where they originated.

The Mendelian, particulate hereditary units—the genes when they were generally accepted at the beginning of our century needed at once to be located somewhere in the cell. Already in 1904 W. S. Sutton and T. Boveri suggested that the Mendel's laws of separation of allelic factors in gametes and independent segregation of nonallelic factors could result from separation of homologous chromosomes and independent segregation of different chromosome pairs in meiotic divisions, which means that the Mendelian factors may be located in the chromosomes.

Soon in Columbia University, New York in Th. Morgan's laboratory it was shown that genes are located in chromosomes and linkage and crossing-over were first described. The first, now classic, cytogenetic experiment was done by C. B. Bridges (1916). He demonstrated that the nondisjunction of X chromosomes in *Drosophila melanogaster* females causes a reversal in the inheritance of sex-linked character. This work in which, both genetical and cytological analysis were performed paralelly has all advantages of cytogenetic experiment; it initiated modern cytogenetics.

At its early period the main task of cytogenetics was to contribute additional evidence for the theory of chromosomal localization of genes. In the early twenties many papers were published in which was proved independent segregation of different chromosomal pairs in meiosis and the relation between linkage groups and the chromosomes. Thus the theory locating genes in the chromosomes was no longer a working hypothesis: it became a well established experimental fact. Later on cytogenetics has much enlarged its scope and interests together with the expanding interests of genetics.

Two main directions of the cytogenetics can be distinguished and defined accordingly as cytogenetics at cellular or individual level, and cytogenetics at populational level which is an integral part of evolutionary genetics.

Cytogenetics at the cellular level was at the beginning mainly concerned with the completion of our picture of the mechanisms of basic hereditary

processes. E. E. Carothers (1913) demonstrated that different pairs of homologous chromosomes do segregate independently in meiosis like non-linked genes, according to second Mendel's law. Then C. Stern (1931) furnished cytogenetic proof that cross-overs do have exchanged chromosomal segments from both parental homologoues. When the different linkage groups in different organisms were established it was proved that their number is equal to or less then the haploid number of chromosomes in each organism. Then the problem arose to ascribe the separate linkage groups to individual chromosomes that could be morphologically distinguished. All kinds of structural and numerical chromosomal aberrations were used in such studies as for instance those of C. B. Bridges in *Drosophila* or of B. McClintoc and M. M. Rhoades in maize.

Using different chromosomal aberrations it became also possible to compare the genetic map distances and the physical distances between genes. First cytological maps of linkage groups were constructed. One of the revolutionary moments was the introduction in cytogenetics of the study of giant salivary chromosomes in *Diptera* and in *Drosophila* particularly by E. Heitz (1933) and T. S. Painter (1934). With salivary chromosomes it was possible to locate exactly different kinds of chromosomal aberrations like inversions or deletions and to use cytogenetic methods to locate genes within single band regions.

Since the whole genetical analysis is based on recombination the exact interpretation of meiotic processes including chromosome replication, pairing, chiasmata formation and separation of homologoues was necessary. A general theory of meiosis was elaborated in the thirties by C. D. Darlington. His book "Recent advances in cytology" published in 1932 was a landmark in the development of cytogenetics and was a great stimulus both for his followers and opponents. The chismatype theory of crossing-over postulated by F. A. Janssens was fully developed and specified by Darlington and has played and is still playing an important role in genetical thinking.

From that time on the close collaboration of geneticists and cytologists is more and more widespread. One such pair should be mentioned: A. F. Blakeslee and J. Belling. To every geneticist these two names are primarily connected with the splendid cytogenetic analysis of *Datura*. The profound analysis of different kinds of polyploids and aneuploids mainly trisomics and then of numerous interchromosomal translocations was a beautiful example of cytogenetics of one species. The proper explanation by Belling of ringforming translocation heterozygotes together with the knowledge of balanced lethal mechanisms known from *Drosophila* stimulated further work in *Oenothera*, the classic object of H. de Vries studies on mutations. The famous contributions of O. Renner (1921 et ssq), C. E. Cleland (1922 et ssq) and others have fully explained by permanent structural hetero-

zygozity the exceptional genetical and cytological behaviour of *Oenothera Lamarckiana* and in the whole genus *Oenothera*.

The vast domain of ploidity research was greatly stimulated by Blakeslee's early studies in *Datura* and also by introducing of colchicine (in 1937) as an efficient polyploidizing agent. After H. J. Muller in 1927 first demonstrated the mutagenic effects of X-rays in *Drosophila* a large field of cytogenic studies of radiation effects and later of different chemical agents on the chromosome breakage and rearrangements was developed. Now when the role of nucleic acids in heredity was been established the study of chromosomes is regarded as one of the most sensitive tests for biological effects of different mutagens and other agents. The distinction between half-chromatid, chromatid and chromosome breakages allow not only the study of sensitivity of different cells but also determining the time of chromosome replication in cells.

Modern cytogenetics at the cellular level in the light of growing knowledge of the structure and role of DNA in heredity has now, of course different, new problems to solve. For instance, do chromosomes replicate semiconservatively as DNA replicate? Recent works of J. H. Taylor give an affirmative answer. But still the problem of chromosome structure remains obscure. How many DNA double helices do they contain or are the chromatids only a single folded DNA molecule? What is the role of proteins in the chromosomes and how are they connected with DNA? Are the DNA in chromosomes continuous or are the genes or blocks of them separated by linkers of different chemical composition? Such and many other problems must be answered by cytogenetics in future. Using now modern methods like electron microscopy, X rays diffraction, autoradiography etc. cytogenetics will also dwindle step by step down to submicroscopic level of organization.

Cytogenetics of developmental processes is now only beginning. Recent studies of sequentional apperance of the s.c. "puffs" on the chromosomes in cells with changing metabolic activities may indicate the genes or regions of chromosomes that are active in the process of information transcription from DNA to messenger RNA. This is the beginning of a new field of cytogenetics connected with the regulation of gene activity and the processes of cellular differentiation in embryogenesis and ontogeny.

Other field of cellular cytogenetics that will develop in future is the study of nonnuclear genetic elements of the cell. The discovery of different kinds of episomes in bacteria, of the presence of DNA in cytoplasmic organellae like for instance in plastids makes the difference between nuclear and extranuclear inheritance less clear. The chromosomes now are no longer the only object of interest for cytogeneticists. The splendid works of T. M. Sonneborn and J. R. Preer on cytoplasmic kappa particles in *Paramecium* using combined genetic and cytologic methods is an excellent example of this new and exciting research line in cytogenetics.

Finally the quite recent discoveries of strange processes of nuclear fusion and maybe chromosomal recombination between cells of different origin in mixed in vitro tissue cultures that will be discussed in Prague Symposium show that for cytogenetics will be in future an unending array of new activities.

Now, let me turn to another field of cytogenetic activities which may be called population or evolutionary cytogenetics. It developed on the basis of cellular cytogenetics since population genetics is based on the knowledge of basic cell or individual heredity. Population cytogenetics has most spectacular achievements. It started from the studies on the distribution and frequency of different chromosomal rearrangements or numbers in different populations as exampliefied for instance in A. F. Blakeslee's studies on *Datura*, and so splendidly developed in *Drosophila* by Th. Dobzhansky, N. P. Dubinin and many other *Drosophila* workers. Such studies showed structural or numerical chromosomal differences in different seasonal, ecological or geographical conditions. They pointed to different selective value of different chromosomal patterns within one species. This kind of studies was also extended to a comparative studies of groups of related taxa and showed that often the differences in intra- and inter-specific variation are more quantitative than qualitative in nature. The cytogenetic analysis of such groups as for instance the genus *Drosophila* done by Dobzhansky and a pleiade of cytogeneticists, the genus *Crepis* (E. B. Babcock, M. Navashin, S. L. Stebbins and others) and the group of general *Triticineae* (H. Kihara and many others) made possible to describe exactly the different processes leading gradually to differentiation both at intra- and inter-specific level. The idea of O. Winge (1925) of amphiploid origin of many polyploid plant species was soon experimentally verified by S. O. Karpetschenko and in 1930 A. Müntzing for the first time synthetized in the genus *Galeopsis* a tetraploid species from its two ancestral diploid species. The experimental synthezis of evolutionary process was a spectacular triumph of cytogenetic methods.

The whole neodarwinistic genetic explanation of the mechanism of evolutionary processes is primarily based on evidence obtained from cytogenetic investigations on natural populations. The only practically attainable on an extensive scale measure of relationship between different taxa is still and will be in future the analysis of chromosome homology in hybrids between different taxonomic units. The amount of research done in this field is tremendous but still much more must be done especially for extra temperate zones of the earth.

Cytogenetics of cultivated plants has much contributed to the reconstruction of the origin of cultivated plants. For instance the study of *Triticinae* has given an exact picture of the origin of cultivated hexaploid wheat. Knowing exactly the origin of its genomes, their homology and homeology we can be assured that

the future progress in wheat breeding on cytogenetic basis will cope with increasing demand of modern civilization. Also new crops will be produced like *Triticale* or other auto- or alloploid synthetized new species, which after thorough cytogenetic control will enlarge our list of cultivated plants.

Cytogenetics of human populations is only beginning. Its rapid development in recent years may contribute in future to much better understanding of many hereditary diseases which pest human populations. Maybe it will help also to prevent the spread of some of the drawbecks of civilization which increase as a result of decreasing selection pressure and increasing mutagenic influences.

The discovery of the units of heredity by G r e g o r M e n d e l here hundred years ago have much contributed to the fruitful union of two for a long time separate lines of research: the cytological and the genetical. Cytogenetics that arose from this union has imposing achievements and still more promising future.

On Some Cardinal Problems of the Contemporary Theory of Mutations

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Introduction

The science of the gene is founded on the discoveries of Gregor Mendel in 1865. However, the science of the material bases of heredity and of the variability of the genes (mutations) belongs to the XXth century. The phenomenon of mutation was stated on the verge of the XXth century by Korzhinsky (1) and Hugo de Vries (2).

In our days it is well-known that the material basis of mutations is caused by the chemical changes of the gene structure and by various alterations in the number and structure of the chromosomes.

The history of life on Earth and the plant and animal breeding as far as our times are concerned, are founded on the utilization of natural mutations. At present, the position is changing. During the last three decades of our century investigators are intensely concentrated on the possibility of causing the occurrence of artificial mutations. As a result of this, the processes of the chemical changes of the gene and of the entire nuclear structure of the cell were wholly under the control of scientists. New aspects have also become clear in the phenomenon of natural mutability. The progress in these works has played not only a scientific but a practical role. The selection of microorganisms changed completely as the result of these achievements. New forms of the mutagenic selection of plants were created and in a number of cases also those of the selection of animal organisms.

In the history of the artificial production of mutations the principal role belongs to the elaboration of the principles underlying raditional and chemical mutagenesis. The discovery of the mutagenic effect of radition belongs to Nadson, Filippov (3) and especially to Muller (4). Works on chemical mutagenesis were begun by Ssacharov (5) and Lobashev (6). Most important discoveries on chemical mutagenesis were published by Rapoport (7) and Auerbach (8). In the history of natural mutagenesis the works by Navashin (9) and Peto (10) tower high, showing that the biochemical changes in ageing seeds cause mutations. Watson and Crick (11), Freese (12) and others have elaborated the modern molecular basis of the mutational process, showing that there are changes in the nucleotide composition of DNA.

Thus, the problem of mutations is represented by an enormous and widely branched region of science. In this report only some problems will be broached, which the author considers cardinal for this most important problem of contemporary biology.

On some problems of the theory of the natural mutation process

It is clear that the principal factors causing the natural occurrence of mutations are metabolites, endowed with a mutagenic effect, the natural background of radiation, the action of temperature and a number of other factors of external and internal media. The course followed by the natural mutation process is already described both from the quantitative and qualitative standpoints. For the general principles underlying natural mutagenesis of great interest is the discovery that the natural occurrence of structural chromosome mutations (chromatid and chromosome rearrangements) proceeds similarly to that found for chemical mutagenesis (13). It appears that in some species (human cells in tissue cultures, cells of root tips of *Vicia faba)* chromosome mutations occur according to the type of delayed mutagenesis, while in others (onion) according to that of undelayed mutagenesis. In the first case chromosome rearrangements appear which take place in experiments on alkylating compounds during chemical mutagenesis when the damages are realised at the synthesis stage (S) of the cell cycle. In the second case both chromosome (damages of stage G_1) and chromatid (damages of S and G_2 stages) rearrangements occur, similar to that taking place during the action of radiation or chemical mutagens of undelayed action.

Nevertheless, the nature of delayed and undelayed mutagenesis is first of all connected with the specificity of the cell's reaction, not with the quality of the chemical mutagens. It is shown (14) that the typical alkylating compound K_{32} which causes in the cells of *Vicia faba* and wheat chromatid rearrangements only, when applied to onion root tips causes in their cells both chromosome and chromatid changes. This shows that even in the presence of metabolites in the cell of the type of alkylating factors only, mutability in some species proceeds according to the type of delayed and in others — according to the type of undelayed mutagenesis. The question arises — why do the chromosomes, reacting with alkylating factors, produce chromosome mutations at the G_1 stage in some species, whereas in others the changes become realized at the S stage ? So far the answer to this question has not been found. In this direction investigations offer great hopes, since the two types of natural chromosome mutations described above, are, of course, connected with fundamental peculiarities of the functional organisation of the chromosomes.

The elaboration of methods for controlling the natural mutation processes

is of paramount importance both for the theoretical studies of nature and also for their economic application. For the advancement of this trend an enormous role is played by the problems of antimutagens, started by Novik and Szillard (15), who showed that some ribonucleosides suppress by 2/3 the natural mutagenesis in *Escherichia coli*.

In experiments on streptomycin it is shown (16) that the latter suppresses the natural origination of lethal mutations in *Drosophila*. In the cells of plants both mutagenic types, i.e. undelayed mutagenesis (17), (18) and delayed mutagenesis in the cells of *Vicia faba* (19), are suppressed by the action of antimutagens (streptomycin, cystein, etc.). The control over the natural mutation process concerns all the most important sides in the origination of mutations. This, evidently, prevents the transition of potential damages into true mutations, because in some cases such mutagens as, for instance, streptomycin, simultaneously protect against a number of mutagenic effects, i.e. ionizing rays and ultraviolet light (20). In some cases the same compound (cysteamine, arginine etc.), depending on their concentration, act as antimutagens, mutagens and antiirradiation compounds (21).

The course followed by natural mutagenesis proceeds on the basis of a powerful intracellular system of natural restoration of damages, not without reason have such cellular metabolites as aminoacids been found among the antimutagens. The question arises — wherein consists the mechnism of the antigen action? Is it a direct elimination of damages from the chromosomes, or does it take place through the changes of the intracellular system of restoration? Of interest in this case are the data on human cells in culture and in the root tip cells of *Vicia faba* and onion, showing that natural chromosome rearrangements are distributed among the cells according to the Poisson distribution from the expected ones (22, 23). This shows that the restoration system may be possibly damaged in those cells where natural mutations occur.

So far the chemical processes taking place in the phenomena of genotypic control during natural mutagenesis remain unknown. This is especially important for those cases in which some of the genes regulate the mutability of some of the other genes. In this case, some mechanism is acting on the level of natural mutability, causing a directed, regulated mutability of a given gene. The discovery of the chemical mechanisms acting in this phenomenon will play an enormous role for the theory of mutations as a whole.

Although the general characters of the factors of the natural mutational process are known, nevertheless, not in a single case is the entire complex of its internal and external factors clear. Some times automutagens may be clearly localised. Thus, in darkly coloured forms of *Vicia faba* the frequency of occurrence of chromosome mutations amounts to 20 per cent (24). Removal of the pod causes a decrease in the mutation frequency of the root cells up to

1·5 per cent. However, the factors causing these residual 1·5% mutations, remain so far unknown.

The mechanisms are unknown which regulate the adaptive levels of the general natural mutability in different species and populations, and the levels of the mutability of separate genes. In forms with a nucleoproteid chromosome organization the protective functions are possibly connected with the protein complex. However, in viruses there are also "hot points", loci of moderate and rare mutability in the chromosomes consisting of DNA. This is a sign emphasizing the specific value of the gene organization. Finally, a most important part may be played by a gene determined cytoplasmatic natural restoration system in the cell.

Investigations on radiation and chemical mutagenesis have in many ways left behind the studies on the nature and causes of natural mutations. Nevertheless, the cardinal properties of heredity become manifest in natural mutagenesis. These problems, along with artificial mutagenesis, must find a central position in the modern investigations on the general mutational theory.

Primary radiational genetic damages and the system of intracellular restoration

The most important problems of contemporary radiation genetics are concentrated on answering the following question: What are the correlations existing between the processes causing the realization into an irreversible form of the primary potential radiational chromosome damages and the reverse processes tending to restore these damages? Every organism possesses an intracellular restoration system whose action is also directed against the mutagenic results of radiation. The questions, such as the effect of small doses, chromosome sensitivity at various stages of the cell cycle, radiosensitivity of the species, evaluation of the rate of doubling doses, the genetic effect of different kinds of radiation, etc., all become confronted with the problem of the correlations existing between the processes of damage and restoration.

K i m b a l l (25, 26) showed on *Paramecium* experiments that under the effect of ionizing radiations at the G_1 stage about 2/3 of mutations occur as potential changes. Either they undergo reparation or they transform into true mutations when they attain the S stage. According to K i m b a l l very effective restoration processes of the potential damages occur during the G_2 stage.

O s t e r (27) and S o b e l s (28) and others, in their experiments on the oxygen effect and modifications of genetic damages after irradiation, have found that changes of the radiosensitivity of the *Drosophila* cells are connected with different restoration processes, occurring after the primary chromosome damages, i.e. on the basis of initial potential changes.

Russell (29, 30) showed in experiments on the irradiation of mice that there exists a correlation between the rate dose and mutation frequency. The mutation frequency fell markedly given a rate dose of 0·8 r/min as compared with 90 r/min. This emphasizes the great importance of the processes of restoration.

Muller (31) discussing these facts of Russell emphasizes that in *Drosophila* the differences in a rate dose of 3000 (1 r/hour and 3000 r/hour) do not change the reaction of the genetic material. According to Muller

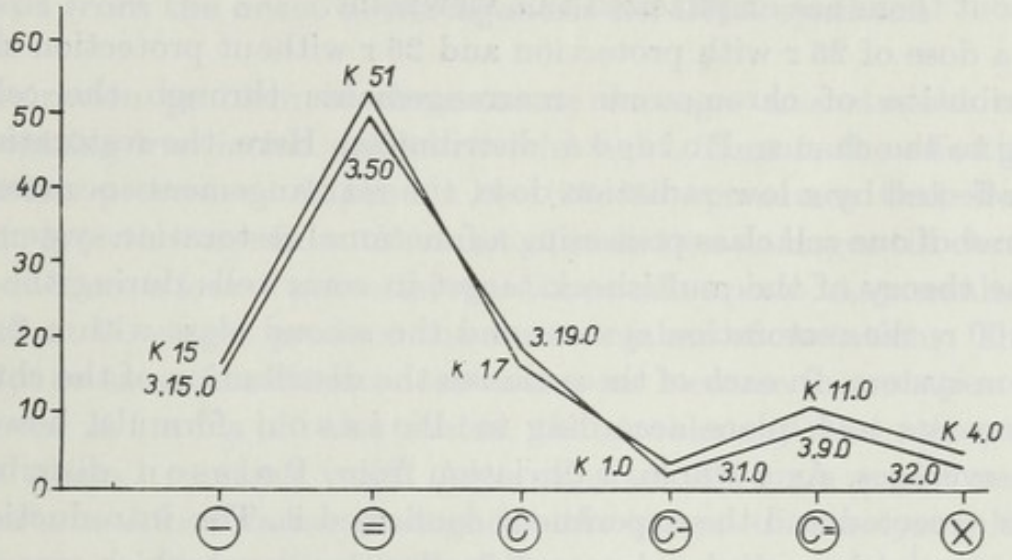

Fig. 1.

this has evidently to do with the fact that considering the length of life and developmental stages of embryonic cells in mice protective systems ought to arise against the effect of natural radiation acting as a form of chronic small dose irradiation. For *Drosophila*, in view of the rapid generation changes, effect of natural radiation plays no role.

Dubinin, Dubinina and Tarassov (23) showed the role played by the natural restoration system during chemical protection against radiation. Dubinin and Dubinina (32) have shown before, and later on Manuilova (33), that the introduction of protectors in the style of AET, serotonin, streptomycin, thiourea, into embryonic human cells in primary tissue cultures, show a clear picture of protection under the action of 50 and 100 rad gamma rays. In the first case the amount of chromosome rearrangements becomes less by 41%, in the second — by 28%. Under the action of a dose of 25 r no protection could be stated.

The study of chromosome rearrangements during level modifications of the mutation process by means of protectors (50 and 100 r doses) did not show any changes in the processes of fusion or non-fusion of the fragments.

This shows that chemical protection concerns the restoration of the potential damages before the formation of true chromosome breaks.

Of fundamental value is the fact of the qualitative differences between the presence of chemical protection against doses of 50 and 100 r and its absence against a dose of 25 r of gamma rays. This difference may be understood admitting the absence of threshold during the occurrence of mutation and the presence of threshold during restoration. In the latter case the presence of a restoration system in the cell must be admitted which serves as multishock target for the radiation effect. A special analysis of the distribution of chromosome rearrangements in the cell during different doses under the conditions of protection and without them has emphasized this viewpoint.

Given a dose of 25 r with protection and 25 r without protection shows that the distribution of chromosome rearrangements through the cells occurs according to the chance Poisson distribution. Here the restoration system was not affected by a low radiation dose, the rearrangements occurred on the background of one cell class possessing a functional restoration system. According to the theory of the multishock target in some cells during the action of 50 and 100 r, the restoration system and the second class with a functioning restoration system. In each of these classes the distribution of the chromosome rearrangements took place according to Poisson formula, however with different averages. As a whole, a deviation from Poisson distribution formula was expected and the experiment confirmed it. The introduction of protective compounds caused a decrease in damage level which was connected with the renewal of the restoration system. Thus, one of the classes was eliminated during the action of this radiation dose, since it was without protection. It was to be expected that in this experimental series the distribution of rearrangements would answer the formula of Poisson and our experiments confirmed it.

This data shows that the protection effect against radiation in human cells is connected with the influence of protectors on the restoration system. This system in man must be much more developed as compared with mice. It is noteworthy that according to Sidney (34), and to our unpublished data, *Drosophila* protectors, well-known for mammals, do not produce a protective effect. The system of the natural restoration of genetic damages is valid for all forms, however in mammals and in some other organisms the genetic evolution has taken place for a partial suppression of the effects of small radiation doses. However, in these forms also part of the mutations, directly acquiring irreversible changes, the principle of threshold absence is completely retained under the action of small radiation doses.

According to our data obtained in experiments on the irradiation of human cells in tissue cultures, this partial genetic adaptation against small radiation doses was the result of the origination of a restoration system which may be damaged only on the basis of a multishock mechanism but now only under the action of high doses. Therefore, high dose damages of such a system will produce

under similar conditions more mutations per dose unit as compared with the mutation number caused by the effect of small doses when an intact restoration system is operating. These phenomena will proceed differently in various species, since they are caused by the presence or absence of partial genetic adaptation to the action of small doses of natural radiation.

On the development of the processes of genetic damages during chemical mutagenesis from the onset of mutagenesis till DNA synthesis

The restoration problem of chromosome damages was studied under the effect of ionizing irradiation and ultraviolet light. Time is the effective factor in restoration processes. K i m b a l l (25, 26) presumes that during the logarithmic growth stage from the onset of radiation damages till chromosome autoreproduction, a loss of potential mutations takes place. As a result damages at the earliest G_1 stages produce the least number of mutations. The nearer to stage S, the same irradiation dose causes an increase in mutation number. However, as K i m b a l l also states, the problem of the role played by "sensitive stages" remains valid. According to K i l m a n the restoration degree in *Paramecium* varies throughout the stages of the cycle. Maximum restoration occurs at stage G_2. Visible differences in radiosensitivity of the cycle are described in the work on the irradiation of human cells (35).

Evidence on delayed chemical mutagenesis shows that in this case for a certain period time is no more a factor lowering the amount of potential damages, on the contrary, it serves as their increasing factor. It is known that in these cases at the beginning, so long as there are cells irradiated at the G_2 stage, no chromosome rearrangements were found. When the cells enter mitosis after mutagen treatment at the S stage, chromatid rearrangements begin to appear. Their number grows and attains its maximum at the moment when the cells treated with mutagen at the beginning of stage G_1, enter the mitotic stage.

Nevertheless, two disputable points remain so far without an answer. First, is the growth of the number of rearrangements after mutagen treatment a true development of the amount of damages? The same situation may be simulated by a gradual decrease in the number of asynchronic G_2 cells even under conditions of equal mutability at the S and G_2 stages. Second, do the initally damaged G_1 cells take part in this state of mutability? Perhaps the alkylyzing mutagens are capable of causing mutations only during autoreproduction of the chromosomes (stage S) through the changes of the DNA precursors?

Both these questions have already been answered. Data about the amount of chromosome rearrangements in onion among the timidine cells, i.e. cells at the S stage treated with mutagen (36). It is clear that the amount of chromatid

rearrangements augments as the factor of time prolongs from the onset of mutagen treatment till the end of stage S.

The second question concerning the occurrence of potential changes at the G_1 stage, which are subsequently at stage S realized into chromatid rearrangements, is difficult to be solved through usual methods. Dubinin *et al.* (36) used an object which is characterized by an undelayed type of natural mutability — root tips of onion. They treated these rood tips with alkylyzing compounds which usually cause only chromatid rearrangements. This treatment of the root tips of onion showed that in this case there occur both chromosome and chromatid mutations. In this case, when there is a mutagenic effect at the G_1 stage, which is proved by the occurrence of chromosome translocations, it is not to be doubted that at the same time we have a classical example of delayed chemical mutagenesis for the chromatid rearrangements.

Thus, we have a picture of the occurrence of potential chromosome damages at various G_1 and S stages, and their transition into true mutations, whose realized size is determined by the factor of time between the moment of damage and the onset of autoreproduction.

Sidorov *et al.* (37) studied the effect of ethylenimine under conditions of C-mitosis. In particular, this made it possible to find a group of diploid cells with a cycle lasting from 20 to 70 hours. It is shown that first there takes place an increase in the number of the chromatid rearrangements, but subsequently the number of rearrangements diminishes. It is apparent that in this case the Time factor plays first a positive role and subsequently it diminishes the number of rearrangements. The simple conception of varying sensitivity of the stages G_1 and S cannot be applied in this case.

Thus, the occurrence of potential chromosome damages may be subjected to the effect of absolutely opposite processes. On the one hand, the intracellular system of natural protection and restoration leads to the elimination of some of the potential changes. On the other hand, some so far unknown factors, cause the development of an initial potential damage and during the period of the time from the moment of damage till autoreproduction they increase the amount of true chromosome rearrangements.

It is difficult to say whether the reparation processes are principally inherent to radiation damages and the development of damages — to alkylyzing compounds. This problem has hardly been studied and in a number of cases there occurs, possibly, a highly complex action.

It is clear that the restoration process and the development of primary potential genetic damages are of paramount importance for comprehending the nature of mutations.

It is highly interesting that both reparation of damages and the development of damages may occur at the stage of one effective chromosome without depending on the processes of autoreproduction (stage of synthesis).

The Watson-Crick-Freese hypothesis has connected the mutation phenomenon at the molecular level with the processes of gene replication.

It is evident that such a mechanism of mutation really exists and that it is of great importance. Nevertheless, it is proven that mutations arise in the DNA molecules which are inert. First of all this concerns mutations arising in phage particles located in resting intercellular states and in such chromosomes which are inherent to *Drosophila* sperm. In all these cases the molecular changes being the cause of mutations take place in the DNA molecules without depending on their autoreproductive capacity.

Resonant and prolonged mutagenesis

The principal enigma concerning the molecular bases of mutations consists therein that the occurrence of mutations in time does not answer the expected ones which follows from our knowledge of the structure and autoreproduction of the DNA molecules.

The DNA thread consists of two polynucleotide chains and its autoreproduction proceeds according to the principles of semi-conservative doubling. Practically speaking, not a single mutagen, touching a thread of the DNA molecule, ought to change the initial molecule in such a way that its progeny should by 100% consist of mutant forms.

The occurrence of mutations must be followed by mosaicism, whose principal form must be the origination of 50% changed cells in the progeny and 50% normal cells.

However, this does not take place. In some case we have so to say an increased form of mutagenesis, when all the progeny of the initial mutant chromosome have mutations. This concerns first of all radiational mutagenesis. In other cases mosaicism arises, but as a rule this concerns only part of the progeny, less than 50%, i.e. we have a picture of delayed mutagenesis. Such a picture is inherent first of all to chemical mutagenesis. Nevertheless, along with this it is known that a number of chemical mutagens may cause the occurrence of "whole" mutations, i.e. when the initial mutant DNA molecule produces 100% changes in the progeny. On the other hand, the phenomenon of delayed mutagenesis can be stated, since mosaicism to a certain degree is subject to the action of radiation.

Muller *et al.* (38) made an attempt to explain the enigma of whole mutations occurring under the action of radiation by applying the Rotation theory. They founded this hypothesis on the idea of the simultaneous breaks of connections between sugar and basis in both complementary bases of two chains in DNA. A 180° turn of the pair of bases, occurring after this break, may change the position of both bases, thus causing a simultaneous change of

both semi-nucleotide chains in the DNA molecule. It is clear that such a molecule produces a mutation in its entire progeny on the base of a semiconservative autoreproduction.

Brookes and Lawley (39, 40) while investigating bifunctional alkylyzing compounds showed that a re-union of the molecule is possible through the connections with the nucleotides of the complementary pair of bases (guanin-cytosin). Even in the case of monofunctional compounds, the connections existing between the alkylyzing group and guanin may have an effect on its complementary cytosin (41).

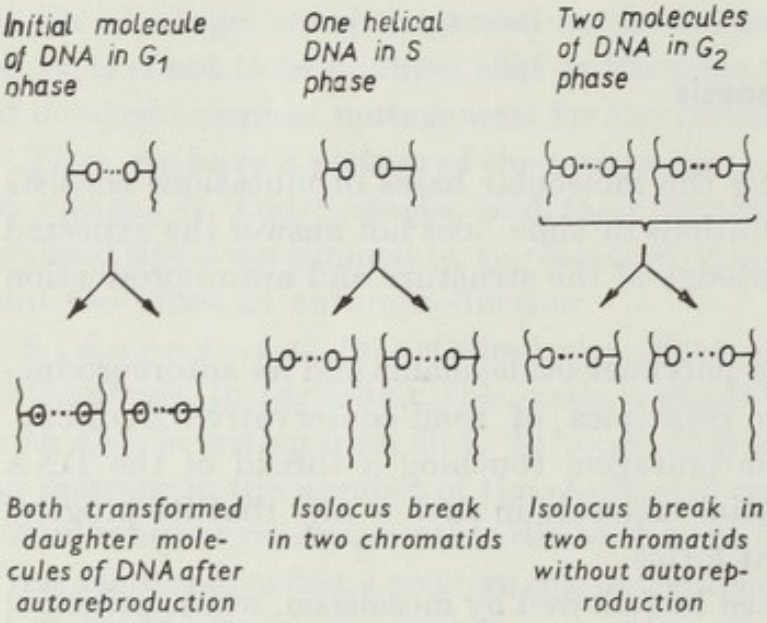

Fig. 2.

The supposition is advanced that the occurrence of non-mosaic pure mutant clones from one initial changed DNA molecule may be also caused by the fact that in one of the complementary threads arises a lethal change.

The mechanism of the occurrence of gene mutations and chromosome rearrangements differs in many ways, nevertheless, a number of primary mechanisms, especially at the stage of potential changes, may be similar.

In the light of the occurrence of whole gene mutations and changes in both chains of the DNA molecule, special interest acquires the category of chromatid changes in the form of different rearrangements, occurring as the results of isolocal breaks. Fig. 2 illustrates the community in the mechanisms of occurrence: whole gene mutations when the changes concern both bases in a nucleotide pair; isolocal breaks at the S stage, when the DNA molecules or their parts segregate into monothread structures; isolocal breaks in two ready chromatids at the G_2 stage. Thus, we see that even at a certain distance the isoloci from different threads are capable of reacting identically to the mutagen action both at the S and G_2 stages. According to the data of Dubinin and Dubinina (35) among the chromatid changes, arising during the irradiation of human cells in tissue cultures, the principal part is played by isolocal breaks. The same takes place during chemical and natural mutagenesis in the cells of plants and animals (13). In the isolocal exchanges we have one of the principal mechanisms of the structural variability of the chromosomes.

Just now we cannot explain the phenomena described on the basis of the known molecular mechanisms of mutations. Under these conditions it is

possible to admit and formulate a general idea concerning the existence of a resonant mutagenesis, i.e. an identical answer of the isoloci to the mutagenic action. In this reaction the degree of the vicinity of the isoloci is apparently of great importance, since it is known that in the nucleus alleles situated far away from each other do not show any resonant mutability.

During resonant mutagenesis, for so far unknown reasons, two components of the initial genetic structure change, there occur either "whole" mutations or isolocal chromatid rearrangements. This mutation type is first of all inherent to ionizing radiations. In the case when under the action of the mutagen one thread changes in the DNA molecule, there occurs a picture of prolonged mutagenesis. The terms "resonant" and "prolonged" mutagenesis offered by us, are assigned to reflect the new sides in the mutation phenomenon. The reexists the term "delayed" mutagenesis. We use this term form describing the delayed occurrence of mutations within the limits of one mitosis only after mutagen treatment (delayed effect). All the other categories of "late" mutations we interpret as "prolonged" mutagenesis. According to our modern concepts (42), depending on the character and processes of the errors, during autoreproduction a mutation may arise during the first, second and subsequent replications of the DNA molecule. Such a type of mosaic occurrence of mutations is inherent to chemical mutagenesis. Nevertheless, also here in some cases resonant mutagenesis takes place, while in other cases the delayed occurrence of mutations lasts for a long time. For instance, in *Drosophila* in some cases mosaicism becomes manifest in the second generation after mutagen treatment, i.e. after 30 cellular generations, including two fertilizations.

Formally the point of view is perhaps not excluded that prolonged mutagenesis is caused by the preservation of the mutagen introduced into the initial cell or by its active products. Certainly, in such cases as with *Drosophila* the probability of such an explanation cannot practically exist.

Green and Krieg (43) have completely excluded this possibility in their experiments on phages. They showed that after the treatment of extracellular phages with ethylmetansulphonate mutations occur after the first, second, third and subsequent replications of the phage. The introduction into the cell of particles treated and non-treated with a mutagen showed that only in the first category of particles occur the phenomena of prolonged mutagenesis.

Thus, prolonged mutagenesis is connected with potential changes which become manifest after a number of cellular generations. It is evident that during all this time till the transition stage into a true mutation, the potential change, primarily arisen perhaps only in one thread of DNA, is transferred throughout the cell generations, retaining its own peculiar properties, characterizing its pre-mutational condition.

However, being transferred throughout the cell generations under the aspect

of potential changes, these changes finish by being transformed into true ones by means of resonant mutagenesis. This follows clearly on the basis of the fact that the isolocal breaks are caused by potential changes. In this case, although the DNA molecule bears both threads with equal potential changes, their simultaneous break during the occurrence of two chromatids requires the action of the same principles of resonant mutability.

Among a number of questions connected with the problem of prolonged mutagenesis stands primarily the following one — what are the factors which determine the transition of the potential changes into true mutations?

On the chain process during mutagenesis

Buiatti and Ronchi (44) have written about prolonged mutagenesis in the root tips of *Vicia faba*. Under the conditions of a C-mitosis new chromatid rearrangements arise in the tetraploid cells of the second cell

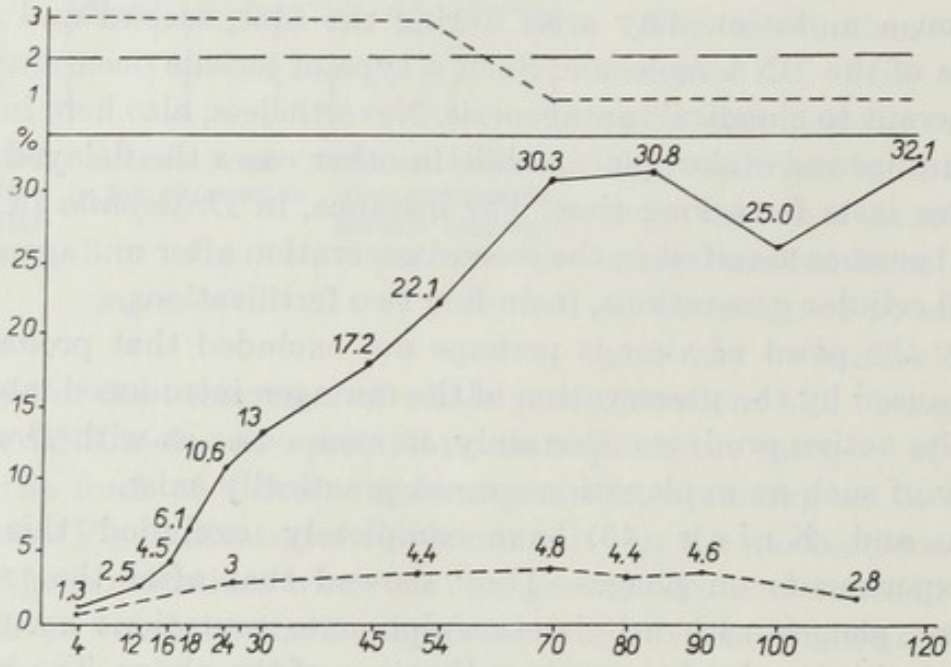

Fig. 3.

generation with about the same frequency per genome as in the diploid ones treated with triethylenimine.

Dubinin and Saprykina (45) described the process of delayed mutagenesis of human cells in tissue cultures under the effect of thiotephine. Being an alkylyzing factor, thiotephine did not affect the chromosomes at the G_2 stage, causing only chromatid rearrangements, and as a whole, within the limits of the first cellular cycle it acted according to the principles of delayed mutagenesis. The mutation process did not finish in the first generation.

Chromatid mutations occurred in a number of following, minimum in two, three generations. Noteworthy was the picture of prolonged mutagenesis. The number of mutations in the second and possibly in the third generations augmented markedly, subsequently it began diminishing. The increase of the number of mutations after the first and second DNA replications in principle coincides with the data of Demerec (46), Demerec and Cahn (47) concerning delayed mutagenesis in *Escherichia coli*. Thus, we have a picture

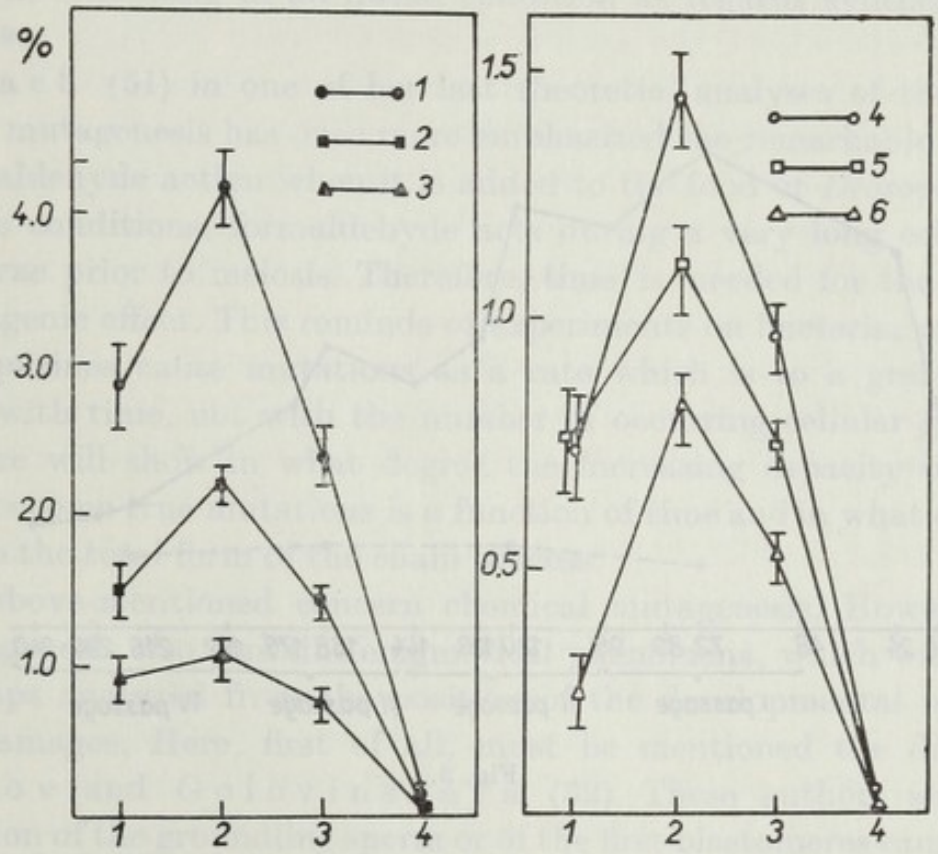

Fig. 4.

coinciding with the requirements of the chain process. First, during two—three generations the frequency of occurrence of true mutations was above a unit, if a unit means the amount of mutations in the first generation ($K > I$). Subsequently the amount of mutations diminishes if a unit reflects the maximum amount of mutations ($K < I$).

Thus, the potential chromosome changes transmitted in a number of cell generations in the case described in the long run undergo processes of lawful development. During a certain period of time the probability of the transition into true mutations augments and subsequently grown the probability of a reparation into initial structures. All this made it possible to formulate the conception concerning a chain process in mutagenesis, without endowing it yet with any definite physical and chemical contents.

Shevchenko *et al.* (48) investigated the mutation frequency in the monocellular alga *(Chlorella vulgaris)* throughout three cellular divisions after treatment of the spores with ethyleneimine. Analysing the size of sectors in the mosaic colonies they showed that mutations arise instantly when the treatment occurs according to the type of resonant mutagenesis, whereas in the second, third and subsequent generations occur prolonged mutations. Fig. 4. shows that there exist characteristic kinetics of mutation frequency for generations, their number increases in the second generation and falls in the third one.

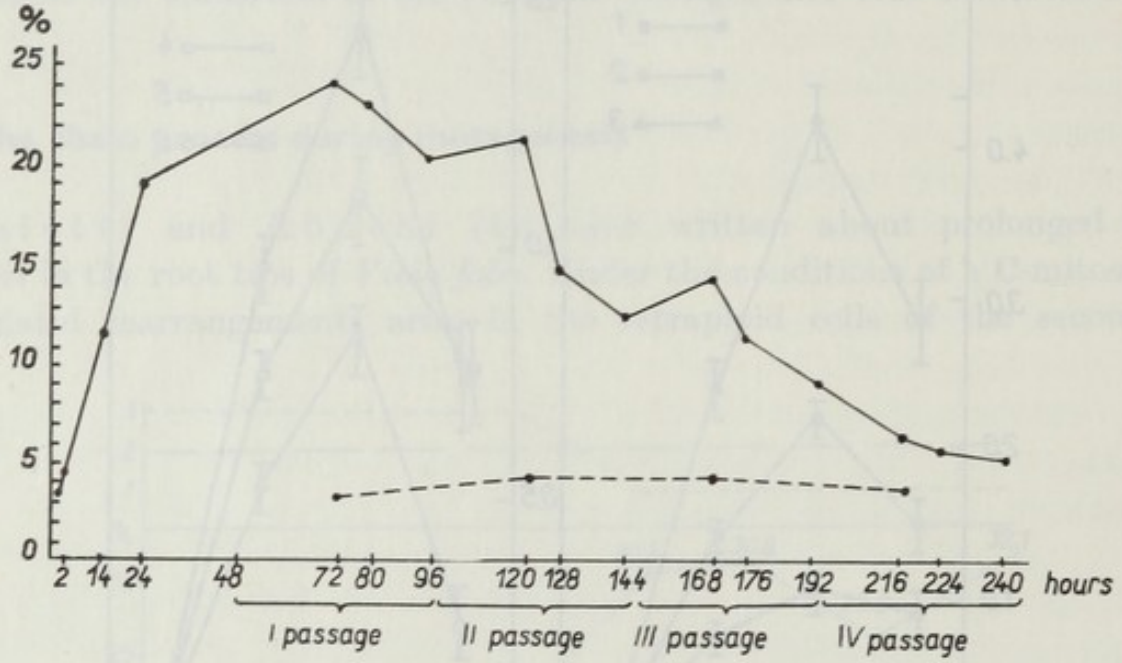

Fig. 5.

Akifiev *et al.* (49, 50) studied the action of the alkylating factor — dipine of the L-cells of mice. An afteraction was found after one treatment with dipine throughout four subsequent passages including from 8 to 12 generations. Fig. 5 shows that in this case also data were found which answer the conditions of chain mutagenesis.

At first it may seem that the data of Buiatti and Ronchi (44) on the comparative equality of the number of gene mutations per genome in diploid and tetraploid cells of the root tips of *Vicia faba* contradict the principles of the course followed by the chain process. Similar data was obtained by Sidorov et al. (37) in their work on the action of ethyleneimine on the root tips of *Crepis capillaris*. However, the comparison of the mutation frequencies in diploid and tetraploid cells is made simultaneously after mutagen treatment. Thus, the chain processes are at the same development level in the diploid and tetraploid chromosomes. A complete picture of the chain process may be obtained only if we, for instance, investigate the diploids at most various moments.

The fact that the amount of mutations per genome changes with time parallelly in the cells 2n, 4n and 8n, being comparatively equal per genome, shows that the chain reaction in the development of the potential changes does not depend on the processes of autoreproduction. The quantity of mutation changes depending on the period of time after mutagen treatment does not depend on the fact whether the chromosome, bearing the potential changes, undergoes one or two replications, whether the chromosome has not undergone reduplication, remaining in an initial condition as regards synthesis of DNA and proteins.

Auerbach (51) in one of her last theoretic analyses of the problems of chemical mutagenesis has once more emphasized the remarkable peculiarity of the formaldehyde action when it is added to the food of *Drosophila* larvae. Under these conditions, formaldehyde acts during a very long cellular stage in male larvae prior to meiosis. Therefore, time is needed for the realization of the mutagenic effect. This reminds of experiments on bacteria, when coffein and other purines cause mutations as a rate which is to a great degree in proportion with time, not with the number of occurring cellular generations.

The future will show in what degree the increasing capacity of potential changes to become true mutations is a function of time and in what degree it is subjected to the total form of the chain process.

All the above-mentioned concern chemical mutagenesis. However, radiational mutagenesis also contains enigmatical phenomena, which will also have to be perhaps analyzed from the position of the developmental processes of potential damages. Here, first of all, must be mentioned the discovery of Romashov and Golovinskaya (52). These authors showed that the irradiation of the groundling sperm or of the first blastomeres causes a mutation process in the embryo as far as the cells of larvae.

On directed mutations

The aim of genetics and one of the greatest problems of the modern natural sciences consists in the elaboration of methods for the production of definite directed mutations. The solution of this problem will entirely change all the facts influencing life by man.

Facts indicate that this problem can be solved. These facts emphasize the principle that the quality of the mutations depends on the quality of the mutagen. This is proved by the facts of the specificity of mutagen action and by the presence of a specific genic control over the mutation process. A specificity occurs during different mutation frequencies of various genes during the natural mutation process and during changes of these correlations upon the action of different mutagens (genic specificity). The same takes place

within complex genes. The study of mutability in the rII region of phage T_4 showed that natural mutation processes have "hot points", i.e. gene regions, illustrating a high mutability. The distribution of hot points on the gene map changes with the application of different mutagens (intragenic specificity). Thus, under the action of X-rays on *Vicia faba*, whose nuclei have six chromosome pairs, the ratio of breaks in one large and five small pairs amounts to 5 : 2. Under the action of iprit this ratio is 50 : 2. Noteworthy is the regional specificity during the occurrence of lethal mutations in *Drosophila* X-chromosomes under the action of formaldehyde. In this case in separate chromosome regions slowly develops a mutation process, possibly on behalf of the regionally grouped potential damages (53).

Gene control has been found both for chromosome rearrangements and also for gene mutations. M c C l i n t o c k (54) found that in maize the chromosome region containing the DS gene (Dissociator) frequently undergoes breaks if the gene Ac (Activator) is at the same time present in the nucleus. If the Ds is transferred into another chromosome region, the latter acquires the capacity for breaks. R h o a d e s (55) found that the allel Dt causes a high mutability of the allel a_1, thus leading to mosaicism at a distance and on maize grain.

This specific picture of gene control emphasizes the presence of directed mutagenesis in natural mutability. It is most important to discover the foundation of the action of such regulators of specific mutability. We are faced with great problems connected with the analysis of all the stages of the mutation process. It is necessary to study the distribution of mutagens in the cell and the character of intracellular derivatives from initial mutagens; the character of mutagen reactions attaining the chromosomes and their proteins; the nature of primary mutations occuring under the effect of changes in DNA; the transformation processes in true mutations under the conditions of a undelayed (resonant) and delayed mutagenesis.

Of paramount importance in the problem of directed mutagenesis is the elaboration of methods for obtaining definite chemical reorganizations of the code groups of nucleic acid. The first examples pertain to the action of nitrous acid, hydroxylamine and other mutagens for DNA phages and viruses (42). In these cases we have to deal with a direct, definite reaction between genetic material and chemical mutagens. This reaction clearly shows the dependence existing between genetic changes and the mutagen quality. For the elaboration of these problems of the greatest importance is the analysis of the phenomena of transformation, transduction and the study of episome heredity.

However, we have to bear invariably in mind that the molecular level is only part of the complex biological organization of heredity. Moreover, the biological organization of heredity will stimulate the progress in the solution of the problem of directed mutations. Of main interest here is the fact that genes

are physico-chemical systems having at the same time a biological organization. If this were not so, in view of the non-specificity of the nitrous bases causing the coding of genetic information we should be helpless in specifically directing the mutation process.

Thus, in the mutation problem towers the gene problem, its biological organization, its chemistry and physics, which are the foundation of unendless quantitative and qualitative reorganizations. In this aspect, central position is occupied by the modern doctrine concerning the fine structure of the gene. The divisibility of the gene, the construction of the gene map on the basis of its separate parts, were stated by Dubinin in the years 1929—1933, when he constructed the Theory of Centres of the gene in *Drosophila* experiments. At present, after the works by Benzer (56, 57) on phage T_4, the works of Demerec on bacteria (58, 59) and others, we have a picture of the molecular structure of the gene.

The elaboration of the gene problem and of the new methods of directing heredity, although they constitute the centre of the modern theory of genetics, play also an economic part. They lie at the foundation of using radiation and chemical mutagenesis in plant breeding experimental polyploidy, heterosis a.o., they enter the economics of plant and animal breeding. In the history of sciences there were scientists who unusually felt and understood every novelty and created a unity of science, life and economics for their country. In the USSR, in the domain of biology Vavilov N. I. was such a scientist — he was a grand plant breeder and geneticist. Our new stage of life requires the elaboration of gigantic problems of new genetics, at the same time making attempts for uniting genetics, plant, animal breeding and medicine, for longevity, health, for the prosperity of mankind, for youth, for the perfection of man.

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Discussion Contributions

The Importance of the Mendelian Methodology for the Solution of a Phaenogenetical Problem in *Drosophila*

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Phaenogenetical studies of a 3. chromosomal mutant "bordo-sterile" were published in 1948 (G. Fábián) Tihany—Zürich: Phänogenetische Untersuchungen an einer Sterilitätsmutante "bordo-steril" von *Drosophila melanogaster*. Arch. Julius Klaus Stiftung Bd. XXIII. 1948 Hft. 3/4 p. 512—517.

The gene caused a very complex mosaic pleitropism. Among the different patterns the most interesting ones were the injuries in the ovaries. Many attempts at finding the primary effect by the transplantation of imaginal buds proved only the strict and uncontrollable destructive influence of the bordo-sterile gene in the homozygote condition.

The following second part of the investigation has not been published so far.

The accomplished histological slides showed that not only the great eosinophil granules in the sterile ovaries but the alloplasmatic eye-pigments were much more coarse-grained than in the normal.

The bos-gene in free recombination with cinnabar, vermilion, apricot gave a quite different effect. The dense red eye pigment became lighter — and at the same time — the double recessives laid normal eggs. Wild +/+ : 82·7% normal (0·48—0·5 mm long) eggs, bos/bos wa/wa 70·4% normal sized eggs, bos/bos v/v 66·3%, bos/bos cn/cn 62·1%, bos/bos homozygote female only 28·7%. The development was sometimes going to the first instar larvae in the "healed" eggs.

Thus, we can conclude that the mosaic pleiotropism should have a common root, the injuries of the colloid system in the mutant cytoplasm during the synthesis of the alloplasmatic granules (pigment or yolk).

The Mendelian methodology — from the first step (localization of the gene) to the last (the use of recombination with mutual gene-effect) was the leading base line to understand this complicated heritable pattern.

Session III

MODERN DEVELOPMENT OF GENETICS

CHAIRMAN: F. JACOB
VICE-CHAIRMAN: B. L. ASTAUROV

Analysis of Genetic Loci

HERMAN W. LEWIS

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We pay homage to M e n d e l today aware that the best method we have for analysis of genetic material even now, despite the impressive advances and refinements in genetic and chemical studies in recent years, is the resolving power of recombination, a method derived directly from the inheritance test developed by M e n d e l . This realization impresses us anew with the great intellectual contributions of the founders of genetics as an exact experimental science and also with the marvelous properties of living systems, namely, unity superimposed on diversity and simplicity superimposed on complexity.

Let us begin by defining the limits of this presentation. The title is: "Analysis of Genetic Loci".What kind of genetic loci and what kind of analysis can be discussed? Genetic loci can be analyzed genetically, cytologically, and chemically, but this presentation will be limited to a consideration of genetic analysis which deals with information obtained by recombination analysis. In modern genetics the resolving power of recombination analysis has been increased greatly by the use of microorganisms to facilitate handling very large population and by the use of special selective techniques. Even in higher organisms it is possible to analyze so-called complex loci by means of genetic tests. Cytological analysis of genetic loci could encompass such studies as those of B e e r m a n n (2) on the puffing phenomena in single bands of the dipteran salivary gland chromosomes and the precise determination of cytological boundaries of members of pseudoallelic series, as illustrated by J u d d ' s analysis of members of the white-eye series in *Drosophila* (19). Chemical analysis could include discussion of recent studies of nucleic acids relevant to the presence of subunits and "linkers" in the DNA molecule. It could also include discussion of the isolation of specific RNA messages and hybridization tests of the complementarity of DNA and RNA (29); deduction about the nucleotide sequence in a fine-structure genetic map inferred from knowledge of the genetic code and the sequence of amino acids in a protein specified by that region of the map (33); and most directly, determination of the complimentary bases to an RNA molecule fully sequenced (16).

"Genetic loci" in the context of modern developments of genetics is also subject to a broad range of interpretation. This term could apply to chromo-

somal loci or extra-nuclear loci. The present discussion will be restricted to chromosomal genetic units, but we must note in passing that the existence of genetic loci outside the nucleus is very probable as shown by the demonstration of DNA in mitochondria and plastids (10). The classical view of the gene as an indivisible elementary biological unit occupying a definite position (locus) in a chromosome was acceptable until the 1950's, because crossing-over had been observed only between genes, not within them. Then, in *Drosophila* (11, 21) and later in *Neurospora* (6), it became apparent that intragenic crossing-over does occur. The analysis of the rII region of the genome of bacteriophage T_2 (3), the major contribution to our present ideas about genetic elements, clearly and emphatically established the experimental feasibility and the operational importance of considering separately the genetic unit of mutation, the genetic unit of recombination, and the genetic unit of function.

B e n z e r ' s high resolution experimental methods dissected the genetic material into indivisible genetic lengths, the units of mutation (4). He called these sites mutons, and they are believed to be the individual nucleotides. Using complementation tests of genetic defects of molecular-level dimensions, these sites were ordered in a linear array, and recombination tests were used to measure the genetic map distance between sites, just as is done in mapping larger segments of the chromosome. The smallest distance which is interchangeable by recombination is called a recon. Using E . B . L e w i s ' (21) modification of the genetic complementation test known as the cis-trans test, B e n z e r determined the genetic unit of function and named it the cistron. The details and rationale of this methodology will be discussed below. Suffice it to say here that a genetic test, rather than physiological or chemical tests, is the criterion for determining the functional genetic unit in a cis-trans test. The expression "one gene: one enzyme" has been replaced with "one cistron: one polypeptide," because (a) the cistron is the genetic unit of function by virtue of the fact that it is the smallest region of the genome that carries information for a single cellular characteristic, and (b) this information specifies a sequence of amino acids. Even with this new precision, however, our notions about the basic genetic unit of function are equivocal because there are several levels of function that can be considered. Since the tertiary structure of proteins depends in great measure upon primary structure, for some purposes the significant functional genetic element is that unit of DNA which specifies a critical amino acid, namely nucleotide triplets or the codon. Among the enzymes geneticists have been primarily concerned with, namely intracellular enzymes involved in biosynthesis, few if any are monomers. In most of these cases a polypeptide chian is not an active enzyme but merely a subunit of such, and accordingly, for some purposes the significant functional genetic unit may be some multiple of a cistron. The operon, a concept devised

to expalin phenomena uncovered in analysis of genetic loci in bacteria, represents an even higher level of genetic function (17). In this case the cistrons including those concerned with control of as well as structural aspects of the synthesis of an assembly of enzymes leading to a single cellular level end-effect, act as a unit as indicated among other criteria by the fact that they are transcribed by a single polycistronic RNA "message". To summarize, in terms of significant biological properties the term "genetic loci" in the title of this paper may be interpreted as a region of the genome influencing a discrete genetic system which is divisible into a range of overlapping subunits varying in size and functional complexity form the muton to the operon.

As already indicated, in modern studies operational genetic tests are the same as in classical studies; only the magnitude of the distances resolved is different. The point mutation of the chromosome has its analogue in base substitutions at single sites, and as in classical cytogenetics, so too at the molecular level, genetic tests have detected deletions, additions, and inverted sequences in small regions of the genetic material. The geometric relation between these modifications from an arbitrarily selected standard is deduced from the frequency with which these changes are detected following appropriate genetic tests.

The classical test for detecting if two mutations that affect the same phenotype also occupy the same position in the genome is to put them into the same cell of heterozygotes, heterocaryons or heterogenotes and observe the resulting phenotype. If the phenotype is mutant, it is assumed the two mutations affect the same cellular process and presumably occupy the same locus, i.e. they are allelic. If the phenotype is not mutant, that is the two mutations are complementary, the classical interpretation assumes they affect different cellular processes, must occupy different loci, and that the wild type allele of each in the heterozygous state must determine the phenotype.

Since the early 1950's many exceptions have been found to the rule that alleles do not complement. The investigations that have contributed most to our understanding of genetic loci include the analysis of the lozenge, white, bithorax, and rosy alleles in *Drosophila*, those genetic regions concerned with the biosynthesis of tryptophan, histidine and adenine in *Neurospora* and the lactose, histidine and arbinose operons in bacteria (17, 1, 20). To avoid overlap with other papers in this symposium, this presentation will draw examples only from analyses in *Drosophila*.

Pseudoalleles in *Drosophila*

Except for the recent analysis of the rosy locus, increased resolving power of recombinational analysis was limited in *Drosophila* because of at least two factors: (1) it depended on increased labor, i.e., examination of more flies

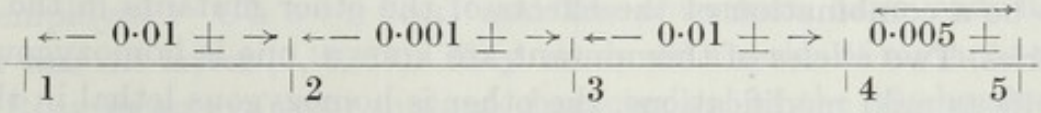
rather than on special screening schemes to detect rare genetic events and (2) the properties of the loci analyzed are observed in the phenotype and are an end result of developmental processes. In microorganisms, properties of loci analyzed can be related to specific alterations at the biochemical level and are closely related to the alteration of the controlling genetic material. In spite of these limitations, recombination was demonstrated in *Drosophila* within the classical gene, and this led to the concept of pseudoalleles. Two independent closely-linked, functionally related recessive mutants are pseudoallelic if: (1) when brought together in a single cell they produce a mutant phenotype (2) they can be separated by s single crossing-over resulting in one homologue carrying both mutants and the other carrying neither and (3) when the mutants are in a coupledor cis relation the wild type phenotype is manifested, and when they are in a repulsion or trans relationship to each other the mutant phenotype is expressed. Although conceptually the tests for intralocus and interlocus complementation are the same, operationally the fomer is much more exacting and demanding. To satisfy the required criteria, it is necessary to rule out the occurrence of reverse mutation, the interaction of a suppressor gene somewhere else in the genome and double crossing-over by the recovery of reciprocal recombination products using closely linked outside markers.

Analysis of Lozenge Locus

The first pseudoallelic series to be studied extensively was lozenge eye mutants in *Drosophila melanogaster* by Green & Green (11, 12). Eighteen lozenge mutants of independent spontaneous and X-ray induced origin were found to be separable by recombination analysis into three distinct loci. The spontaneous and induced mutants are distributed in each subunit. The length of the pseudoallelic series is 0·14 map units and going from left to right, the first and second subunits are separated by 0·083 map units, and the second and third are 0·051 map units apart. These 18 mutants are also separable phenotypically into three classes by pleiotropic effects, but these do not coincide with the spatially separated subunits. Lozenge has been localized in the salivary gland chromosomes to a region which is difficult to examine, and the exact number of bands included in this region has not been determined. More recently a new lozenge mutant of spontaneous origin has been discovered which represents a fourth recombinational subunit located between the first and second region of the lozenge locus. Its phenotypic interaction is interesting in that it is complementary to proximal pseudoalleles but non-complementary with more distal mutants in the lozenge series (14).

Analysis of White Eye Locus

In an attempt to map a locus more exhaustively in *Drosophila* for comparison with genetic fine structure analysis of microbial loci, Green chose to analyze the white eye locus (13). White was the first mutation studied in *Drosophila*, and analysis of its inheritance by Morgan in 1910 launched the field of *Drosophila* genetics. This locus was also the first multiple allelic series found in *Drosophila*; so perhaps it was Green's sense of history, as well as the fact that recombination between mutants at this locus had been previously reported (22, 26), that led to this choice. His analysis included 36 white mutants of spontaneous, X-ray and chemically-induced origin. In addition to testing the spatial distinctness of these mutants by recombination tests, he also attempted to refine the detection of other distinctive subunits or classes using six functional criteria. Specifically, he tested these mutants with respect to their compensating ability in dosage tests, their phenotypic interaction with a suppressor of apricot-eye, their interaction with an enhancer of the eosing eye color mutant, their interaction with ruby and garnet mutants (non-allelic eye color mutants which are known to interact with some white mutants), and lastly their ability to act as a suppressor of zeste. Although the functional criteria were only useful in distinguishing the left and right halves of the white locus, the recombinational analysis in this study and the work of others have revealed to date five separable subunits of the white locus measuring 0·026 map units.

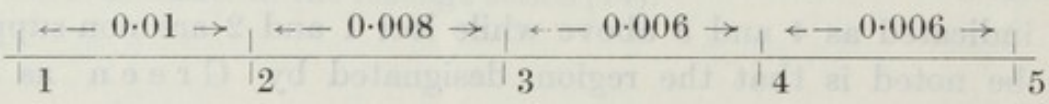


In a subsequent cytogenetic analysis of zeste located about 0·5 units to the left of white on the genetic map, Green found that there is a high degree of homology between the two loci as measured by pairing or synaptic behavior. Further he demonstrated through study of single band deficiencies in the salivary gland chromosomes that manifestation of the zeste phenotype depends upon band 3c1, a band that is considered part of the white region. From these facts and the previously noted phenotypic interdependence of zeste and certain white alleles, Green concluded that zeste and white are components of a single functional locus (15). This locus has a length of approximately 0·6 units on the genetic map and extends from region 3A3 to 3C3 inclusive of the salivary gland chromosome, an area including about 15 bands. The mechanism explaining the behavior of this locus as a functional unit will be expecially interesting. The white mutants that act as a dominant suppressor of zeste are the loci indicated as 4 and 5 above while loci 1 and 2 are non-suppressors. Also to be noted is that the region designated by Green as a single

functional unit includes a locus with an eye color effect known as an enhancer of bithorax whose relationship with the zeste and white will have to be explained.

Analysis of Bithorax Locus

The bithorax pseudoallelic series in *Drosophila* carries information which is manifested in more complex phenotype that has phylogenetic importance. This series analyzed by E. B. Lewis may therefore provide a basis for new approaches to analysis of problems in ontogeny and phylogeny (23). The series are composed of five subunits each of which is separable by recombination and the mutants of each are distinguishable phenotypically. The entire series occupies 0·03 units of the genetic map. Starting at the left of the series, the first mutant (bithorax) is recessive, and its effect is to transform the structures of the anterior metathorax into structures of the anterior mesothorax. That is, the anterior portion of the haltere is transformed into a structure that resembles the anterior portion of wing. The degree of transformation depends on which allele of this mutation is present. Four are presently known. The second subunit (contrabithorax) is expressed as a dominat, and its effect is to modify the posterior mesothorax to resemble the posterior metathorax. The third subunit (Ultrabithorax) also is dominantly expressed, and its effect seems to be a combination of the effects of the other mutants in the pseudoallelic series. Two alleles of this mutant are known: one is homozygous viable and manifests mild modifications, the other is homozygous lethal in the adult stage and results in extreme modifications. Mutants of the fourth sub-unit (bithoraxoid) are expressed as recessives and are associated with two functions: (1) conversion of the structures of the posterior metathorax into structures resembling the posterior mesothorax, and (2) conversion of the first abdominal segment into a thoracic segment. Three alleles of this mutation are known and each expresses the second type of conversion in constant and symmetrical, though different degrees. From the most extreme expression, it can be concluded the anterior portion of the first abdominal segment is metathoracic-like, while the posterior portion is mesothoracic-like. The last subunit of the series (postbithorax) is expressed as a recessive, and its effect is to transform the posterior metathorax into a posterior mesothorax; that is, a halter is transformed in the posterior portion of a wing. The genetic distances between these subunits is shown below:



By combining mutants of group 1 and 5 a fly with two pairs of wings can be produced.

Many mutants of this pseudoallelic series show marked cis-trans effects, and in some cases, these effects are greatly intensified by the introduction of heterozygous chromosome rearrangements of the cis and trans types. This intensification, a type of position effect unique to this series, is called "the transvection effect". The interpretation of the functional analysis of this pseudoallelic series assumes that each class of the pseudoallelic series has a unique but related function and that the functioning of all of them is closely coordinated. Based on the occurrence of the different types of position effect observed; namely, changes resulting from physical separation of some members of the series from others by chromosomal rearrangement as well as the cis--trans and transvection phenomena, Lewis has suggested a model of interchromosomal diffusion of the products of the different subgroups of the series from one homologue to the other.

Rosy Analysis

Until recently, all attempts to demonstrate an array of fine-structure subunits in *Drosophila* loci, comparable to those demonstrated in the genome of bacteria and viruses, failed. Was this due to an intrinsic difference in the organization of the functional genetic units or to differences in resolving power of the genetic tests employed? Chovnick and his coworkers have shown that the answer was the latter (7, 8, 27). They analyzed a series of mutants at the rosy locus. Rosy in an eye color mutant characterized at the biochemical level by the absence of the enzyme xanthine dehydrogenase, and this locus is not considered a pseudoallelic array. A key feature of this analysis is that it uses a genetic test that selectively screens a very large population of zygotes for very rare recombinational events. Using a series of recessive lethals near the rosy locus as selective factors and closely linked recessive markers, any pair of rosy mutants can be tested in crosses in which all non-crossovers within this region die, about 95% of all zygotes. When the recombinants survive as a result of crossing over within the rosy locus, the recombination units can be ordered by the results of two series of crosses which comprise the test. The linkage relations of the selective and non-selective genetic markers to rosy are shown below:

$$\underset{l_1}{|} \leftarrow 3{\cdot}1 \rightarrow \underset{l_2}{|} \leftarrow 2{\cdot}5 \rightarrow \underset{m_1}{|} \leftarrow 2{\cdot}0 \underset{m_2}{|} \leftarrow 0{\cdot}4 \rightarrow \underset{ry}{|} \leftarrow 0{\cdot}1 \rightarrow \underset{m_3}{|} \leftarrow 5{\cdot}7 \rightarrow \underset{l_3}{|} \leftarrow 0{\cdot}4 \rightarrow \underset{l_4}{|}$$

The two series of crosses in the selective system is illustrated below with an example of ry^x located to the left of ry^y.

$$\frac{l_1\ l_2\ ry^x\ +\ +\ +}{+\ +\ +\ ry^x\ l_3\ l_4}\ ♀A \qquad \frac{l_1\ l_2\ +\ ry^y\ +\ +}{+\ +\ ry^x\ +\ l_3\ l_4}\ ♀B$$

$$\times \quad \frac{l_1 + ry\ \ l_3 +}{+\ l_2\ ry + l_4} \qquad + + + + + +$$

$$\nearrow \quad ♂ \text{ surviving offspring}$$

$$\searrow \quad + ry^x\ ry^y\ +\ +$$

If ry^y were to the left of ry^x the reciprocal result would be expected, i.e., the double mutant would be produced in the cross using female A and the wild type would result from the cross using female B.

Fifteen rosy mutants have been analyzed to date and have been separated into at least six distinct recombinational units. On the basis of the mutants analyzed thus far, the genetic length of the rosy locus is 0·008 map units long. One of the mutants has been shown to involve an intragenic rearrangement. The smallest distance resolved is $2{\cdot}6 \times 10^{-4}$ map units and using R u d k i n ' s maximum estimate of the amount of DNA/map unit this distance is approximately 40 nucleotides in length. It is estimated that 10^7 failures of recombination are needed to permit the conclusion that two mutants have been tested in populations greater than 10^6. To determine the structural and functional limits of the rosy region, C h o v n i c k and his colleagues analyzed 73 mutants associated with chromosomal changes involving the rosy locus as indicated by their eye color phenotype and 24 non-rosy visible or lethal mutants associated with chromosome changes near this locus. This study permits the generalizations that there is only one genetic functional unit concerned with xanthine dehydrogenase activity in this region and that adjacent genetic units are functionally and spatially distinct from the rosy region.

Discussion and Conclussions

In an effort to examine what we can learn from analysis of genetic loci in *Drosophila*, an obvious question arises: did pseudoalleles originate as tandem duplications by unequal crossing-over ? If this is so, are members of the series adjacent units with identical structure and function except for the relatively slight modifications incorporated during evolution by which we recognize them as different ? Or do members of the series have different functions, each dependent in time or space upon the products controlled by other members of the series resulting in a sequential series of reactions leading to the phenotype ? Or are both views correct and to pseudoalleles represent varying intermediate stages in the evolution of genetic organization from small single units carrying the information for a single polypeptide chain to large multifunctional units as the operon ? If pseudoalleles are small duplicated regions on the chromosome, we may observe a higher incidence of asymmetrical pairing and unequal crossing-over in these regions. While data on this point are not extensive

enough to permit generalizations, the analysis of exceptional offspring resulting from crossing-over within the white locus supports this suggestion (18, 19). Among other things it has been shown that recombination within the white locus is greatly increased in duplication/normal heterozygotes.

It is apparent from the studies described in this paper, that the biologically meaningful genetic units are not a single type of unit but a spectrum of units varying in size and functional complexity. The term "gene", created to denote an abstraction, is not useful in describing these units as known today. Assuming the factors affecting recombination are the same throughout the genome, the small sample of loci analyzed in *Drosophila* to date shows a range of sizes from 0·008 to 0·140 cross-over units, a 17·5-fold difference; and the size of the entire rosy locus is in the same order of magnitude as the smallest sub-unit resolved at other loci. In terms of functional complexity conclusions must be qualified because they are not based on biochemical data or information about the synthesis of specific proteins. Nevertheless, it is reasonable to assume that the entire rosy locus carries information specifying only a single polypeptide chain which is part of the active xanthine dehydrogenase molecule and that each member of the bithorax pseudoallelic array specified a different polypeptide chain, each of which is sequentially dependent upon the others in time or space. With respect to the white-eye pseudoallelic array it is reasonable to assume that each member of the series carries the information specifying a polypeptide chain, but it is as reasonable to assume that they are duplicates of each other as it is to assume they are sequentially interdependent. The question has often been posed as to whether or not the basic genetic units are organized in higher organism as they are in microbial systems. The answer is probably yes, but they are organized in varying units of complexity at each level. There is no intrinsic reason for assuming that all elementary units of heredity must be uniform. Since genetic elements undergo evolution as do all other biological systems, it is reasonable to expect genetic systems in various stages of evolution in all phylogenetic levels. Comparison of the organization of the genetic units controlling tryptophan synthesis in *Escherichia coli* and *Neurospora crassa* or histidine synthesis in *Neurospora* and *Salmonella* bear importantly on this point (5,25). In the case of tryptophan synthesis comparative genetic and biochemical studies have led to the suggestion that during evolution two enzymes with independent activities combine of form an enzyme complex.

A related observation concerns the high degree of variability that probably exists within gene loci at the molecular level. The analogous phenomena that occur at the cytological and molecular levels, calls attention to the fact that in addition to base changes, alteration of the informational units most likely result from duplications, deficiencies, rearrangements and recombination. All of these have been suggested in analysis of the exceptional offspring of the *Drosophila* studies described. It is interesting to note that it was not very long

ago that a major question in genetics was whether or not point mutations are really losses or rearrangements at submicroscopic levels (30). Clues of a high degree of variability of genetic loci are detected in the fact that even within the spatially distinct regions of the chromosome occupied by members of pseudoallelic series, groups of alleles are known which in a number of instances are phenotypically distinguishable. Actually, clues regarding the variability of genetic loci were provided a number of years ago by Stern in his isoallele concept (31). Isoalleles are wild-type alleles which cannot be distinguished phenotypically, but which are recognized as different by more sensitive detection methods. How common are isoalleles? Perhaps current studies on protein polymorphism in Drosophila will provide an answer. Lewontin and Hubby have designed population genetics experiments bearing on this question and to date have found, using electrophoretic methods, that approximately 33% of the proteins tested are maintained in populations polymorphically (24).

In concluding I would like to speculate about the type of studies that will be carried out in the future in the analysis of genetic loci. The major advances will undoubtedly come from studies focussed at the molecular level. One approach that will be useful will be inferences and deductions from structural studies of proteins. It is possible that such studies will generate a new cycle of understanding of biochemistry which in turn will lead to a new level of understanding of genetic functions. Sequential reactions, tightly linked genetically and biochemically, may be more common that we presently suspect. The biosynthetic reactions and enzyme systems that have been studied to date probably represent a small fraction of those which exist and our understanding of these is far from complete. Undoubtedly cases will be uncovered in which enzymatic function, which we presently regard as due to a single activity, will be separated into two or more component activites. Just as biochemical genetics with *Neurospora* stimulated a surge of knowledge in intermediary metabolism, so may finer resolution genetic studies lead to finer biochemical processes, or vice versa.

Until recently, all studies of genetic loci essentially defined genetic function in terms of information specifying polypeptide chains, but genetic loci do not have to be restricted to this function. In some cases the RNA transcribed from a specific region of the genome may be regarded as the specified end-product and not an intermediate messenger between the DNA and its specified product. The amino acid transfer RNA molecules should be regarded in this way, and the recent determination of the nucleotide sequence of the alanine transfer RNA by Holley and his co-workers makes it possible to define a genetic locus in terms of its nucleotide sequence (16, 28). It is possible that some such loci can be identified genetically as suppressor genes. Garen has shown that specific suppressor genes of alkaline phosphatase mutants in *E. Coli* act by

bringing about the substitution of specific amino acids at the orginally altered site in the protein. The presence of different suppressor genes results in different amino acid substitutions at the nonsense codon site (9, 32). In other words the mode of action of suppressor loci may be the exploitation of the synonomy of the genetic code and this may be brought about by the production of specific transport RNA molecules. Although this is sheer speculation at this time, it illustrates how advances in molecular genetics may offer new approaches to the structural and functional analysis of genetic loci.

It is possible that in the near future it may also be possible to analyze experimentally new classes of genetic loci which represent of control such factors as initiators of DNA replication or initiation and punctuation information for transcription and translation of RNA.

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Genetique cellulaire chez les bacteries

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I. Genetique et microorganismes

La naissance de la génétique dont nous commémorons aujourd'hui le centième anniversaire avec l'oeuvre de Mendel est contemporaine, notamment, de deux autres événements importants de la biologie : la naissance de la microbiologie expérimentale avec les travaux de Pasteur et la découverte de ce qui devait devenir les acides nucléiques, par Miescher. Ces événements, indépendants les uns des autres, constituent les points de départ de la biologie cellulaire contemporaine.

De par sa nature même, l'hérédité a d'abord été étudiée chez les organismes à reproduction sexuée. D'où la corrélation, qui dans l'esprit de nombreux biologistes, s'est longtemps établie entre la notion d'hérédité et celle de reproduction sexuée. Il faudra attendre le milieu de ce siècle pour que soit étendu aux bactéries et même aux virus le concept d'hérédité tel qu'il fut formulé d'après l'étude des organismes supérieurs. Álors seulement la notion d'hérédité pourra être élargie. Aujourd'hui, elle est devenue une expression nouvelle de la théorie cellulaire : c'est la capacité de reproduction identique que possède chaque cellule et qu'elle transmet à travers les générations. Le reste, la sexualité, la diversité infinie des formes, la différenciation cellulaire ne sont que des « complications » élaborées au cours de l'évolution, des variations sur un même thème fondamental. On peut parfaitement imaginer un univers sans complication, un univers seulement peuplé de cellules identiques se reproduisant à l'infini. Cet univers, on le trouve en fait dans une culture de bactéries.

La génétique des microbes et des virus a été la source de nombreuses surprises pour le biologiste. La plus importante de ces surprises a peut-être été d'offrir un accès à la chimie du matériel génétique grâce à la démonstration par Avery et ses collaborateurs (1944) que la spécificité génétique est portée par le DNA. Pour la première fois, il devenait possible de donner un contenu chimique et physique aux vieux concepts biologiques d'hérédité, de variation et d'évolution. Cette interprétation chimique et physique des phénomènes génétiques, c'est très précisément ce qu'a apporté la structure du DNA proposée par Watson et Crick (1953).

L'autre surprise a été de constater que par leur vitesse de croissance, par la

souplesse de leur adaptation aux milieux les plus divers, par la variété des mécanismes qui permettent de transférer à une population bactérienne un gène choisi, au moment voulu et dans des conditions déterminées, les bactéries et les virus se prêtent tout particulièrement à l'étude de la cellule, de son fonctionnement, de sa reproduction. Depuis les travaux de Beadle et Tatum (1941), de Lederberg (1947), de Davis (1950), nous savons, en effet, qu'avec un peu d'imagination on peut exercer sur une population de microorganismes une pression sélective suffisante pour isoler, presqu'à volonté, des individus chez lesquels une fonction choisie est détériorée par mutation. Et l'une des méthodes les plus efficaces pour reconnaître les mécanismes normaux de la cellule consiste précisément à déceler les anomalies chez de tels montres bien choisis.

L'étude des bactéries et des virus a ainsi permis de poursuivre l'analyse du matériel génétique et de son fonctionnement à partir du point où l'avait conduite la génétique classique (cf Pontecorvo, 1958). On sait le succès de cette recherche. En moins de vingt ans, la fusion de la génétique avec les autres disciplines biologiques et même avec la chimie et la physique a permis de reconnaître la structure des gènes, de trouver le produit primaire de leur action, c'est-à-dire le messager, et de comprendre, sinon dans ses détails du moins dans ses principes, la machine à traduire le langage nucléique en langage protéique : cent ans après Mendel, le code génétique se trouve bien près d'être complètement déchiffré (cf. Nirenberg et al., 1965).

II. Genetique et integration cellulaire

Les méthodes de la biologie expérimentale, celles de la génétique comme celles de la biochimie sont avant tout analytiques. Elles visent à disséquer la cellule en ses éléments et si elles ont progressivement changé d'objet elles ont conservé leur but. L'unité de Mendel s'est peu à peu transformée en gène, la boule du chapelet chromosomique. Puis le gène est devenu une séquence de nucléotides, c'est-à-dire une séquence de sites multiples que peut modifier la mutation et distinguer la recombinaison (cf Pontecorvo, 1958; Benzer, 1957). Dans chaque cellule, un (ou deux) exemplaires d'une certaine séquence nucléique déterminent une certaine séquence peptidique et par là même gouvernent une certaine fonction. Celle-ci diffère de celles déterminées par d'autres séquences nucléiques et il en est ainsi pour des milliers de fonctions différentes.

Dans le même temps, il est apparu de plus en plus clairement que cette notion purement structurale du fonctionnement des macromolécules biologiques ne pouvait suffire à rendre compte des propriétés de la cellule. Chacun

des systèmes que l'on sait aujourd'hui reconnaître, purifier et analyser fonctionne de façon beaucoup plus subtile, intégré dans la cellule qu'isolé dans un tube à essai. Si nous pouvons espérer comprendre, du moins dans ses grandes lignes, le rapport qui existe entre les fonctions des macromolécules et leurs structures chimiques, nous savons aussi que leurs propriétés peuvent varier suivant les autres molécules qui leur sont associées. Deux examples permettent d'illustrer ce point.

Le premier est celui des protéines dites allostériques (Monod, Changeux et Jacob, 1963), c'est-à-dire qui possèdent au moins deux sites spécifiques grâce auxquels elles reconnaissent différents métabolites. Dans certaines conditions, par exemple en l'absence d'un certain métabolite inhibiteur I, la proteine-enzyme sera active: elle se trouvera dans une certaine conformation qui lui permet de reconnaître un certain substrat S, et de convertir ce substrat selon une réaction donnée. En présence de I, la protéine adoptera une autre conformation qui l'empêchera de reconnaître S ou de le transformer. Le métabolite I qui se fixe sur un autre site que S et qui le plus souvent ne présente aucune relation chimique structurele avec S, jouera le rôle de signal régulateur. Suivant la concentration intracellulaire de I, la réaction transformant S se fera à une vitesse donnée qui peut être nulle ou maximum. Récemment, Gehrart et Schachman (1965) ont montré que l'aspartyltranscarbamylase, qui intervient comme premier enzyme dans la séquence conduisant à la synthèse des nucléotides pyrimidiques et dont l'activité est réglée par la concentration de CTP, est en réalité un polymère formé par l'union d'au moins deux chaînes peptidiques : l'une reconnaît le substrat, l'aspartate, et l'autre l'inhibiteur, le CTP. C'est la réunion de ces deux chaînes qui donne à l'enzyme ses propriétés allostériques, donc régulatrices, particulières. Il est donc clair que l'association dans la cellule de certaines protéines avec d'autres protéines ou avec différents métabolites peut entièrement modifier leurs propriétés.

Un autre exemple est fourni par la réplication du DNA chez les bactéries. D'une part, il existe de nombreux arguments expérimentaux en faveur d'un mécanisme semi-conservatif, selon les prédictions que Watson et Crick déduisirent de leur modèle. D'autre part, grâce au travail de Kornberg (1961) et ses collaborateurs, on connaît un enzyme capable de polymériser des déoxynucléotides selon un ordre dicté par une séquence de DNA servant de matrice. Cependant, si un fragment de DNA bactérien est transféré à une bactérie réceptrice par transformation ou par conjugaison incomplète, ce fragment est incapable de se répliquer en tant que tel. Il ne se réplique qu'une fois intégré, après recombinaison avec l'une des structures génétiques présentes dans la bactérie-hôte.

De fait, l'étude, chez les bactéries, des deux activités chimiques liées au DNA, c'est-à-dire la réplication — copie des deux chaînes en séquences

désoxyribonucléiques — et la transcription en messager — copie d'un segment d'une chaîne en séquence ribonucléique — révèle dans les deux cas l'existence d'unités génétiques plus complexes que l'unité de fonction déterminant la séquence d'une chaîne polypeptidique.

III. L'unite de replication dans la cellule bacterienne: le replicon

Chez les bactéries, le DNA est organisé en structures beaucoup plus simples que celles trouvées chez les organismes supérieurs. L'information de base, nécessaire à la croissance et à la division d'une bactérie, est portée par l'une de ces structures, désignée le plus souvent comme le «chromosome bactérien». D'autres structures, non indispensables, comme les épisomes, peuvent être ajoutées à la cellule bactérienne et chacune de ces structures se comporte aussi comme une unité intégrale. Le chromosome bactérien est le mieux étudié parmi ces unités: génétiquement (voir fig. 1), il constitue un seul groupe de liaison qui se comporte comme une structure fermée ou circulaire (Jacob, et Wollman, 1961); structuralement, il semble formé d'une seule double chaîne de DNA, longue de 1,2 à 1,4 mm et circulaire (Cairns, 1963); biochimiquement, c'est aussi une unité car la réplication semble commencer à un point fixe, puis progresser le long de la structure pour revenir au point de départ (Meselson et Stahl, 1958; Cairns, 1963; Sueoka et Yoshikawa, 1963; Bonhoeffer et Gierer, 1963). Enfin, la régulation de cette réplication paraît aussi être un processus intégral, car dans des conditions normales de croissance, un nouveau cycle de réplication ne peut commencer avant la fin du précédent (Maaløe, 1961; Pritchard et Lark, 1964). Bien que les autres unités génétiques

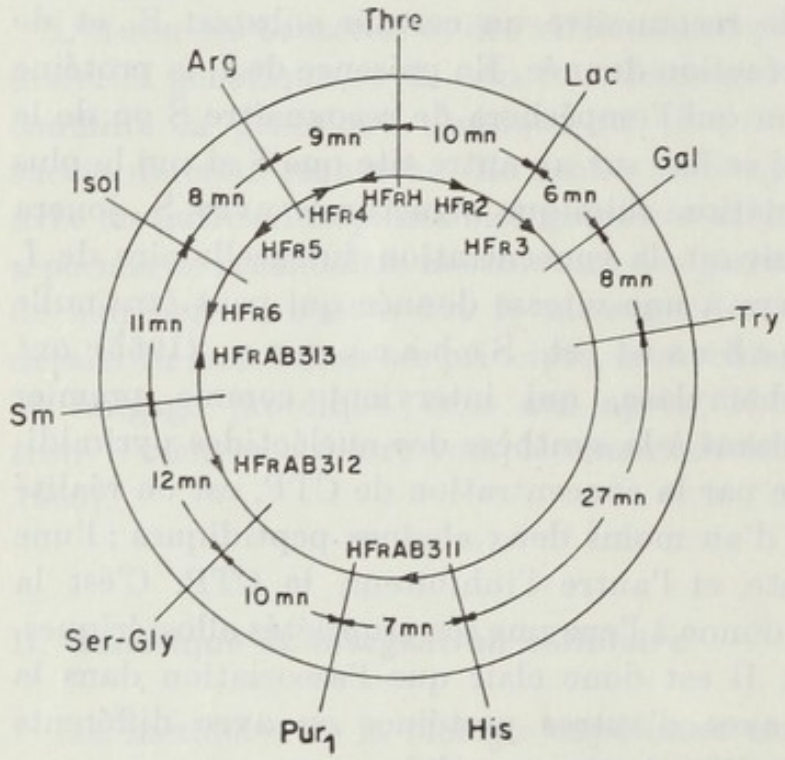

Fig. 1. Schéma représentant le groupe de liaison d'*E. coli*. — La ligne extérieure représente la position de certains caractères sur le groupe de liaison. La ligne médiane représente les interfalles de temps qui séparent la pénétration de ces caractères dans des croisements Hfr x F⁻. La ligne interne représente l'origine et la direction de transfert par différentes souches Hfr.

de la bactérie soient moins bien connues, il semble qu'elles se comportent de façon analogue.

L'équipement génétique d'une bactérie peut donc être considéré comme formé de structures indépendantes, contenant chacune une molécule de DNA, de longueur variable, et se répliquant indépendamment les unes des autres, mais chacune en étroite coordination avec la croissance cellulaire. Comme on l'a déjà fait remarquer, la capacité de réplication autonome n'appartient pas à n'importe quelle séquence de DNA introduite dans la cellule bactérienne. C'est la propriété de ces unités intégrales qui ont été désignées sous le terme de replicons (Jacob, Brenner et Cuzin, 1963). Les mêmes gènes, suivant qu'ils seront incorporés dans un « chromosome bactérien » ou dans le facteur sexuel, ou encore dans un phage tempéré, pourront être répliques avec des fréquences et selon des modalités fort différentes.

Chacune de ces unités de réplication possède des déterminants génétiques qui gouvernent et règlent la réplication de cette unité particulière : dans chacune de ces unités, chromosome, épisome ou phage tempéré, on peut en effet obtenir des mutations qui empêchent la réplication de cette même unité, mais non des autres (Jacob et al., 1963 ; Kohiyama et al., 1963). La nature et les propriétés de ces mutations suggèrent qu'elles modifient un produit diffusible qui agirait sur une « ponctuation » du réplicon, permettant à la réplication de commencer.

En outre, deux réplicons peuvent fusionner pour donner naissance à une nouvelle structure dont la réplication sera gouvernée et réglée par un seul des deux systèmes qui la forment, le plus souvent celui du chromosome bactérien. C'est ce que l'on observe dans le cas des bactéries lysogènes ou celui des mâles dites Hfr, chez lesquels le DNA soit du phage, soit de l'épisome sexuel F, s'est inséré dans le chromosome bactérien. Comme l'a souligné Campbell (1962), le seul mécanisme permettant d'unir deux structures nucléiques par un événement unique est que ces deux structures soient circulaires, leur union naissant d'un crossing-over au niveau d'une région d'appariement.

Les réplicons bactériens semblent être fixés à la membrane cellulaire (Ryter et Jacob, 1964). A l'aide du microscope électronique, on peut montrer en effet chez *B. subtilis* que chacun des corps nucléaires est fixé à un «mésosome», structure formée par invagination de la membrane (voir tableau I). Si les bactéries sont placées dans un milieu hypertonique, les mésosomes se dévaginent progressivement; mais le lien qui unit mésosomes et DNA est suffisamment solide pour que, en se dévaginant, le mésosome entraîne avec lui le corps nucléaire qui apparaît alors directement attaché à la membrane (voir tableau II).

On peut marquer la membrane de *B. subtilis* à l'aide de tellurite de sodium: le tellure cristallise en fines aiguilles le long de la membrane. On peut alors

étudier au microscope électronique la synthèse de cette membrane et l'on constate (voir fig. 2) que cette synthèse ne se fait pas uniformément sur l'ensemble du pourtout bactérien, mais en des zones déterminées au niveau des points d'attachement des corps nucléaires (Jacob, Ryter et Cuzin, 1965). Après réplication du DNA, c'est donc la croissance de la membrane entre les points où s'attachent les deux structures nucléiques formées par la

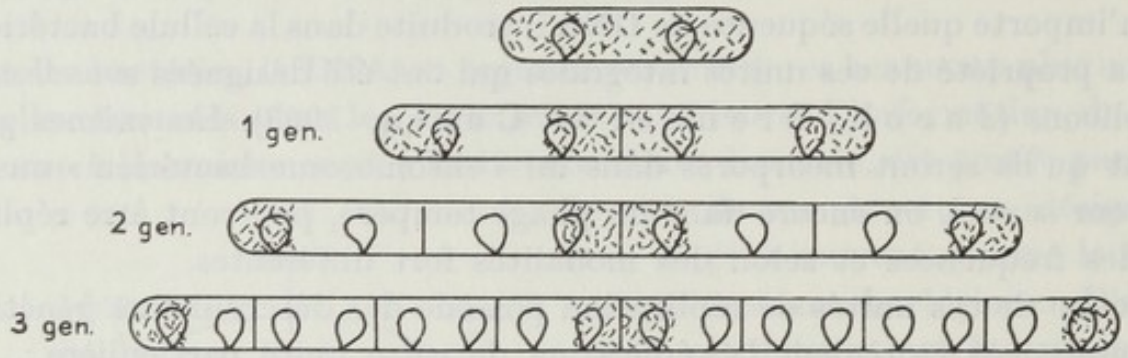

Fig. 2. Schéma montrant la croissance de la membrane bactérienne après marquage de *B. subtilis* avec du tellurite.

Des bactéries en voie de croissance exponentielle sont laissées sans aération en présence de 0,05 % de tellurite de potasse. Après 20 minutes, les bactéries sont lavées et placées dans un milieu frais où la croissance peut reprendre. A des temps variables, des échantillons sont examinés au microscope électronique. On constate qu'après le traitement, la membrane est uniformément marquée par des aiguilles de tellure. En étudiant la manière dont sont distribuées les aiguilles après 1, 2, etc. générations, on peut se former une idée sur la croissance de la membrane qui se fait, non uniformément, mais dans des zones précises comme il est représenté sur ce schéma. Celui-ci résume de nombreuses séries d'observations. (Jacob, Ryter et Cuzin, 1965).

réplication qui paraît assurer la séparation de celles-ci et leur distribution chez les deux bactéries-filles lors de la division. Si l'on étudie le comportement de deux réplicons indépendants, comme le chromosome et l'épisome sexuel à l'état autonome chez *E. coli*, on constate que ces deux structures ne ségrègent pas indépendamment au cours des divisions, mais restent associées; il paraît donc probable que chacune de ces structures est attachée à un même fragment de membrane qui reste intact pendant la croissance et la division bactérienne et constitue ainsi l'unité de ségrégation (Cuzin et Jacob, 1965). Enfin, les caractéristiques de la conjugaison bactérienne indiquent que c'est vraisemblablement dans la membrane que se fait la réplication et que celle-ci est réglée en étroite coordination avec la croissance et la division cellulaire.

Ainsi arrive-t-on à se représenter l'équipement génétique des bactéries comme formé de molécules de DNA circulaires constituant des unités de réplication indépendantes. Ces unités sont associées à un même élément de membrane qui gouverne leur réplication en coordination avec la croissance (voir fig. 3). L'information génétique de base est contenue dans le plus grand

des réplicons, mais de l'information supplémentaire peut être ajoutée par fixation d'autres réplicons à la membrane.

C'est donc la membrane qui, chez les bactéries, semble jouer le rôle dévolu aux chromosomes chez les organismes supérieurs. Il est remarquable que cette conception de réplicons attachés à un même squelette, la membrane, soit à certains égards similaire à celle obtenue par l'étude des chromosomes chez les organismes supérieurs. Là aussi les techniques d'étude les plus diverses semblent indiquer qu'un chromosome serait formé de plusieurs unités de réplication peut-être attachées à une structure commune (cf Taylor, 1964; Pavan, 1963). Il semble bien que l'une des étapes importantes du passage de l'organisation cellulaire des procaryotes à celle des eucaryotes implique des invaginations de la structure membranaire suivie de différenciation en organites spécialisés (mitochondries, appareil génétique) dont les fonctions appartenaient à l'origine à la membrane bactérienne.

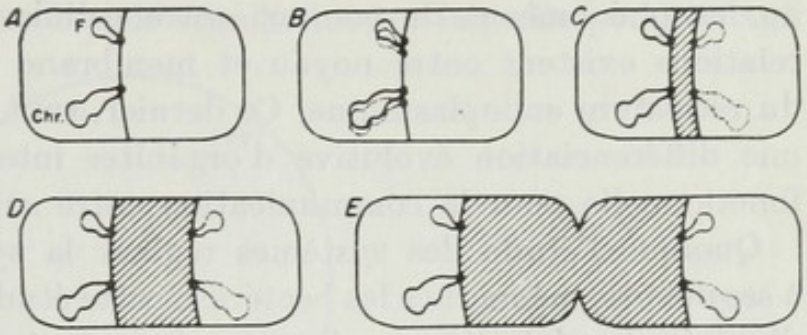

Fig. 3. Schéma de la réplication du DNA chez les bactéries. — La bactérie représentée héberge deux unités indépendantes: le «chromosome» et l'épisome sexuel F. Les deux réplicons sont représentés attachés à la membrane en deux sites distincts. A une certaine étape du cycle de la division, la membrane transmet à chaque réplicon un signal permettant à la réplication de démarrer. La réplication progresse linéairement, chaque réplicon tournant lentement à travers la membrane dans laquelle on admet que se trouve le complexe enzymatique assurant le réplication. Pour chacun des réplicons, deux exemplaires sont ainsi formés dont on admet qu'ils sont attachés côte à côte à la membrane. La synthèse de la membrane est censée survenir entre les régions où s'attachent les deux exemplaires de chaque réplicon, les entraînant ainsi de chaque côté, le septum se formant dans la région médiane. Aucun cycle de réplication nouveau n'est permis jusqu'à ce que la membrane, ayant retrouvé son état d'origine à la suite de la division cellulaire, ne transmette un nouveau signal. Le processus est simplifié en ce sens que : 1) les bactéries ont généralement de 2 à 4 corps nucléaires (et non de 1 à 2), la réplication du DNA se trouvant en avance d'un cycle sur la division et 2) chaque étape est censée être terminée avant que ne commence la suivante. (Jacob, Brenner et Cuzin, 1963)

Un autre aspect qui mérite d'être souligné est le rôle que semble jouer la membrane bactérienne dans la régulation de la synthèse du DNA (cf Jacob et al., 1063). La meilleure illustration jusqu'ici en est fournie par les phénomènes de la conjugaison bactérienne : selon toute vraisemblance une réaction de surface survenant au moment de l'accolement du mâle et de la femelle déclenche en quelque sorte un cycle de réplication du DNA chez le mâle, l'une des structures ainsi synthétisées restant dans le mâle tandis que l'autre est progressivement transférée dans la femelle à mesure qu'elle

est formée. Il est bien évident que la situation est beaucoup plus complexe dans les cellules d'organismes supérieurs. Toutefois, dans ce dernier cas, la surface cellulaire doit jouer un rôle important dans la division cellulaire, des signaux venus de la surface étant sous une forme ou sous une autre, transmis au noyau comme en témoignent les processus morphogénétiques ou les phénomènes de contact entre cellules. Ill est concevable que des relations existent entre noyau et membrane cellulaire, par l'intermédiaire du réticulum endoplasmique. Ce dernier, tout en reflétant en quelque sorte une différenciation évolutive d'organites internes conserverait une valeur fonctionnelle pour la communication entre surface cellulaire et DNA.

Quoique l'étude des systèmes réglant la synthèse du DNA soit encore à ses débuts, même chez les bactéries, cette étude révèle clairement l'existence d'unités de réplication qui peuvent contenir jusqu'à plusieurs milliers de gènes et dont la spécificité de réplication paraît gouvernée par un système fait d'au moins deux éléments génétiques: un gène de structure déterminant la synthèse d'un produit cytoplasmique spécifique qui lui-même «reconnaît» une ponctuation de l'unité, c'est-à-dire vraisemblablement une certaine séquence permettant l'amorce de la réplication. A partir de là, toute séquence attachée à cette ponctuation peut être répliquée par le système.

IV. L'unite d'activite genetique dans la cellule bacterienne: l'operon

L'étude, non plus de la réplication, mais de l'activité du matériel génétique bactérien révèle l'existence d'autres unités souvent plus complexes que l'unité de fonction.

Nous savons aujourd'hui que, lorsqu'il est exprimé, un gène peut fonctionner à grande vitesse de façon continue. Le produit primaire du gène est une copie ribonucléique de l'une des chaînes du DNA, le messager, qui porte aux ribosomes l'information structurale nécessaire pour mettre en ordre les acides aminés formant la structure primaire d'une protéine (J a c o b et M o n o d, 1961). Chez les bactéries, la durée moyenne de vie d'un messager est courte et n'excède pas quelques minutes, ce qui lui permet de contribuer à former quelques dizaines d'exemplaires seulement de la chaîne peptidique correspondante. Pour produire une quantité importante de la protéine, le gène doit donc produire du messager de façon constante.

Chez les bactéries, les gènes de structure gouvernant la structure de protéines appartenant à une même chaîne biochimique sont souvent adjacents. Ils constituent une seule unité d'activité, coordonnée et polarisée, désignée sous le nom d'opéron (J a c o b et M o n o d, 1961). Il y a de nombreuses raisons de penser que l'opéron produit un seul messager qui s'associe aux ribosomes pour produire la série des chaînes polypeptidiques déterminées

par les différents gènes de structure de l'opéron (Attardi et al., 1963 ; Guttman et Novick, 1963; Martin, 1963 ; Spiegelman et Hayashi, 1963). L'activité de l'opéron est réglée par un autre gène, dit régulateur, qui produit un répresseur cytoplasmique. Celui-ci reconnaît une structure déterminée par l'une des extrémités de l'opéron et appelée opérateur. Il se forme ainsi une boucle régulatrice sur laquelle peuvent agir

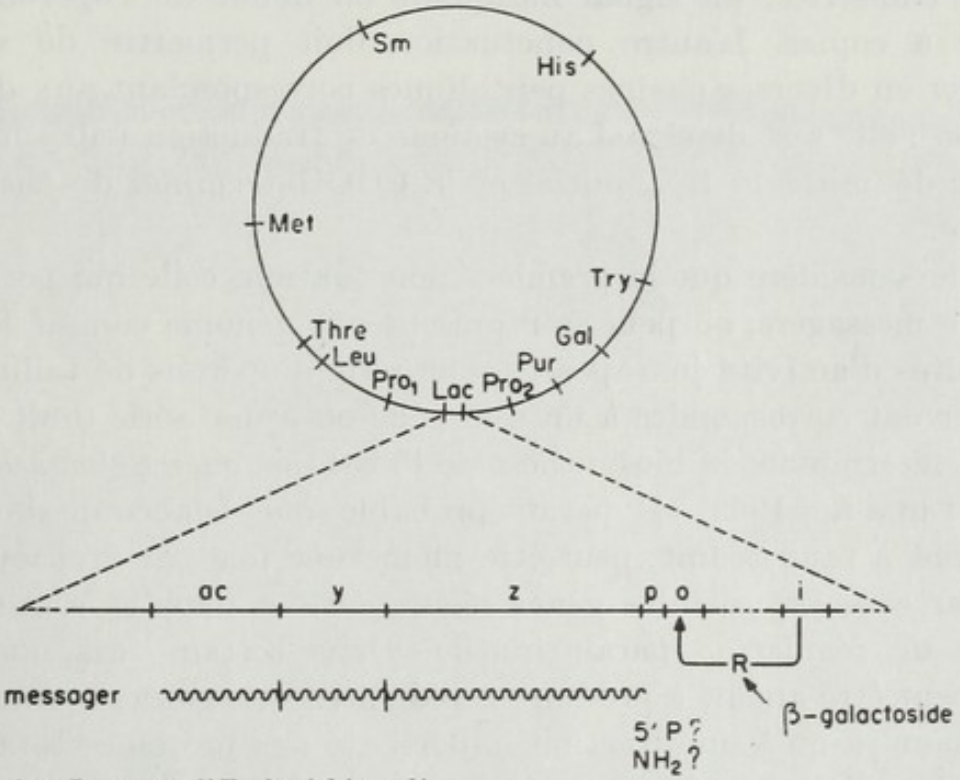

Fig. 4. La région Lactose d'*Escherichia coli*.
Le cercle représente le chromosome d'*E. coli* et la position de la région Lactose (Lac) parmi d'autres marqueurs. Audessous est représenté un agrandissement de la régin Lactose. i : gène régulateur ; o : opérateur ; p : promoteur ; z : gène de structure de la β-galactosidase; y : gène de structure de la β-galactoside-perméase ; ac : gène de structure de la β-galactoside-transacétylase. Les gènes de structure synthétisent vraisemblablement un seul messager (dont le début 5'P est vraisemblablement du côté opérateur) qui s'associe aux ribosomes pour former un polysome où sont synthétisées les diverses chaînes peptidiques (dont le début NH_2 est vraisemblablement du côté opérateur). Le gène régulateur produit un répresseur spécifique qui, agissant au niveau de l'opérateur, bloque la production de messager, et par là même des protéines. Les β-galactosides inducteurs agissent sur le répresseur pour l'inactiver, permettant ainsi la production de messager, donc des protéines déterminées par l'opéron.

des métabolites spécifiques jouant le rôle de signaux chimiques spécifiques venus du cytoplasme ou du milieu. Ces signaux entraînent l'activation, ou l'inactivation du répresseur, et par là même permettent ou bloquent la production de messager, donc des protéines correspondantes (voir fig. 4).

Un tel système implique l'existence d'une double ponctuation dans le texte nucléique. L'une doit permettre de « découper » la longue chaîne de DNA en « tranches de transcription » correspondent aux opérons : elle doit servir de reconnaissance à la RNA polymérase pour lui indiquer là où doit débuter

(et éventuellement là où doit finir) la transcription d'un opéron et quelle chaîne doit être copiée. On peut, dans certaines conditions, obtenir des insertions de la région lactose dans une autre région du chromosome, insertions dirigées soit dans un sens, soit dans l'autre (S i g n e r et B e c k w i t h, résultats inédits) ; comme l'expression de l'opéron se fait tout aussi bien dans les deux cas, il faut admettre que l'une ou l'autre chaîne du DNA peut être transcrite, un signal indiquant au début de l'opéron quelle est la chaîne à copier. L'autre ponctuation doit permettre de « découper » le messager en diverses chaînes peptidiques correspondant aux divers gènes de l'opéron : elle sert de signal au système de traduction (ribosomes, tRNA, etc.) pour délimiter le HN_2 initial et le COOH terminal de chaque chaîne peptidique.

Si l'on ne considère que la première ponctuation, celle qui permet la production de messagers, on peut se représenter le génome comme formé d'une série d'unités d'activité juxtaposées, une série d'opérons de tailles variables car ils peuvent correspondre à un seul gène ou à une série (huit dans le cas des gènes déterminant la biosynthèse de l'histidine chez *Salmonella* (A m e s et H a r t m a n, 1963). Il paraît probable que beaucoup de ces unités fonctionnent à taux réduit, peut-être même une fois par division cellulaire, comme par exemple certains gènes régulateurs et dans ce cas, un système spécifique de régulation paraît inutile. Dans certains cas, au contraire, l'opéron peut être amené à produire rapidement une grande quantité de protéines (allant jusqu'à une fraction importante des protéines totales synthétisées par la cellule bactérienne). Alors intervient la boucle spécifique de régulation gouvernant l'activité de l'opéron par l'intermédiaire de l'opérateur.

Dans le cas du système Lactose d'*E. coli*, l'analyse d'une série de délétions montre que l'opérateur est situé en dehors du premier gène de structure de l'opéron (voir fig. 4) dont il paraît séparé par une région, désignée sous le nom de promoteur, indispensable à l'expression de l'opéron tout entier (J a c o b, U l l m a n n et M o n o d, 1964). Selon toute vraisemblance, le promoteur correspond à l'une des ponctuations, soit de transcription (pour la RNA polymérase), soit de traduction (pour les ribosomes par example). Il y a des raisons de penser que l'opérateur n'est pas traduit en chaîne peptidique, mais on ignore encore s'il est transcrit ou non en messager, c'est-à-dire si le répresseur agit au niveau du messager ou du DNA lui-même. Il n'est pas possible de détailler ici les arguments expérimentaux ou les hypothèses (S t e n t, 1964) sur le site d'action du répresseur. Cependant la combinaison de résultats récents, obtenus dans divers laboratoires (cf S t r e i s i n g e r, 1965), indique que la synthèse du messager (terminaison 5'P) et celle de la première chaîne peptidique (terminaison HN_2) débutent du côté opérateur de l'opéron. L'interprétation qui s'accorde le plus simplement avec les résultats de l'analyse génétique et notamment avec l'étude de délétions

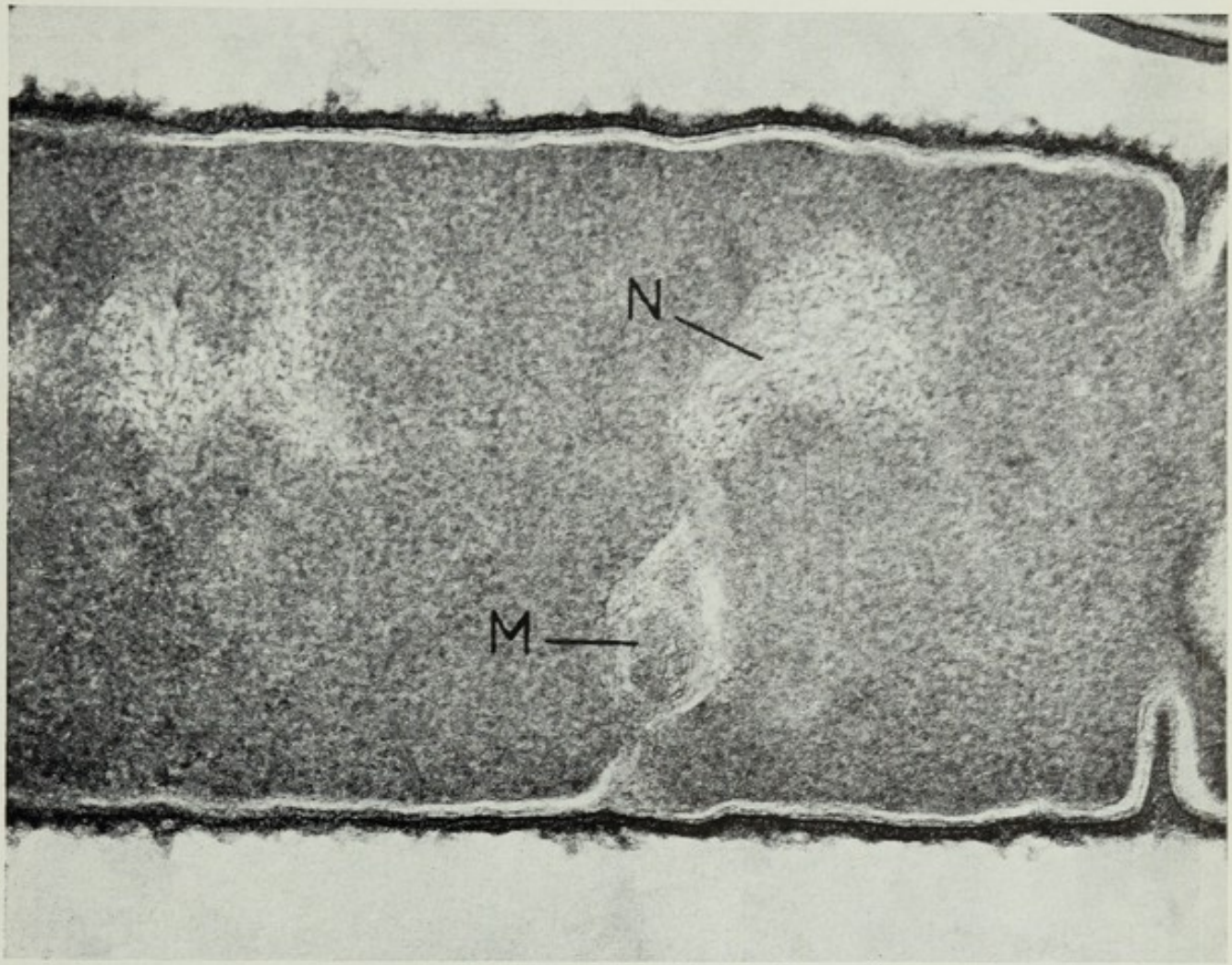

Tableau I. Section de *B. subtilis* en voie de croissance.
Le corps nucléaire (N) est lié à la membrane par l'intermédiaire d'un mésosome (M) (R y t e r et J a c o b, 1964).

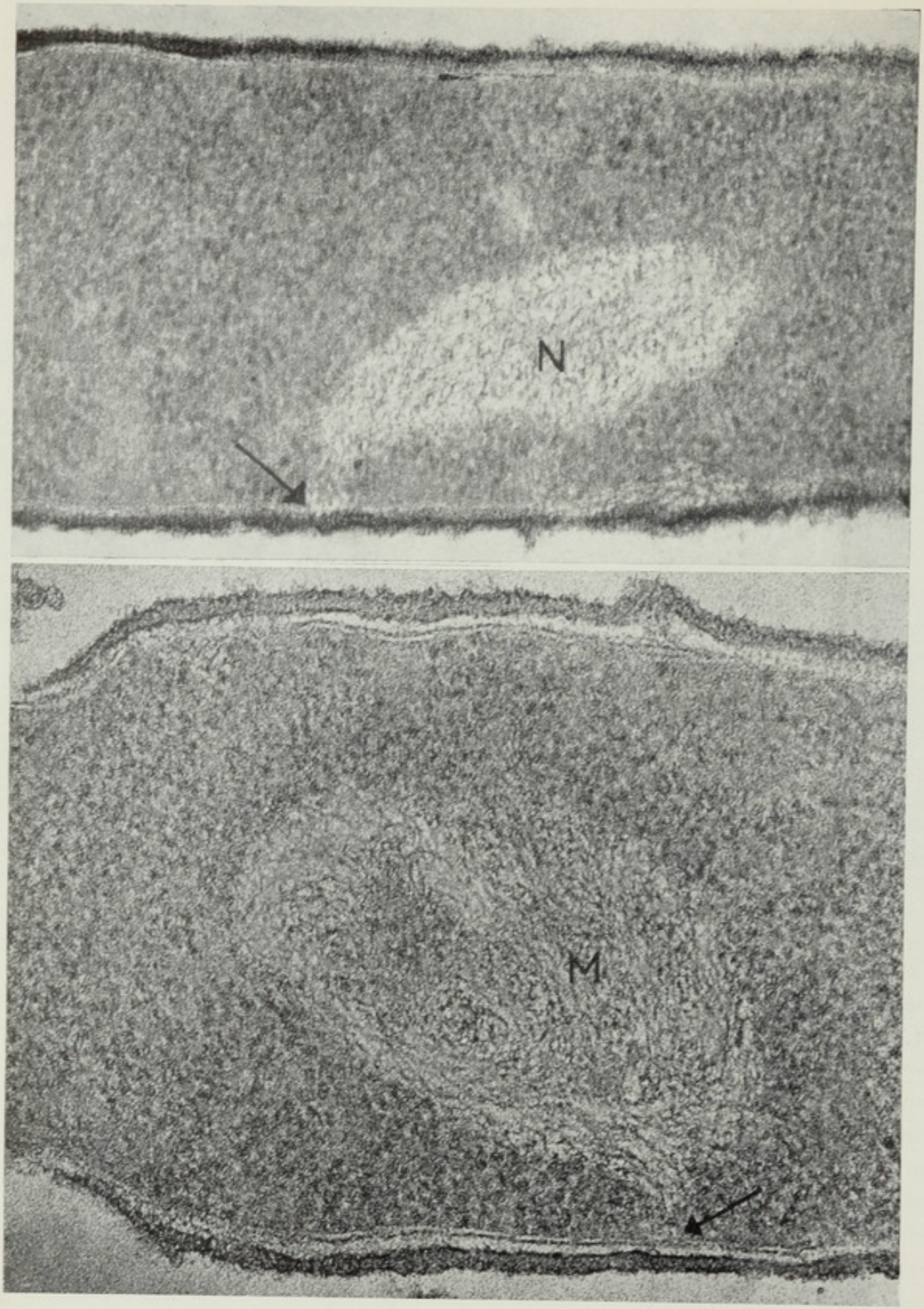

Tableau II. Section de *B. subtilis* placé pendant 30 minutes dans du saccharose 0,5 M.
Les mésosomes ont été expulsés du cytoplasme. En se rétractant, ils entraînent avec eux les corps nucléaires (N) qui apparaissent alors directement liés à la membrane.

(Ryter et Jacob, 1964)

couvrant différents segments de l'extrémité opérateur de l'opéron, c'est que le promoteur représente la ponctuation de transcription, celle que reconnaît la RNA-polymérase pour commencer à ce niveau sur l'une des chaînes, la synthèse du messager de l'opéron. L'opérateur ne serait pas transcrit en messager et la répression se ferait directement au niveau du DNA.

La conception du matériel génétique formé d'opérons dont l'activité est

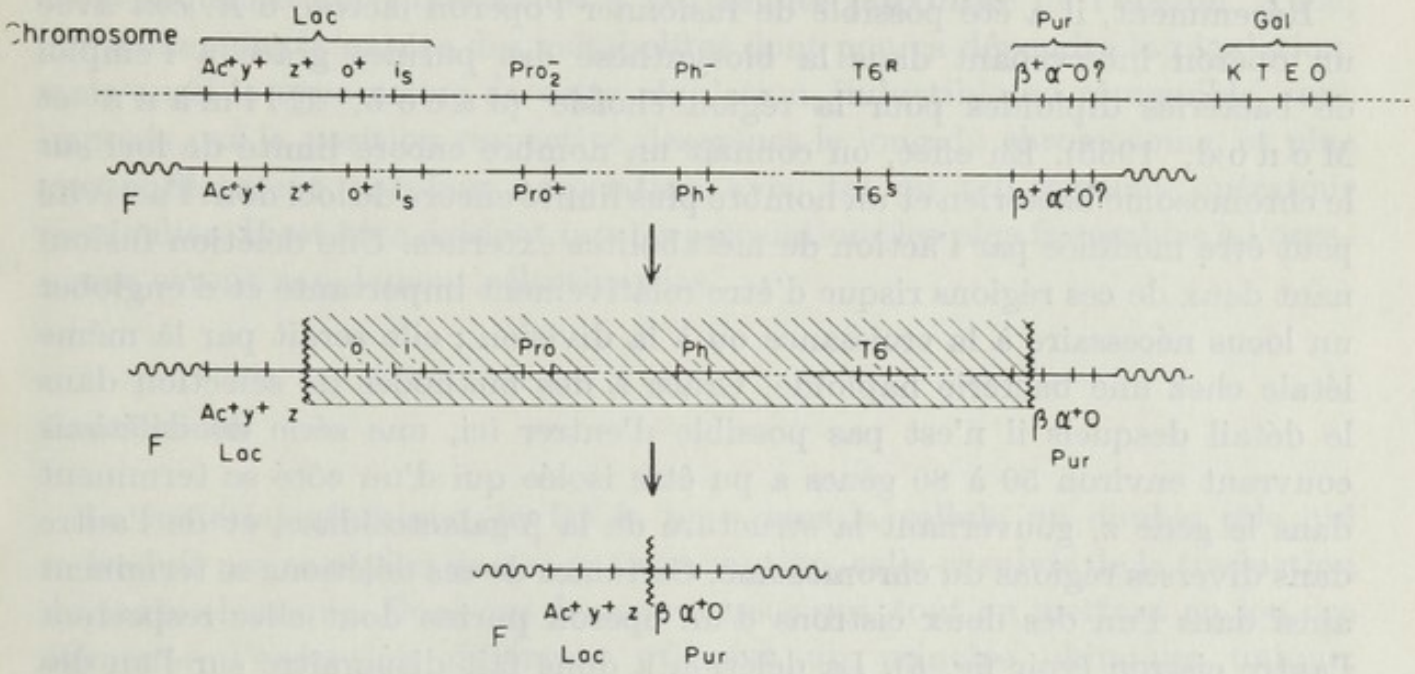

Fig. 5. Délétion fusionnant un fragment de l'opéron lactose et un fragment d'un opéron purine chez *E. coli*.

La partie supérieure du schéma représente la structure diploïde hétérozygote d-origine, la bactérie hébergeant un épisome sexuel ayant incorporé par recombinaison un important fragment du chromosome. Dans le schéma du milieu, la région hachurée représente la zone détruite par une délétion survenue dans l'épisome. Le schéma du bas représente la structure formée par la délétion. Celle-ci a réuni un fragment terminal du gène z (déterminant la β-galactosidase) avec un fragment initial d'un gène Pur β (déterminant un enzyme de la biosynthèse des purines). Un nouvel opéron serait ainsi formé par le gène Pur α (déterminant une protéine de la biosynthèse des purines), une structure formée par une partie du gène z et une partie de Pur β (produisant selon toute vraisemblance une chaîne peptidique hybride constituée par une séquence Pur β, côte NH_2 terminal, et par une séquence de z, côté COOH terminal), les gènes v (déterminant la β-galactoside--perméase) et Ac (déterminant la β-galactoside transacétylase). L'expression de l'opéron est réprimée par les purines, vraisemblablement au niveau d'un opérateur purine, lui-même sensible à un répresseur activé spécifiquement par les purines. (Jacob, Ullmann et Monod, 1965)

réglée par un site unique que détermine l'opérateur, comporte une prédiction expérimentale précise : dans le cas où un remaniement chromosomique disjoindrait des gènes de structure de leur opérateur pour les associer à un autre opéron, gouverné par un autre opérateur, l'activité de ces gènes de structure serait de ce fait soumise à une régulation nouvelle.

De tels remaniements chromosomiques ont déjà été observés, qui modifient la régulation de gènes appartenant soit à l'opéron histidine chez *Salmonella*

(Ames, Hartman et Jacob, 1963), soit à l'opéron tryptophane (Matsushiro et al., 1962), soit à l'opéron Lactose (Jacob et al., 1964) chez *E. coli*. Dans tous ces cas, cependant, les gènes de structure étudiés devenaient attachés à une région non identifiée du chromosome, et soumis à un système de régulation inconnu et non modifiable par les changements de milieu.

Récemment, il a été possible de fusionner l'opéron lactose d'*E. coli* avec un opéron intervenant dans la biosynthèse des purines grâce à l'emploi de bactéries diploïdes pour la région choisie (Jacob, Ullmann et Monod, 1965). En effet, on connaît un nombre encore limité de loci sur le chromosome bactérien et un nombre plus limité encore de loci dont l'activité peut être modifiée par l'action de métabolites externes. Une délétion fusionnant deux de ces régions risque d'être relativement importante et d'englober un locus nécessaire à la croissance ou à la division ; elle serait par là même létale chez une bactérie haploïde. Grâce à des méthodes de sélection dans le détail desquels il n'est pas possible d'entrer ici, une série de délétions couvrant environ 50 à 80 gènes a pu être isolée qui d'un côté se terminent dans le gène z, gouvernant la structure de la β-galactosidase, et de l'autre dans diverses régions du chromosome. Certaines de ces délétions se terminent ainsi dans l'un des deux cistrons d'un opéron purine dont elles respectent l'autre cistron (voir fig. 5). La délétion a donc fait disparaître sur l'un des segments génétiques de cette bactérie diploïde une fraction du gène z, l'opérateur o et le gène régulateur i du système lactose, les gènes Pro_2 (biosynthèse de la proline), Ph (synthèse de la phosphatase alcaline), T6 (sensibilité au phage T6) et un fragment du cistron β de la région purine. Alors que chez une bactérie sauvage, beaucoup de ces caractères ne sont pas cotransductibles deux à deux, un même phage qui s'est multiplié sur la souche portant la délétion peut cotransduire des caractères de la région Lactose et de la région purine.

La synthèse des deux protéines de la région Lactose, β-galactoside perméase et transacétylase, déterminées par les deux gènes y et Ac que la délétion a laissés intacts, ne sont plus inductibles par les β-galactosides, ce que l'on pouvait attendre puisque la délétion a détruit les deux éléments o et i déterminant la régulation du système. Mais cette synthèse est devenue répressible par l'addition de purines. Il est donc clair que le fragment de l'opéron lactose qui persiste après délétion s'est fusionné avec le fragment de l'opéron purine laissé intact par la délétion. Un nouvel opéron est donc formé comprenant ces deux fragments soudés, opéron qui selon toute vraisemblance produit un seul messager contenant l'information génétique pour la synthèse de protéines impliquées soit dans la biosynthèse des purines, soit dans l'utilisation du lactose. Mais le sytème qui détermine la synthèse et la régulation de ce messager, c'est-à-dire le promoteur et l'opérateur, doivent être ceux de l'opéron purine.

De la même façon, des délétions fusionnant l'opéron lactose avec un opéron gouvernant la biosynthèse du tryptophane ont récemment été isolées (Signer et Beckwith, résultats inédits). Là encore l'expression de gènes de l'opéron Lactose devient répressible par le tryptophane.

Le type de régulation auquel est soumise l'expression de gènes appartenant à un opéron donné dépend donc exclusivement de l'opérateur, c'est-à-dire de la séquence nucléique située à l'extrémité proximale de l'opéron. Ainsi, non seulement la nature des métabolites dont pourra dépendre la régulation, mais aussi le type même de cette régulation, inductible ou répressible, sont imposés par la position respective des gènes le long du chromosome, et plus particulièrement par leur association avec tel ou tel segment opérateur particulier. Il est bien évident que les associations les plus favorables à l'organisme seront rapidement sélectionnées.

Conclusions

Le matériel génétique, le DNA, joue dans la cellule un double rôle qui se traduit par sa réplication et sa transcription, celle-ci suivie de la traduction du texte chimique. Dans ces deux processus qui, tout en mettant en jeu des éléments d'exécution différents utilisent un principe chimique unique, l'appariement antiparallèle des bases, le DNA intervient directement comme matrice.

Ces deux activités chimiques du DNA sont commandées et réglées en coordination avec les autres activités cellulaires par des boucles spécifiques de régulation elles-mêmes génétiquement déterminées. Au niveau du DNA, certaines séquences nucléiques définissent les ponctuations qui « découpent » en quelque sorte le génome cellulaire en unités de réplication ou de transcription. D'où l'importance de la position d'un gène dans le matériel génétique comme l'a longtemps souligné Goldschmidt (1946). Les conditions dans lesquelles un gène est répliqué ou exprimé dépendent des ponctuations spécifiques auxquelles ce gène est associé.

Au niveau des boucles de régulation, c'est la structure même des protéines régulatrices qui leur permet de « reconnaître », pour s'associer avec elles, d'une part certaines molécules jouant le rôle de signaux chimiques spécifiques, d'autre part certaines séquences nucléiques pour commander, en fonction des signaux reçus, l'activité chimique de l'unité génétique adjacente.

Les problèmes qui se posent dans l'étude génétique d'une cellule, même aussi simple que la cellule bactérienne, sont donc une fois encore les vieux problèmes d'intégration et d'association qui permettent aux composantes moléculaires de former les superstructures de la cellule. Comment les molécules se trouvent-elles, se reconnaissent-elles, se combinent-elles pour former une

membrane, une mitochondrie, un chromosome ? Comment transmettent-elles des signaux pour moduler l'activité de leurs associés ? Voilà les problèmes que la biologie et la génétique de la cellule ont à résoudre dans les années à venir.

Il est peu de branches de la science qui aient parcouru un chemin aussi long, en un temps aussi court, que la génétique. Née ici il y a un siècle, elle a progressivement remodelé nos conceptions sur le êtres vivants, leur fonctionnement, leur évolution. Elle est maintenant installée au coeur même de toute la biologie. Le chemin parcouru peut se mesurer si l'on considère qu'il y a cent ans, un hommè pouvait encore renouveler la pensée scientifique dans la solitude d'un monastère. Devenu aujourd'hui un rouage dans une machine compliquée, le généticien s'affaire fréquemment dans un sous-sol, autour d'une énorme centrifugeuse, conscient que dix autres laboratoires font, au même moment, la même expérience. Et pour le chercheur qui trop souvent a de la biologie une vision aussi fragmentaire que celle de Fabrice del Dongo à la bataille de Waterloo, Mendel représente l'un des derniers à avoir pu accomplir une révolution comme on accomplit une oeuvre d'art, dans l'isolement, le calme et l'indépendance.

Ce travail a bénéficié de l'aide de la « National Science Foundation », du Commissariat à l'Energie Atomique et de la Délégation Générale à la Recherche Scientifique et Technique.

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Contributions of Plant Virus Research to Molecular Genetics

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The lectures of the Mendel symposium should cover as completely as possible the development of genetics in the first 100 years of its existence. The investigations of phytopathogenic viruses have only in the last 10 years contributed to the development of genetics. Mendel's method of investigation, the crossing of closely related strains and the analysis of distribution of characters in the progeny, has not proven successful in the case of phytopathogenic viruses. In the case of bacteria, and above all with many bacteriophages, processes which take place in a cell after meeting the hereditary substance of various partners and which lead to a recombination of genes, contribute considerably to the understanding of genetic fine structure. There have been many unpublished attempts in various laboratories, including our own, to demonstrate recombination after the mixed infection of plant viruses. These attempts were unsuccessful. Published data (Best 1961, 1964; Best and Gallus 1954; Watson 1960; Aach 1961c) which indicate positive results, even if they should prove to be correct, are too sporadic. In any case, they would not be considered in serious genetic analyses.

If something is to be said at this symposium about phytopathogenic viruses, and that means above all about tobacco mosaic virus (TMV), it should be for the following reasons: With TMV, the material which was hypothetically required from Mendel's studies on pea plants over a hundred years ago — the so called "cell elements", later called "genes" — was isolated and purified in rather large amounts. The same thing had been already achieved 12 years earlier with bacteria (pneumococci), although with much smaller absolute amounts of substance. For the first time in 1958 changes in the genetic material of TMV could be obtained in a test tube by chemical treatment. Mutations could be produced by known chemical reaction. This alone would suffice to give TMV word of mention at this symposium. I shall, however, briefly discuss several other contributions to molecular genetics achieved from investigations on phytopathogenic viruses. These are as follows:

1. Genetic information can also be stored in RNA.
2. Chemomutagenesis of pure RNA in vitro.
3. Nucleic acid — protein correlation ("genetic code").

1. Genetic information can also be stored in RNA

The genetic material of the chromosomes of higher animals and plants is DNA. The same is valid for bacteria, many bacteriophages and zoopathogenic viruses. The genetic material of the plant viruses, some animal viruses and several bacteriophages is RNA. With the exception of a few bacteriophages, the genetic material in the case of DNA exists as a double strand (Watson and Crick 1953). In this double strand one strand is complementary to the other in such a manner that a nucleotide with the base adenine is paired with one containing the base thymine. Likewise, a nucleotide with the base guanine is paired with one containing cytosine. In TMV, and also in other phytopathogenic viruses, the nucleic acid is, as already mentioned, RNA (Schwerdt u. Loring 1947). The protein coat can be removed and the RNA demonstrated to be infectious (Gierer and Schramm 1956, Fraenkel-Conrat 1956), providing ribonucleases are removed or inactivated by the isolation procedure and during infection. This means that the RNA must contain the total genetic information for its identical reduplication and for the production of its protein coat. The RNA of TMV exists as a single strand which in the absence of its protein coat can form extensive α-helical structure in solution (Spencer *et al.* 1962). By quantitative comparison of nuclease action on infectivity, viscosity and molecular weight of the RNA it was found that the rate of decrease of viscosity and infectivity follows a first order reaction. This means that each cleavage of the molecule destroys the infectivity (Gierer 1958).

At the time of this work it was already known that in the case of bacteria (Avery *et al.* 1944 with pneumococci) and phages (Hershey and Chase 1952) DNA is the genetic material and not nucleoprotein, as was long supposed. Since 1956 we know that RNA can also be the genetic material. For organisms containing either type of nucleic acid, all specific differences between two strains lie only in the differences of the sequence of the four bases. This seems so obvious to us today, yet only 10 years ago it was not at all obvious. The fact that isolated TMV-RNA was barely infectious was interpreted to mean that reconstituted virus, that is nucleic acid much more infectious due to protection from nuclease attack by its protein coat, represented a "resynthesis" of elementary systems of life (Stanley 1955, personal communication). Today by the use of bentonite (Fraenkel-Conrat *et al.* 1961) and the application of high salt concentration and weak alkali reaction (Sarkar 1963, 1965), we have at our disposal the means to maintain infectivity of the RNA without reconstituting it with protein.

2. Chemomutagenesis of pure RNA in vitro

As already mentioned, the recombination of genetic material following mixed infection of phytopathogenic viruses, or of RNA-containing bacterial viruses, could so far not be used for genetic structural analysis. On the other hand, it has been known for some time that mutations occur with phytopathogenic viruses. With TMV, for example, there occur in the light-green/

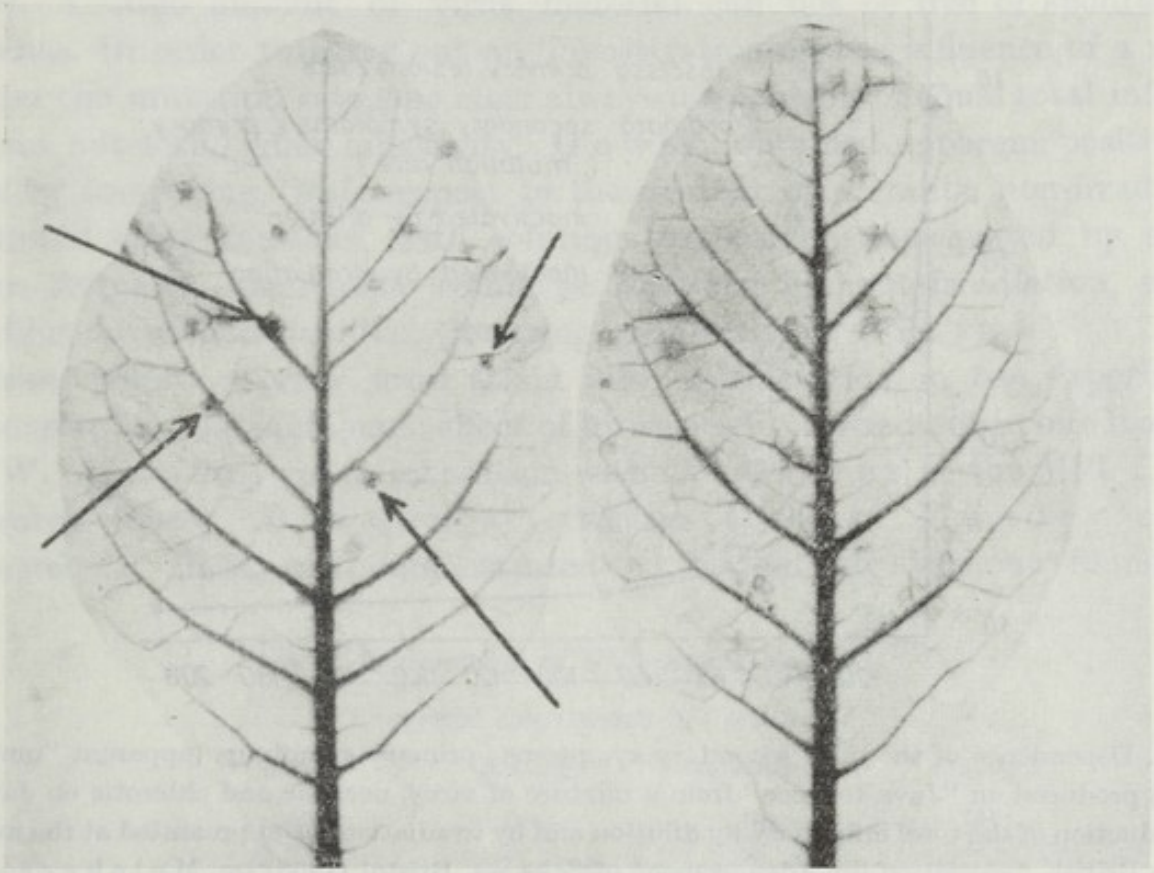


Fig. 1. Two leaves of *Nicotiana sylvestris* (right: with standard TMV, left: with TMV which was previously propagated at high temperature several days before photography. (Chlorophylls and carotenoids were removed in the morning with hot alcohol and the leaves were placed in iodine-potassium iodide solution. The primary lesions are coloured blue, since at these positions enzymatic starch hydrolysis was blocked in the night. On the right leaf inoculated with control virus only chlorotic lesions which are difficult to recognize in the intact leaf can be seen. On the left leaf there occur, in addition, 4 necrotic lesions from mutant TMV indicated by arrows. Photograph (first publ. by Melchers 1960) from unpublished experiments (1940).

dark-green mosaic of the systemic symptoms yellow spots from which homogenous particles of yellow strain TMV can be isolated. This occurs even with TMV carefully and repeatedly propagated over single lesions. This means that as often as is desired one initiates virus propagation starting from a single virus particle. It is indeed of merit that Jensen (1933, 1936, 1937), Holmes (1934, 1936) and McKinney (1935, 1937) have experimentally verified the mutability of phytopathogenic viruses. The systemic differences

in symptom: light-green/dark-green mosaic as compared with green/yellow mosaic, were used by Pfankuch, Kausche und Stubbe (1940) and Melchers (1948) for the attempt to increase the mutation rate by X-rays. These attempts, however, proved unsuccessful (Freksa, Melchers and Schramm, 1946).

For quantitative studies a test was required in which the parental material and mutants could with simplicity and certainty be distinguished from one

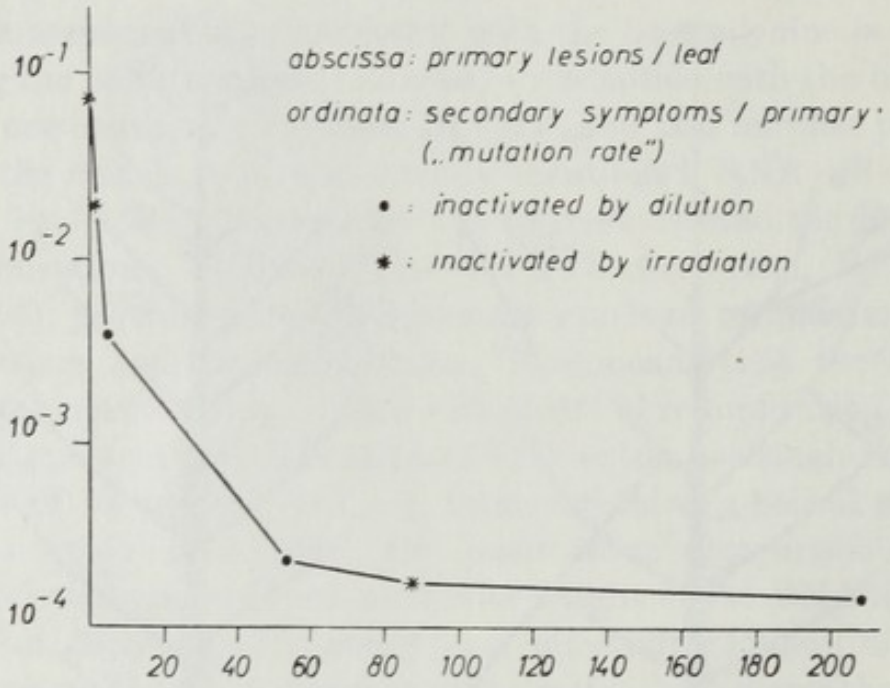


Fig. 2. Dependence of the ratio secondary symptoms / primary symptoms (apparent "mutation rate") produced on "Java tobacco" from a mixture of virus, necrotic and chlorotic on Java, on the reduction of the total infectivity by dilution and by irradiation. First presented at the meeting of the British Association for Advancement of Sciences, Bristol (1955) by Melchers. Data Tab. 9. from Mundry (1957).

another, easily counted and independent of one another in their occurrence. In the laboratory jargon of that time we said that one needs a "ClB-method"* for TMV mutations.

Ordinary TMV is systemic on *Nicotiana sylvestris* and on some varieties of *N. tabacum* (for example, "Java"). It also produces primary chlorotic lesions, which can be made more visible with iodine as zones of inhibition of starch hydrolysis. There exists a group of mutants which give primary necrotic lesions on these test plants (Fig. 1). The first two conditions (good differentiation of lesions and easily countable lesions) are fulfilled. The third condition (independency of one another) is fulfilled only in the case of lower concentra-

*) The famous method of H. J. Muller in *Drosophila* to count easily and exactly a group of mutations, namely the lethals and visibles in the X-Chromosomes.

tions of virus. The leaf of a plant represents by no means as simple a "substrate" as an artificial fungal or bacterial culture medium in a petri dish, a bacterial lawn for bacteriophages, or even a "monolayer" of a cell culture for zoopathogenic viruses. The fact that the phenomenon called "interference" or "mutual exclusion" was totally disregarded led to the result that the conclusions from experimental work on the rate of mutations produced by irradiation (Gowen 1941) were not supportable (Melchers 1949, Mundry 1957). A large amount of virus material can not be free of spontaneous mutants. In order to carry out an investigation on the influence of a mutagen on the mutation rate, one must always use controls of equal total infectivity and not with higher infectivity. Gowen obtained apparent positive results by comparing, with respect to the content of mutants, non-irradiated, undiluted virus solutions, with solutions extensively inactivated by irradiation. Actually, his results could be obtained without irradiation, simply by dilution with water (i.e., lowering of infectivity) (Fig. 2).

These points of view were taken into consideration in the experiments demonstrating the mutagenic effect of nitrous acid, carried out in our Institute by W. Mundry in collaboration with A. Gierer of the MPI f. Virus Research (1958). Bawden's criticism (1959) of Mundry's and Gierer's data was demonstrated to be entirely without foundation

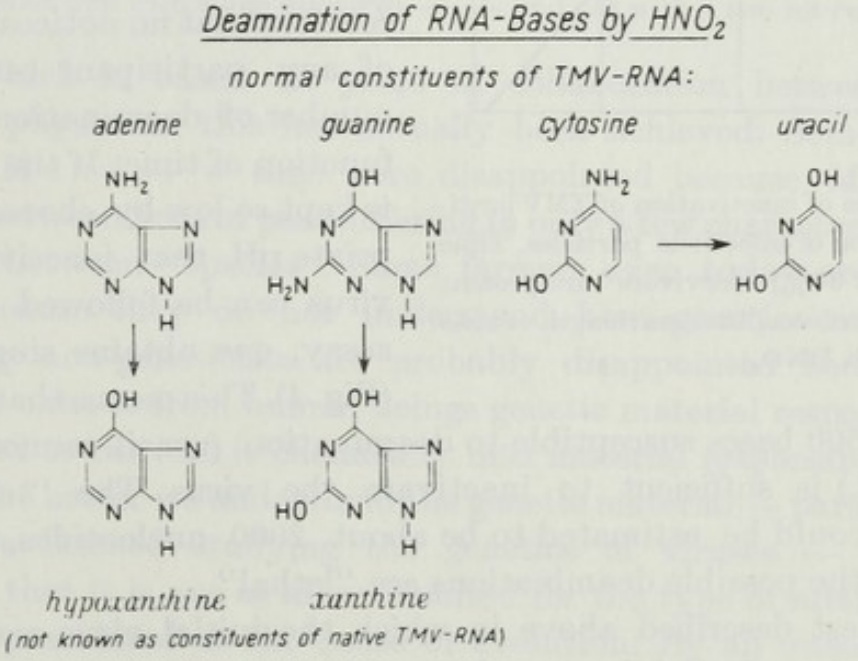


Fig. 3. Base conversions of the nucleotides of RNA resulting from incubation with HNO_2.

(Mundry 1959). However, it should not be stated that such criticism of other publications is uncalled for: so for all publications in which there were no controls diluted to the same infectivity as the treated material.

It was fortunate that chemists were so advanced in their results at this time that a careful investigation could be carried out on the mutagenesis of TMV-RNA, the pure genetic material of tobacco mosaic virus. But today one should not overlook the fact that the quantitative test just mentioned and its satisfactory application to chemomutagenesis in the test tube is not "trimming on the cake", but a "conditio sine qua non".

The other necessary condition was worked out by Schuster und Schramm (1958). They investigated analytically the possible alterations which are evoked by treatment of TMV-RNA with HNO_2: namely the conversion of cytosine to uracil, of adenine to hypoxanthine and of guanine to xanthine (Fig. 3). In addition, they were able to show that the overall structure, that is, above all the sugar phosphate bonds of the RNA chain, was not affected by the deaminations. If the reaction is performed at constant hydrogen ion concentration, constant temperature and at such a high concentration of the participants of the reaction that no noticeable reduction of any participant can occur, the number of deaminations is simply a function of time. If the reaction rate is kept so low by choosing an appropriate pH that inactivation of the virus can be followed by biological assay, one obtains single hit curves (Fig. 4). This means that one deamination per $\sim$ 4500 bases susceptible to deamination (uracil cannot be deaminated by HNO_2) is sufficient to inactivate the virus. The "target size" of this reaction could be estimated to be about 2000 nucleotides, that is, only about half of the possible deaminations are "lethal".

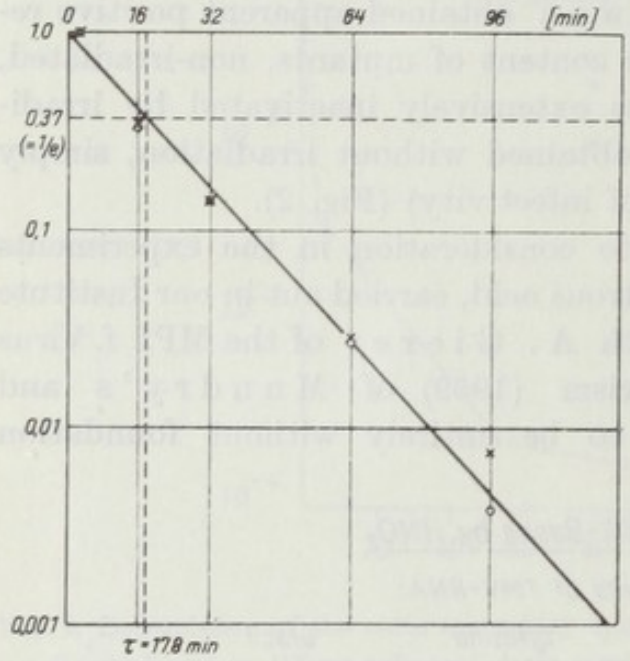


Fig. 4. Dependence of inactivation of TMV (ordinate: concentration of infectious particles. Time τ at which 1/e ($\approx$ 37%) "survivors" are present is indicated) on the dose. (Abscissa: length of time of incubation with HNO_2).

Using the test described above in which the initial virus material causes chlorotic lesions on Java tobacco, whereas the mutants cause necrotic lesions, it could be shown that a single deamination, such as the conversion of cytosine to uracil, is the cause of mutation (Mundry and Gierer 1958) (Fig. 5). Later it was shown by Vielmetter and Schuster (1960) with bacteriophages that in addition to the conversion C $\rightarrow$ U, the conversion A $\rightarrow$ H (hypoxanthine) is mutagenic. Hypoxanthine probably is "read" frequently as guanine in the reduplication process due to its steric structure.

Since xanthine seems to be read preferably as guanine, the conversion G → X is not mutagenic. The reactions A → (H) → G and C → U are the only remaining causes for mutations induced by HNO_2 treatment.

Optimistically speculating geneticists have for many decades hoped that one day it would be possible to extract genes from a cell, alter them by chemical means and reintroduce them into the cell. In the work of Mundry and

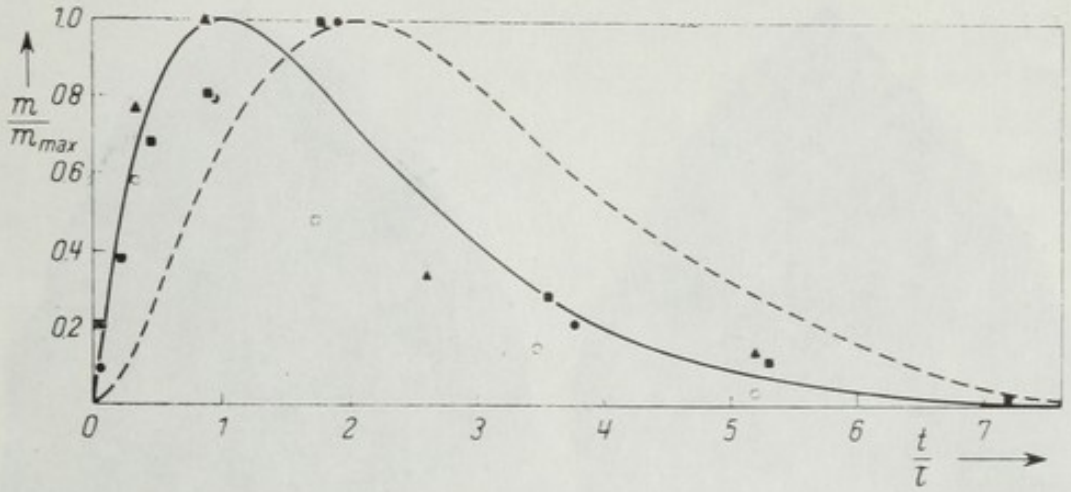


Fig. 5. Dependence of the number of mutant primary lesions (necrotic on "Java") relative to the maximum (ordinate) on the "dose" (abscissa, t = time of treatment with HNO_2, τ = time in which 1/e (37%) survivors in a particular experiment were still present). The experimentally determined values fit well with a one-hit curve ——— and not with a two-hit curve — — —.

Gierer, which is based on years of collaboration between biologists, chemists and physicists, this has actually been achieved. Some well-known biologists of Mendel's time were disappointed because Mendel had made crosses between lines of peas differing in only a few characters and had not made crosses between "species". Some farmers even today are angry with Mendel because they do not understand how genetics are applied in breeding. Many non-geneticists are probably disappointed because it is not yet possible to extract from human beings genetic material responsible for low intelligence and to convert it chemically into material responsible for higher intelligence. The better we understand the genetic material — particularly from what we have learned studying the genetics of viruses — the more it becomes clear that it is not at all well-suited for the type of alterations which Lamarck postulated as the cause of evolution. By an uncomprehensible disregard of all the facts, a lamarckian school of thought calling itself "progressive" insisted on adhering dogmatically and conservatively to concepts of the early 19th century, thereby hindering the actual progress of science and its application in practice.

Through the work of Mundry and Gierer (1958) whose results were quickly confirmed for bacteriophages (Vielmetter and Wieder 1959), bacteria (Kaudewitz 1959) and the transforming DNA of

pneumococci (Litman et Ephrussi-Taylor 1959), it was made quite clear that the two mutagenic steps A → G and C → U have not only quite different effects on the phenotypic appearance, but also affect different gene segments or even different genes. In *Drosophila*, using the ClB method, one observes only one group of mutants out of all the possible ones. Using the

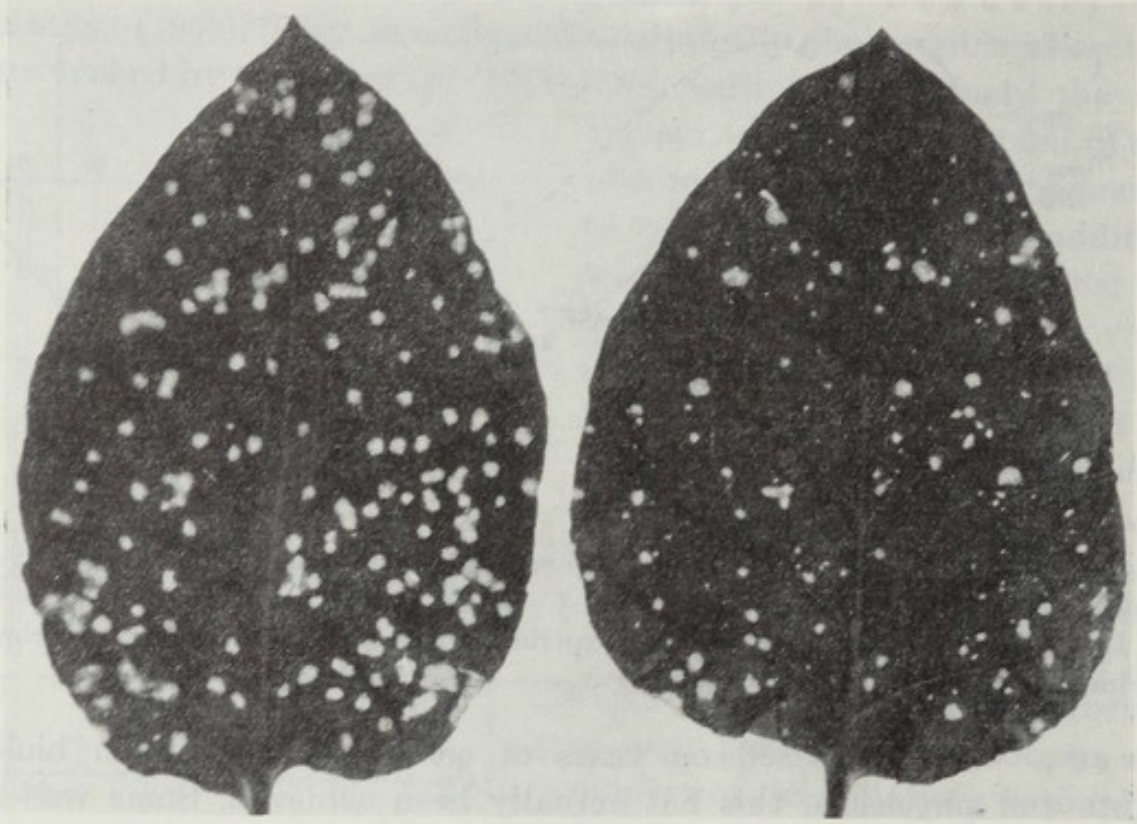


Fig. 6. Two leaves of *Nicotiana tabacum* "Xanthi necroticum". — Left: infected with TMV strain *vulgare*, untreated. "Control".The necrotic lesions are approximately equal in size. Right: infected with HNO_2 treated *vulgare*. "Experiment". The lesions vary considerably in size. Many of the variations are constant in further transmissions.

test on *Nicotiana sylvestris* or "Java tobacco", one likewise obtains out of all possible mutants just one group of easily countable mutants. But it was also shown in the work of Mundry and Gierer that several other symptom alterations appear after HNO_2 treatment of the RNA (Fig. 6 and Plates I—IV). It would be a great misunderstanding if one were to conclude from the application of the "systemic → necrotic test" in the HNO_2 experiments that it is possible to alter particular genes in a definite direction by chemical means. The alteration of an adenine to guanine or a cytosine to uracil has quite different consequences depending on the position of the altered nucleotide in the whole chain. This will be shown more clearly in the next section of this lecture.

3. Nucleic acid-protein correlations ("genetic code")

By the work of Gierer and Schramm (1956) and Fraenkel-Conrat (1956) it was shown that the protein of TMV contains no genetic material and cannot be part of the genetic material. The protein with its specific size, form, serological reactions and detailed amino acid sequence, which we know today, can be synthesized in the plant cell only if the RNA of the virus is introduced into the cell. "Characters" are observed in the protein (as in the symptoms which a virus produces) which are one way or another expressed under the influence of the gene, in this case, part of the RNA.

The symptoms of virus infected plants behave exactly like characters of an organism being genetically controlled. Often they depend not only on one gene but on several genes, on the entire genotype and also on external factors. This holds also good for the symptoms produced in virus infected plants. Whether the tissue would have a necrotic or systemic reaction to a definite virus will depend on the genotype of the plant (often on a particular one of its genes) and on external factors, above all the temperature. For plants with the genetic constitution *NN* coming from *Nicotiana glutinosa* and today incorporated in many varieties of *N. tabacum* like "Xanthi necroticum", all known TMV strains and mutants will cause a necrotic reaction below a certain temperature. Above this temperature infection will lead to systemic rather than localized necrotic reactions. (Jockusch 1966, Melchers, Jockusch and v. Sengbusch, 1966). Injury to the growth of the leaf blade which is caused systemically by some viruses strongly depends on external factors.

In contrast, the primary structure of the protein, i.e. its aminoacid sequence, depends exclusively on its nucleic acid, that is on the sequence of its nucleotides, as far as can be judged today. In any case, no difference in the composition of the coat protein could be found after multiplying the virus in quite different hosts (Aach 1960, 1961 a and b).

However, as observed by Jockusch in our laboratory (1964), there are both temperature sensitive and resistent strains and mutants of TMV at elevated temperature. Although it is at present unknown what alteration of the primary structure is required to convert a strain sensitive at higher temperature into a resistent one or vice versa it can be stated that the ability to form a resistent or sensitive coat at high temperature is a consequence of the structure of the protein subunits.

That the structure of the virus protein coat is highly specific for the virus and not the host has been shown by serological means. That there can exist differences in the aminoacid composition of coat proteins undetectible by serological techniques has recently been made apparent, e.g. v. Sengbusch (1965).

The most accurate description of the protein of TMV strains is the determination of the sequence of all 158 aminoacids (Tab. 1). We have reason to assume that the primary structure would determine the secondary (α-helix), tertiary (folding and winding) and, by consequence, quaternary structure (aggregation of the subunits to form the coat) (Anderer 1959). Although we do not yet know in detail how the special arrangements are determined from the linear sequence of the aminoacids, we have now one of the most intimate analyses

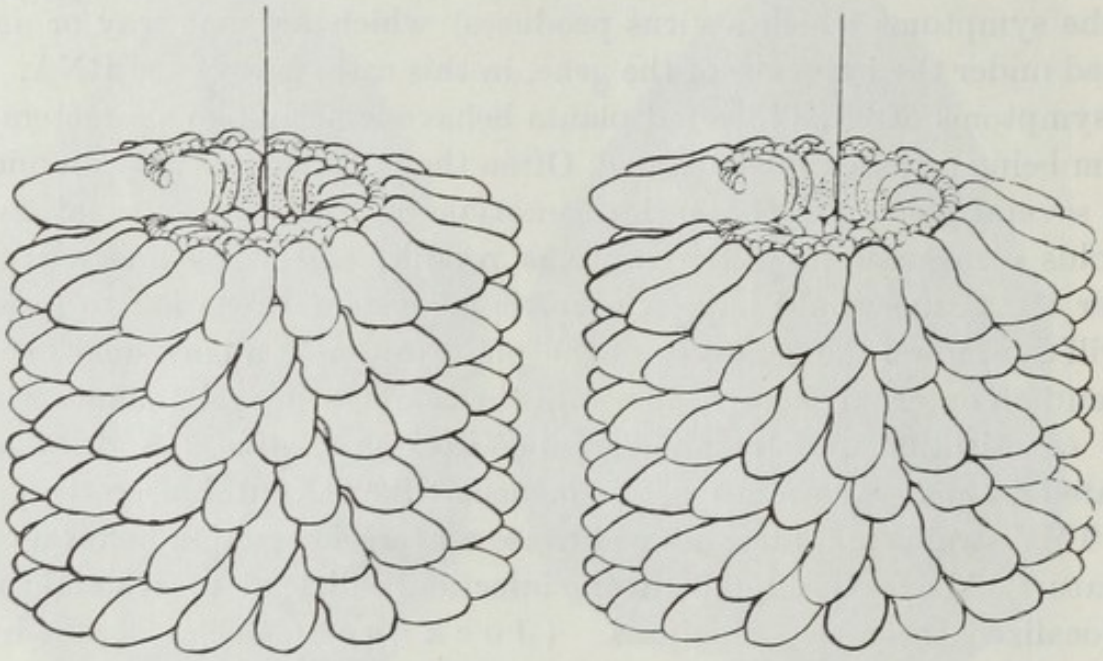
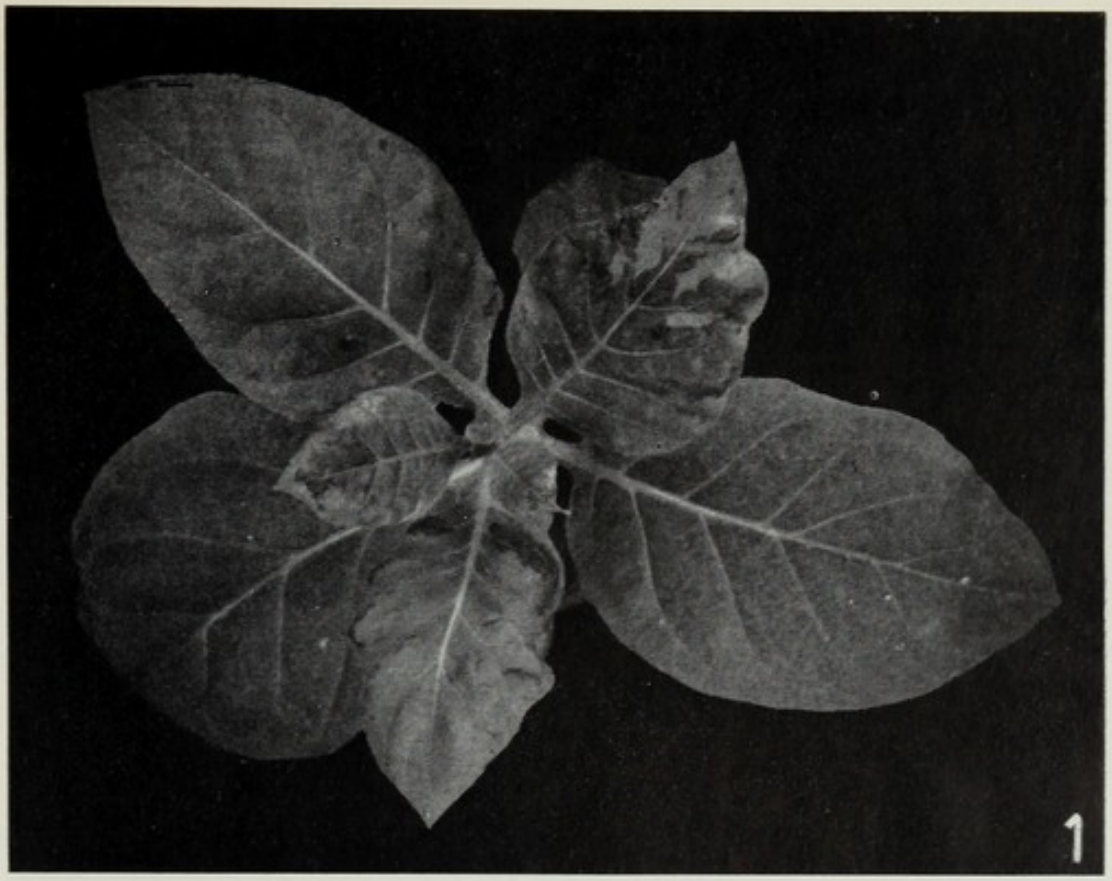


Fig. 7. Models of the quaternary structure of the TMV strain *vulgare* (left) and *dahlemense* (right) based on X-ray diffraction studies (Caspar).

of biological objects, the complete sequence of the amonoacids of the TMV strains *vulgare* and *dahlemense*, and many mutants showing only one or two exchanges, as compared with *vulgare*. At present, the knowledge of the primary structure of *dahlemense* and *vulgare*, differing in 29 positions, does not provide a physical explanation for the differences in quaternary structure observed in X-ray analyses (Caspar 1963; Caspar and Holmes 1966). (Fig. 7.) That one day this will be possible is hardly to be doubted. Exact knowledge of the aminoacid sequence of various TMV strains will be useful as soon as certain segments of the RNA chain will be correlated with certain segments of the protein chain. Such studies have been initiated (Mundry unpubl.).

Though not applying to them directly, the extensive analyses conducted by Wittmann and Wittmann-Liebold on spontaneous and, in particular, on HNO_2-induced mutations are of interest for the protein-nucleic acid correlation. The fact that the mutants screened on the basis of varying symptoms (Tab. 2) showed most frequently none, seldom one, very



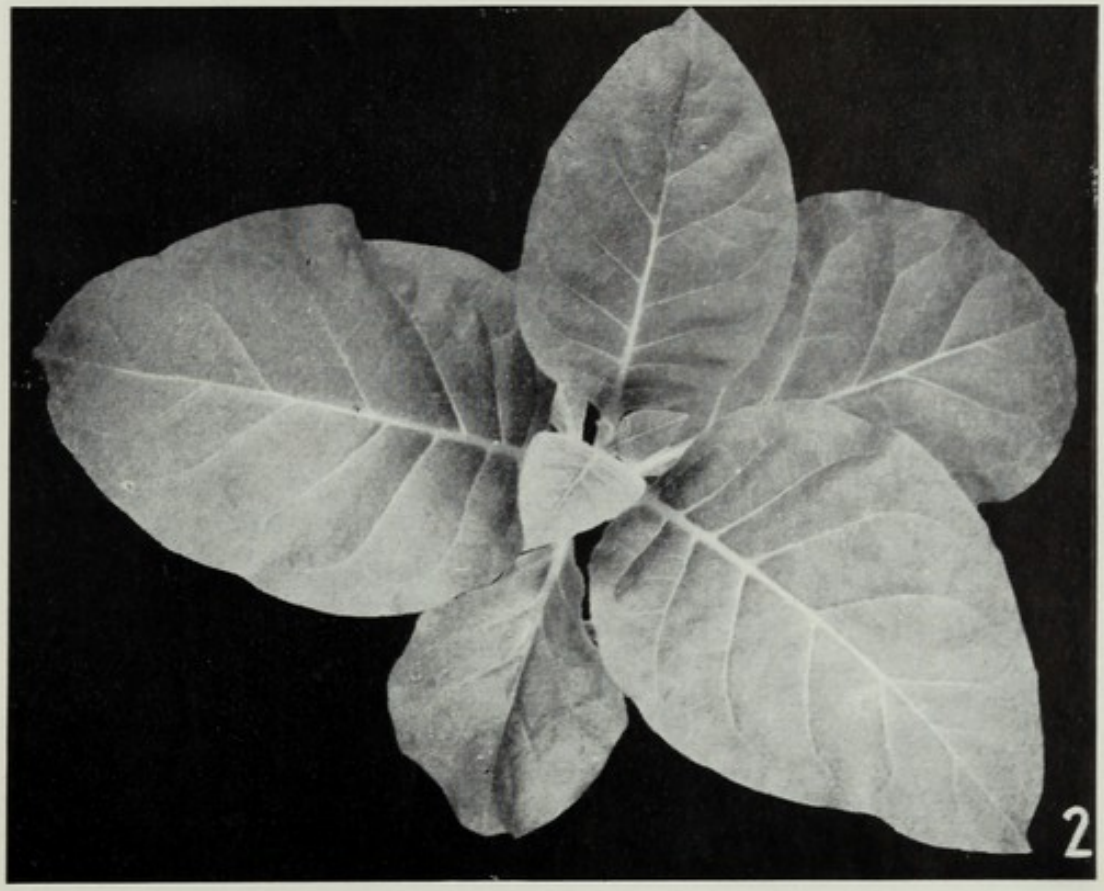


Plate I. Secondary symptoms of TMV strain *vulgare* (*1*) and nitrous acid mutant Ni 54 (*2*) on *Nicotiana tabacum* "Samsun". From Mundry and Gierer (1958, p. 624 + 625).

Plate II. Secondary symptoms of TMV nitrous acid mutants Ni 45(1) and Ni 18(2) on *Nicotiana tabacum* "Samsun". From Mundry and Gierer (1958, p. 624 + 625).

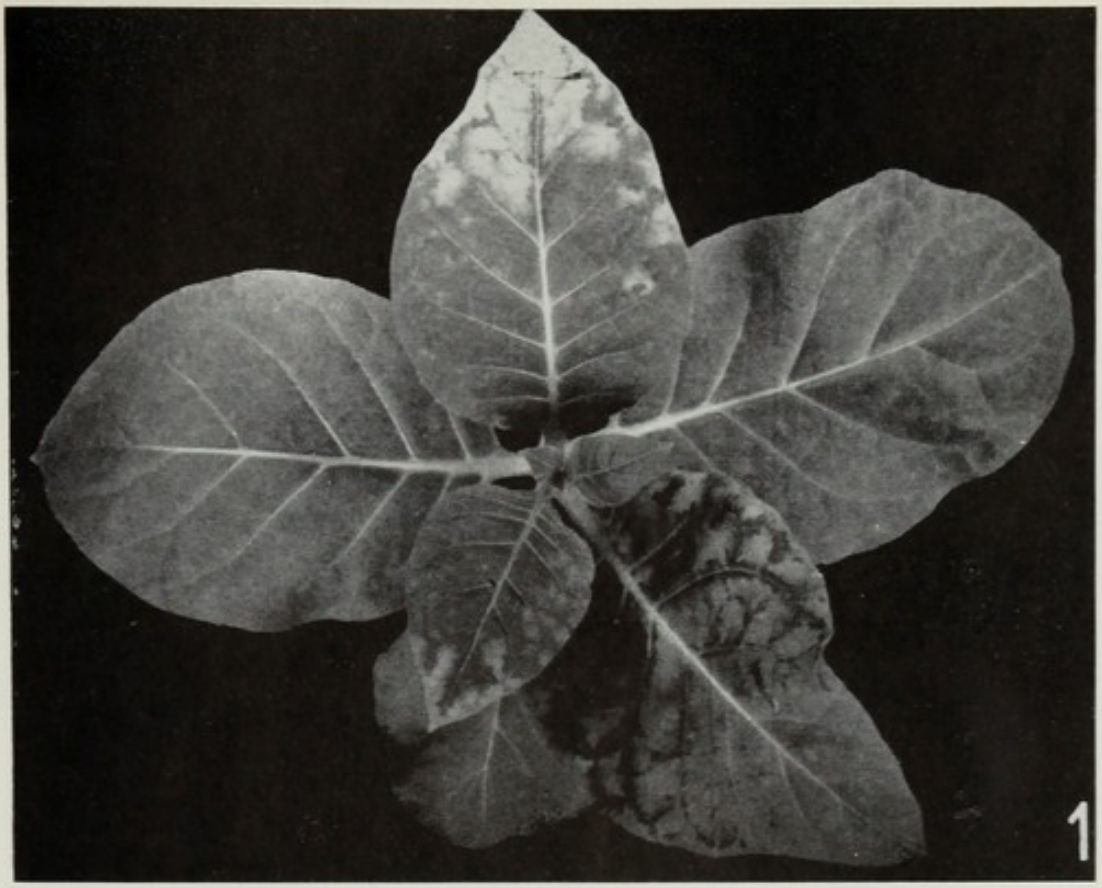


Plate III. Secondary symptoms of TMV nitrous acid mutants Ni 20(1) and 53(2) on *Nicotiana tabacum* "Samson". From Mundry and Gierer (1958, p. 624 + 625).

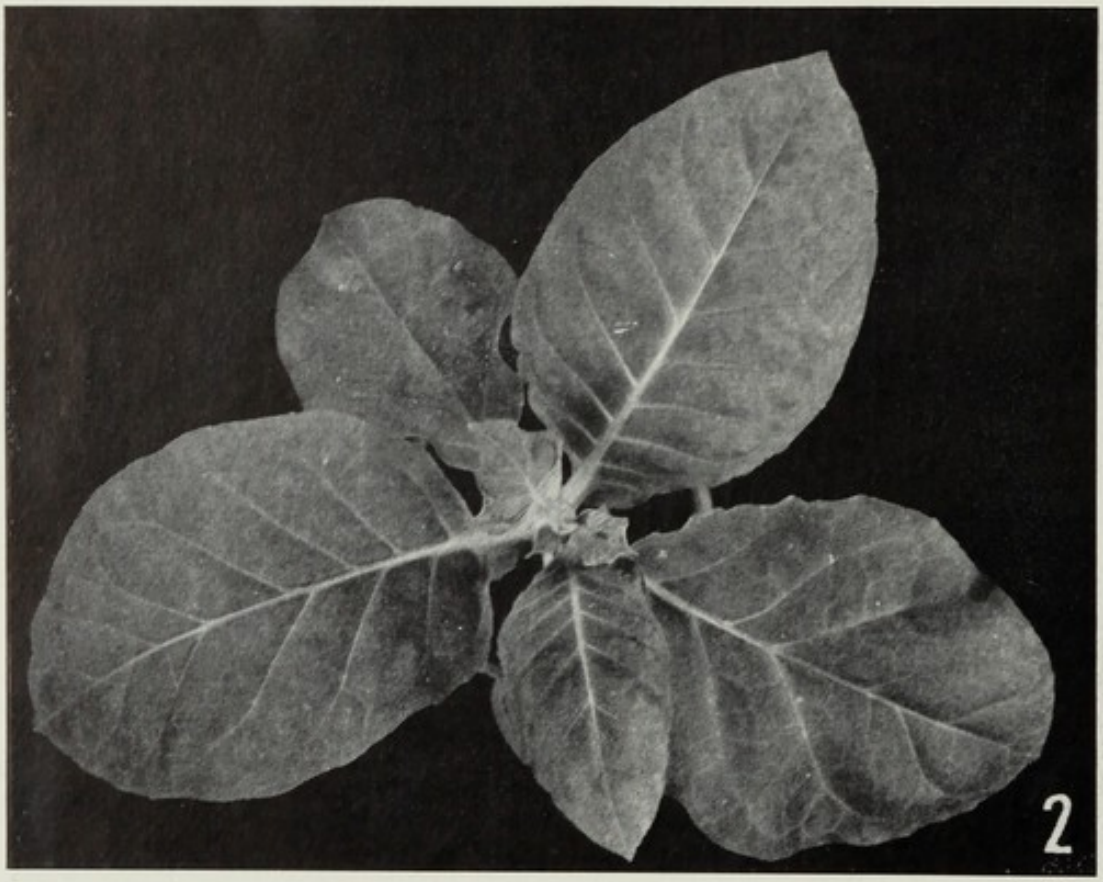


Plate IV. Secondary symptoms of TMV nitrous acid mutants Ni 12(1) and Ni 10(2) on *Nicotiana tabacum* "Samson". From M u n d r y and G i e r e r (1958, p. 624 + 625).

Tab. 1. The primary structure (aminoacid sequence) of TMV strain *vulgare* (V) and strain *dahlemense* (D), which was isolated from tomatoes. Exchanges in aminoacid occur in 29 positions (Anderer, F. A., Wittmann-Liebold and Wittmann 1965).

	1	2	3	4	5	**6**	7	8	9	10	11	12	13	14	15	**16**	17	18
V	Acetyl.Ser–	–Tyr	–Ser	–Ileu	–Thr	**–Thr**	–Pro	–Ser	–GluN	–Phe	–Val	–Phe	–Leu	–Ser	–Ser	**–Ala**	–Try	–Ala–
D	Acetyl.Ser–	–Tyr	–Ser	–Ileu	–Thr	**–Ser**	–Pro	–Ser	–GluN	–Phe	–Val	–Phe	–Leu	–Ser	–Ser	**–Val**	–Try	–Ala–

	19	20	21	22	23	**24**	25	**26**	27	28	**29**	**30**	31	32	33	34	35	36	*37*
V	Asp	–Pro	–Ileu	–Glu	–Leu	**–Ileu**	–AspN	**–Leu**	–Cys	–Thr	**–AspN**	**–Ala**	–Leu	–Gly	–AspN	–GluN	–Phe	–GluN	–Thr–
D	Asp	–Pro	–Ileu	–Glu	–Leu	**–Leu**	–AspN	**–Val**	–Cys	–Thr	**–Ser**	**–Ser**	–Leu	–Gly	–AspN	–GluN	–Phe	–GluN	–Thr–

	38	39	40	41	42	**43**	44	45	**46**	47	48	49	**50**	51	52	53	54	**55**	56
V	GluN	–GluN	–Ala	–Arg	–Thr	**–Val**	–Val	–GluN	**–Arg**	–GluN	–Phe	–Ser	**–GluN**	–Val	–Try	–Lys	–Pro	**–Ser**	–Pro–
D	GluN	–GluN	–Ala	–Arg	–Thr	**–Thr**	–Val	–GluN	**–GluN**	–GluN	–Phe	–Ser	**–Glu**	–Val	–Try	–Lys	–Pro	**–Phe**	–Pro–

	57	**58**	59	60	61	62	63	**64**	**65**	**66**	**67**	68	69	70	71	72	73	74	75
V	GluN	**–Val**	–Thr	–Val	–Arg	–Phe	–Pro	**–Asp**	**–Ser**	**–Asp**	**–Phe**	–Lys	–Val	–Tyr	–Arg	–Tyr	–AspN	–Ala	–Val–
D	GluN	**–Ser**	–Thr	–Val	–Arg	–Phe	–Pro	**–Gly**	**–Asp**	**–Val**	**–Tyr**	–Lys	–Val	–Tyr	–Arg	–Tyr	–AspN	–Ala	–Val–

	76	77	78	79	**80**	81	82	83	84	85	**86**	87	88	89	90	91	92	93	94
V	Leu	–Asp	–Pro	–Leu	**–Val**	–Thr	–Ala	–Leu	–Leu	–Gly	**–Ala**	–Phe	–Asp	–Thr	–Arg	–AspN	–Arg	–Ileu	–Ileu–
D	Leu	–Asp	–Pro	–Leu	**–Ileu**	–Thr	–Ala	–Leu	–Leu	–Gly	**–Thr**	–Phe	–Asp	–Thr	–Arg	–AspN	–Arg	–Ileu	–Ileu–

	95	96	97	98	99	**100**	**101**	102	103	104	105	106	107	108	109	110	111	112	113
V	Glu	–Val	–Glu	–AspN	–GluN	**–Ala**	**–AspN**	–Pro	–Thr	–Thr	–Ala	–Glu	–Thr	–Leu	–Asp	–Ala	–Thr	–Arg	–Arg–
D	Glu	–Val	–Glu	–AspN	–GluN	**–GluN**	**–Ser**	–Pro	–Thr	–Thr	–Ala	–Glu	–Thr	–Leu	–Asp	–Ala	–Thr	–Arg	–Arg–

	114	115	116	117	118	119	120	121	122	123	124	125	126	127	128	**129**	**130**	131	132
V	Val	–Asp	–Asp	–Ala	–Thr	–Val	–Ala	–Ileu	–Arg	–Ser	–Ala	–Ileu	–Asp	–AspN	–Leu	**–Ileu**	**–Val**	–Glu	–Leu–
D	Val	–Asp	–Asp	–Ala	–Thr	–Val	–Ala	–Ileu	–Arg	–Ser	–Ala	–Ileu	–AspN	–AspN	–Leu	**–Val**	**–AspN**	–Glu	–Leu–

	133	134	135	136	137	**138**	139	140	**141**	**142**	**143**	144	145	146	**147**	148	149	150	151
V	**Ileu**	–Arg	–Gly	–Thr	–Gly	**–Ser**	–Tyr	–AspN	**–Arg**	**–Ser**	**–Ser**	–Phe	–Glu	–Ser	**–Ser**	–Ser	–Gly	–Leu	–Val–
D	**Val**	–Arg	–Gly	–Thr	–Gly	**–Leu**	–Tyr	–AspN	**–GluN**	**–AspN**	**–Thr**	–Phe	–Glu	–Ser	**–Met**	–Ser	–Gly	–Leu	–Val–

	152	153	154	**155**	156	157	**158**
V	Try	–Thr	–Ser	**–Gly**	–Pro	–Ala	**–Thr**
D	Try	–Thr	–Ser	**–Ala**	–Pro	–Ala	**–Ser**

Tab. 2. Summary of mutants of the TMV strain *vulgare* analysed for aminoacid exchange by Wittmann and selected according to differences in symptom as compared with *vulgare*

exchanges	Number of mutants			
	nitrous acid	hydroxy-lamine	spontaneous	5-FU
0	112	5	8	8
1	35	1	5	3
2	7	0	2	0
3	0	0	1	0
> 3	0	0	0	0
sum	154	6	16	11

rarely two, and, as far as chemically treated material was concerned never more than two exchanges, leads to the following conclusion: By far not all of the approximately 6500 nucleotides are needed to determine the 158 aminoacids of the coat protein. That is, in TMV-RNA there is not only one gene (cistron) determining the coat protein, but also others for other characters.

Although it can never be ruled out that any particular mutant analysed by Wittmann and Wittmann-Liebold has been a spontaneous and not a HNO_2-induced one, the fact that there is a Poisson-distribution of number of aminoacid substitutions in the case of NHO_2-induced mutations is a good argument that the number of spontaneous mutants present in the samples prior to the treatment and other contaminating laboratory and greenhouse strains cannot be very large. [From 112 (= 73%) without exchanges one calculates according to Poisson: $e^{-m} = 0{\cdot}73$; 35·3 for 1; 5·6 for 2; 0·58 for 3; 0·04 for 4 exchanges (cf. Tab. 2, column 1 and 2)]. If, however, multiple replacements would appear with frequencies not following a Poisson-distribution, this would imply a selection of preexisting spontaneous mutants or contaminants, and would argue against their being produced by chemical treatment.

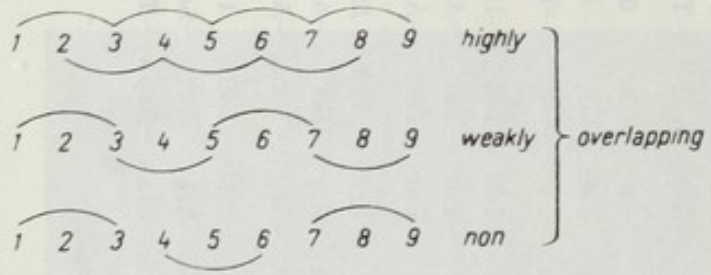


Fig. 8. Schematic representation of a highly, a weakly and a non-overlapping triplet code.

The conclusion of biochemical genetics that one gene (cistron) determines one enzyme raised the question of the existence of a "code" which should make intelligible the determination of the aminoacids from the nucleotide sequence. Such a code could be highly overlapping, weak by overlapping, or even non-overlapping, such as discussed by Gamov (1954) (Fig. 8). This question can be tested on the aminoacid exchanges of the TMV mutants. In the case of an overlapping code, i.e., if for example a cytosine-containing nucleotide

were to code for two different neighbouring aminoacids, the conversion of this particular C into U would cause an exchange of both of the neighbouring aminoacids. The exchanges which have been localized in the aminoacid chain of TMV do not show any evidence for this. The code is, therefore, non-overlapping (Wittmann and Wittmann-Liebold) (Fig. 9).

If one wants to code for the 20 aminoacids which are present in proteins with groups of the four existing bases — this must be done in order to understand how genetic information is translated from nucleic acid to protein — then obviously a group containing two bases, a so-called doublet code, does not suffice. In this case only $4^2 = 16$ different "code words" can be formed. If three are used (i.e, a triplet code), then using a triplet

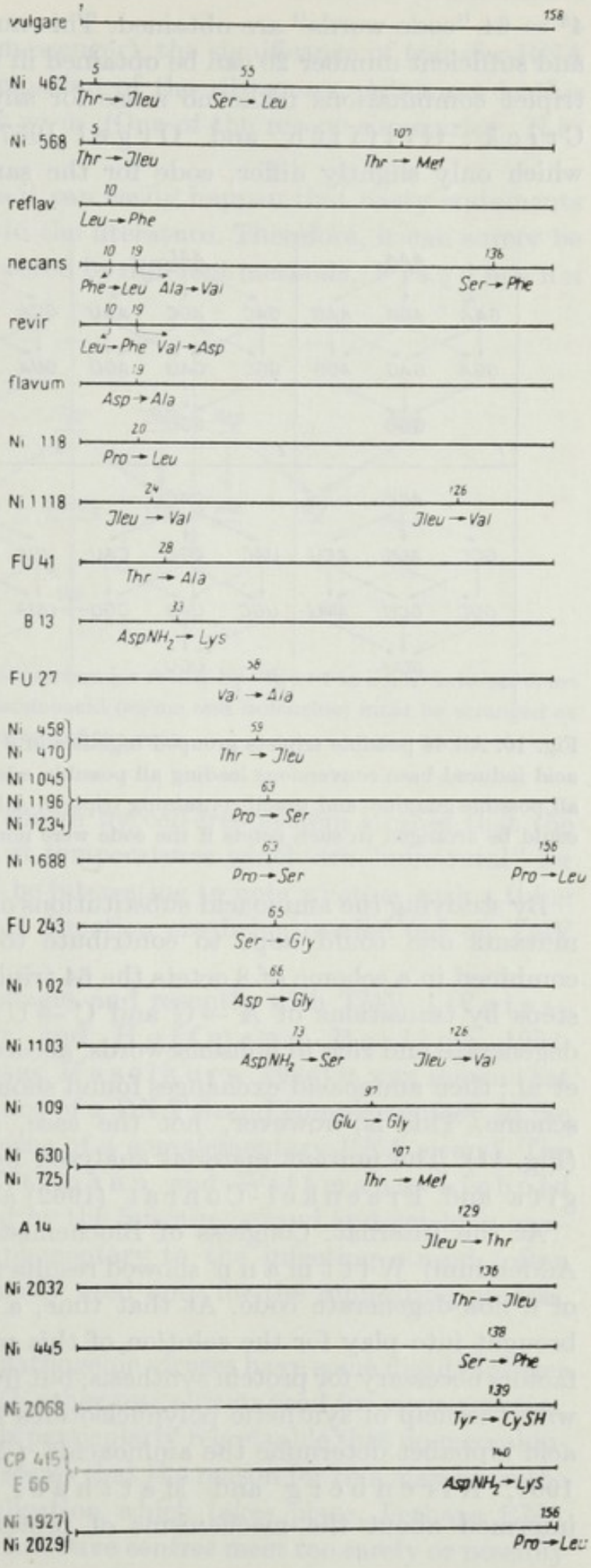


Fig. 9. Exchanges localized (up to autumn 1965) in the sequence of aminoacid of TMV coat protein for spontaneous mutants, mutants isolated after incubation with nitrous acid (Ni) and mutants isolated after fluoro-uracil (FU) treatment. For these cases in which more than one exchange occurs, the exchanges are not neighbouring, as would be expected for an overlapping code (from Wittmann-Liebold and Wittmann, 1965 a b).

$4^3 = 64$ "code words" are obtained. This number is too high. The necessary and sufficient number 20 can be obtained in two ways: 1. One assumes that 44 triplet combinations make no sense for any of the 20 aminoacids (see e.g. Crick, Griffith and Orgel 1957), and/or 2. Many code words, which only slightly differ, code for the same aminoacid (degenerate code).

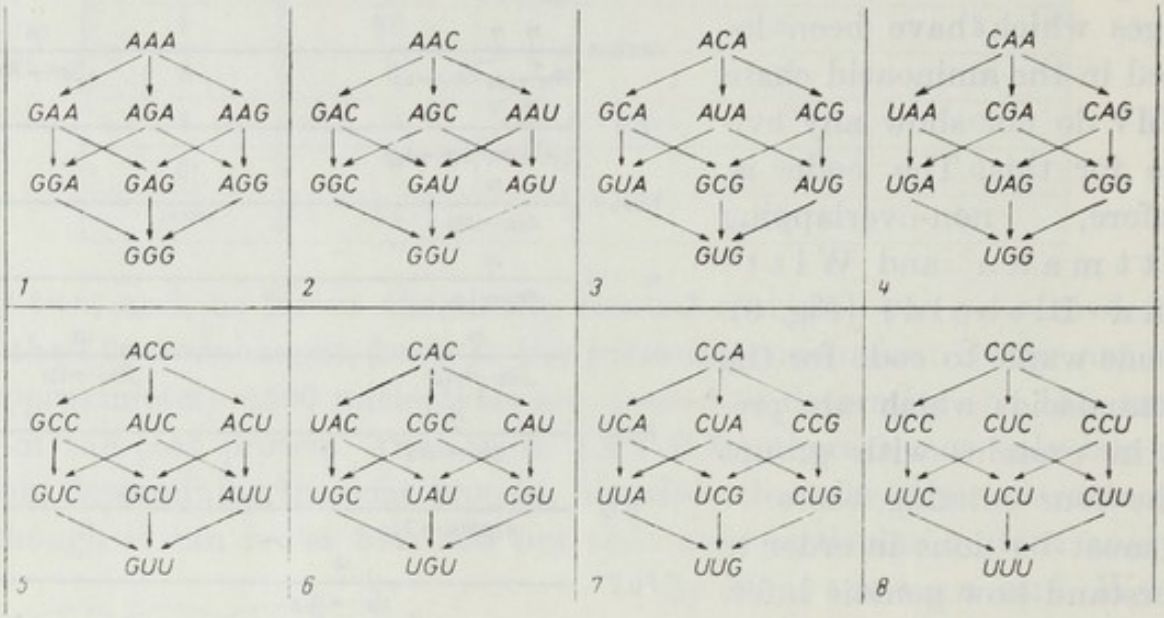


Fig. 10. All 64 possible triplets grouped together in 8 octet schemes depicting from the nitrous acid induced base conversions leading all possible adenine- and cytosine containing triplets to all possible guanine- and uracil-containing triplets. All aminoacid exchanges produced by HNO_2 could be arranged in such octets if the code were non-degenerate (Gierer 1961).

By studying the aminoacid substitutions of a large number of HNO_2-induced mutants one could hope to contribute to this problem. Gierer (1961) combined in a scheme of 8 octets the 64 triplets convertible in single mutagenic steps by transitions of A → G and C → U (Fig. 10). If the code were non-degenerate and rich in nonsensewords, according to the assumption of Crick et al., then aminoacid exchanges found should have agreed with such an octet scheme. This is, however, not the case, as Wittmann has shown (Fig. 11). The mutant material analysed by Tsugita (1962) and Tsugita and Fraenkel-Conrat (1962) also agrees with a degenerate code.

At the Internat. Congress of Biochemistry 1961 in Moscow (publ. in the Addendum) Wittmann showed results not consistent with the assumption of a non-degenerate code. At that time, a completely different method was brought into play for the solution of this problem: In systems containing all factors necessary for protein synthesis, but free from intact cells, it was revealed with the help of synthetic polynucleotides how the code words of the nucleic acid alphabet determine the aminoacids (Matthaei and Nirenberg 1961, Nirenberg and Matthaei 1963). Today, we are also well-informed about the mechanisms of protein synthesis, the transmission of

information from DNA to RNA (messenger), the significance of transfer-RNA (and its structure) and the participation of the ribosomes. Advances in this field storm upon us almost every week. (One of the recent summaries: Nirenberg *et al.* 1965).

At such a rapid pace of progress it can easily happen that hasty statements and poorly based findings appear in the literature. Therefore, it can surely be of value if the same question is answered by different methods. Friedmann

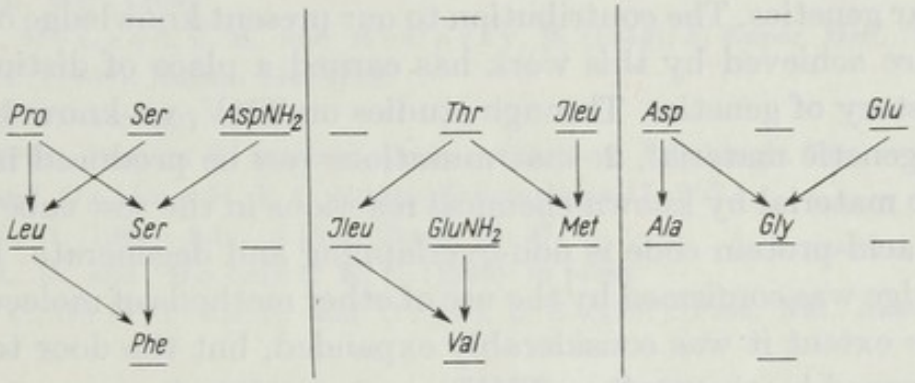


Fig. 11. Attempt to arrange the aminoacid exchanges found by Wittmann into an octet scheme (Fig. 10). The fact that the same aminoacid (serine and isoleucine) must be arranged at two different positions supports the degeneracy of the code.

and Weinstein (1964) have shown by cell-free system studies that the coding of proteins by nucleic acid at temperatures which are "unnatural" for the system is not error-free. It will be interesting to note whether such a thing occurs in vivo. Experiments in this direction are being carried out on TMV by Wittmann.

With RNA-containing bacteriophages and recently with TMV (Weissmann *et al.* 1964, Kaerner and Hoffmann-Berling 1964, Ammann *et al.* 1964, Shipp and Haselkorn 1964) it was shown that replication does not proceed by means of a DNA strand complementary to the infectious RNA strand, but by means of a complementary RNA strand. The results of the experiments of Wittmann and Wittmann-Liebold show that the protein is determined by the infecting strand and not by a complementary one. The strand complementary to the infecting strand (often called the minus strand) is apparently used only for the replication process.

As already mentioned, the phytopathogenic viruses have some disadvantages for genetic studies, as compared with other test objects used for virus genetics, above all, the bacteriophages: 1. It is particularly regrettable that no recombination analysis has been possible. It seems that the reason for this may lie in the type of RNA-dependent RNA replication which takes place. Perhaps RNA replication pools resulting from two infective centres meet too rarely or possibly

never. 2. The quantitative infectivity assay is notorious for its low "plating efficiency" and high fluctuation. 3. The quantitative mutation analysis is rendered difficult by interference and selection phenomena.

Although we had to renounce the recombination analysis and the surmounting difficulties in the infectivity and quantitative mutation test, we feel that we were rewarded by the success achieved from the work in cooperation with chemistry. The relatively large amounts of not very complicated nucleic acid and protein obtainable are the great advantage of the phytopathogenic viruses for molecular genetics. The contribution to our present knowledge of the genetic fine structure achieved by this work has earned a place of distinction in the 100 year history of genetics. Through studies on TMV, we know 1., that RNA can be the genetic material, 2. that mutations can be produced in chemically pure genetic material by known chemical reactions in the test tube, and 3. that the nucleic acid-protein code is non-overlapping and degenerate. Fortunately, this knowledge was confirmed by the use of other methods of molecular genetics and to some extent it was considerably expanded, but the door to this knowledge was opened by the work on TMV.

At the end of the previous section I mentioned that the invalidity of every evolutionary hypothesis, which deals with the direct effect of environmental factors on the hereditary substance in the sense of L a m a r c k , will be more understandable after an explanation of the principles of the genetic code. I hope that this is the case. Changes in the base sequence of nucleic acids can be induced by HNO_2 treatment by introduction of base analogues (e.g. fluoruracil) or by changes sometimes occurring from simple "accidents" in replication resulting from "mistakes" in base pairing e.g. spontaneously. Because of the degeneracy of the code such changes must not but may leap to an aminoacid replacement in protein. This replacement can be very important for the protein and for its significance in the organism — it can even be lethal! On the other hand, the replacement can also be of no particular consequence. A replacement of only one aminoacid can force the coat protein of TMV to become temperature sensitive. Yet, the difference of 29 aminoacids between the naturally occurring TMV strains *vulgare* and *dahlemense* has no influence on temperature sensitivity. Avoidance of the temperature sensitivity in spite of 29 aminoacid exchanges is plausible on the basis of selection. However, it is inconceivable at this time how the formation or avoidance of temperature sensitivity takes place by the direct influence of higher or lower temperature on the nucleic acid of TMV. The Lamarckian attempts to explain evolution, although they were possibe hypotheses in the first decades of the 19th century, have proven today as a result of experimental work to be completely idealistic and, if need be, psychologically explainable speculation.

* Acknowledgment. I am grateful to Dr. Larry Bockstahler for translating the manuscript n english.

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Principles of Immunogenetics

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I am very fortunate to be able to attend this Symposium, and to do honor to the work and memory of Gregor Mendel, the father of genetics. I propose to share with you a comment made a few years ago by a geneticist (Dreyfus) of Sao Paulo, Brazil, who stated that when anyone asked him about his "work" he replied that his work was fun, and he was paid for doing it. What more can anyone ask in this life than to have the opportunity of engaging in an activity that he or she prefers to any other, to consider it to be fun, and to be paid for it. Whether this debt to Gregor Mendel extends over 50 years, as Professor Crew stated, or over shorter periods, each of us owes a great debt to Mendel for establishing the principles on which our activities are based.

The term immunogenetics implies that this field includes the concepts, principles, and technics of both genetics and immunology. If one accepts the basic assumption that the antigens of living organisms are genetically determined, and that the production of antibodies may well depend at least in part upon the genetic make up of the antibody producing cells, the interlocking relationships of the two disciplines become readily apparent. In this paper some biological phenomena will be considered that have been made possible by the combination of these two disciplines, rather than to consider the principles of either discipline.

To date, the antigens of the erythrocytes have been given more attention that other aspects of this general subject. It is interesting that the first report[1] of individual differences in human blood — the well-known ABO system — was made in the same year as the rediscovery of Mendel's paper. A few years later it was proposed[2] that these antigenic characters of the erythrocytes were heritable. However, it was not until 1924 that the now accepted mode in inheritance was described[3], as the result of statistical analysis of the proportions of the your types. Two other systems, the MN and the P, were demonstrated[4,5] before 1930, but further search for additional characters during the next few years was not rewarded, and predictions were made that there probably were not other genes in man with antigenic effects on the erythrocytes than were then demonstrable. As is now well known, this predic-

tion of defeatism was dramatically exploded by a succession of events following the classical discovery[6] that a pregnant woman could be immunized against the cells of her unborn fetus. The majority of the cellular antigens in man that have been recognized, since this particular observation and explanation, have depended upon antibodies engendered during pregnancies or by transfusions.

Thanks to the recognition of the original ABO blood groups and the reciprocal appearance in the sera of the specific antibodies against them, and to subsequent findings, blood transfusions can now be made practically without hazard to the recipients. In addition, the knowledge of the heritable pattern of the respective cellular antigens has justified their use in disputed cases of parentage and in various aspects of medicolegal cases. Relatively recently, these cellular characters of man are being much more widely used than in previous years for studies of probable migration patterns and of similarities and dissimilarities among the races of man. The principal limiting factor for such studies is the supply of antisera specific for the respecitve characters.

The antigens of the ABO system have been demonstrated[7,8] in the majority of the tissues and organs of the body, if present on the erythrocytes, and in secretions[8], as saliva, in the presence of a secretor gene. One might anticipate that all the antigens of the erythrocytes would be present on the surfaces of all other cells of the body, because of the presumed presence of all the causative genes in the other cells, but this does not appear to be the case.

Compatibility of the antigens of the erythrocytes is not an accurate criterion for the successful transplantation of tissues. Recent reports[9] and much unpublished experimental material show that certainly the lymphocytes, and probably other types of white blood cells, may display antigens not demonstrable on the erythrocytes. Much current experimental work is designed to test whether the antigens of the leucocytes may be a safe index for successful transplantation of tissues and organs in man.

An almost unbelievable complexity of cellular antigens has emerged from studies in several species of animals other than man[10]. For example, the number of different combinations possible of the antigenic factors, or specificities, recognized on the erythrocytes in cattle is greater than many trillions-practically beyond comprehension by the human mind. A somewhat lesser number of factors is recognized in other species, such as sheep, pig, horse, chicken and mouse. Practically all these antigenic characters have been demonstrated following transfusions of blood between individuals of the respective species. Seemingly, the presumed small antigenic differences between individuals of a species are more readily demonstrated by antibodies produced by isoimmunizations than by those produced by heteroimmunization — i.e. immunization of another species.

In cattle, there are at present 11, possibly 12 or 13, genetic systems re-

cognized of the cellular antigens. These consist of very simple systems, such as the presence of a cellular antigen in comparison to its absence, and of complex system in which many antigenic factors may be recognized by virtue of the respective reactions with specific reagents. The most complex of these systems consists of 45—50 well-defined antigenic factors, of which a few may appear singly, but the majority are found only in combination with one or more other factors. The simplest explanation of the genetic pattern in this complex system is to assume a series of multiple alleles, more than 275—300 being known at the present time. But as has been noted in all other series of multiple alleles that have been intensively studied, recombination has been observed between allelic product that for a time acted as units in inheritance, and this also seemingly obtains among the antigenic factors of this system. Hence it is reasonable to conclude that the causative genes form a complex locus, with recombination possible among the antigenic products.

In this connection it should be stated that experience with other organisms allows the proposal that if two alleles are present in a fairly high frequency in a poplulation, it may be expected that occasionally the two should be found on the same chromosome. On this basis the genes for contrasting cellular antigens should occasionally behave as a unit. In man, for example, the low frequency of the gene for the B blood group might mitigate against its union with the gene for A, eccept possibly in some Asiatic populations. However, the frequencies of the alleles for M and N are 0·531 and 0·468[8], respectively, suggesting that infrequently the two alleles may be present on the same chromosome. This condition could account in part for the observed excess of MN offspring from inter se matings of MN individuals.

The cellular antigens provide genetic markers that can be routinely used for solutions of cases disputed parentage in domestic animals, particularly if the economic value of the individual animal is high. In addition, such genetic markers may reveal biological events that could not otherwise be detected. For example, owners of cattle have known for centuries that the female born twin to a male in cattle usually is infertile. About 50 years ago it was reported[11] that there was a union of the circulatory systems of cattle twins in utero, providing an explanation of some kind of influence of the male in the female twin. The 20 years ago it was found [12] that cattle twins could possess two kind of red blood cells-those conforming to its own type and those to the type of the co-twin. The explanation offered at that time still is accepted, that the cells ancestral to the blood forming tissues migrate from each twin to the other by virtue of the union of the circulatory systems, become established and produce teir own type of blood cell thereafter.

Thus the anastomosis of the circulatory systems of twins in cattle results in (a) two types of blood cells in the twins, and (b) infertility accompanied by

varying degrees of abnormal development of the sexual organs in the female of the twins. But if there is no admixture of the blood of twins in cattle of unlike sex, the female is as fertile as if born singly. Twin births in cattle are relatively infrequent, while in sheep twin births are common, but erythorcyte mosaicism is a rare event. One recorded case[13] of such mosaicism in a female of unlike sexed twins in sheep indicated that the female was infertile. In ontrast, erythrocyte mosaicism of unlike sexed twins in humans has not been accompanied by infertility of the female[8]. In brief, one can easily explain the two kinds of blood cells in twins of any species if there has been anastomosis of the blood vessels in utero, but the reason for the accompanying effect upon the sexuality of the female in some species and not in others is still unexpalined.

The ability of each twin in cattle to carry two kinds of blood cells posed a problem, primarily because the foreign type of cells might produce an immune response, even death, if administered after immunological competence had been attained following a single birth. The situation existing in cattle twins could be explained by assuming that antigens foreign to an individual could be "tolerated" if introduced during embryonic life, presumably before the cells of the embryo were able to respond to the invasion of foreign substances. This explanation was in accord with one theory of antibody production[14], and has been experimentally tested by M e d a w a r and co-workers[15], among others, who subjected embryos to a foreign antigen and demonstrated their tolerance to that antigen following birth. A totally new field of a study of what is called "actively acquired tolerance" has resulted from these findings. One general result of this area of research has been the recognition that some immunological competence is possessed by individuals at an earlier age than had previously been believed to obtain, and that tolerance may be induced in adults, at least in some species and to certain antigenic substances.

The succes of failure of a tissue graft to grow in a recipient depends upon the genetic similarity between the donor and recipient. Rejection of the graft indicates an immune response on the part of the recipient to a foreign tissue, and standard genetic procedures can reveal the minimum number of genes by which the donor and recipient differ. The recognition that a genetic basis could be provided for the study of tumors arising in experimental animals provided new life for the study of tumors, at a time only three decades ago when other approaches in these studies had resulted in severe disappointments[16]. One early observation[17], that the transplantation of a tumor from one strain of mice into another strain resulted not only in the rejection of the tissue but also in the production of antibodies for the erythrocytes of the donor, was the initial step in uncovering a complicated gene complex (the H_2 locus). This gene complex has major effects on the histocompatibility of normal and tumorous tissues, and also on antigenic factors of the red blood cells, so that tumors

arising in an inbred strain can be analyzed for any change that may have occurred at this major locus.

One may well ask whether hemolytic disease of the newborn occurs in other species that man. In some species, as the horse, the female may be immunized by the cells of the fetus, but the antibodies pass to the young only through the colostrum. In other species antibodies may be induced in the mother by immunizing her with blood cells containing antigens of the male to which she is mated, and the cells of the fetuses may be coated with the antibodies from the mother through the placenta, sometimes without harmful effect, as in the rabbit, or the placenta may be impermeable to the antibodies and the young will be subjected to the antibodies only by way of the colostrum, as in the dog and the pig. In the chicken, and presumably in birds in general, antibodies engendered in the female against the cells of the male can be passed on to the chicks by way of the egg yolk, and can produce hemolytic disease, often causing death. However, all attempts to produce hemolytic disease of the newborn in cattle have failed. Even if the female carried a high titer of antibodies against the blood cells of the calf, no harmful effects on the cells of the calf have been observed. (See Stone and Irwin[18] for specific references of this subject.)

Nearly all the cellular antigens of the various species of animals studied to date appear on the cells of an individual only if present on the cells of either or both parents. Exceptions to this general rule have been noted in man and in sheep, i.e. the Bombay type in man in which an independent gene inhibits the expression of the genes for A and B[19,20], and the recessive gene in sheep which inhibits the expression of the R antigen[21].

Another exception has been noted in certain species hybrids in pigeons and doves, and also in rabbits, *Drosophila* and possibly in cattle, in which an antigenic factor may appear in the offspring that is not present of the cells of either parent, or of either parental species. This has been called a "hybrid substance", or an "interaction antigen". Let us use an example in which the hybrid substance appears only on the cells of heterozygotes for recognizable antigens[22]. If the assumption is made that the genes effecting the recognizable antigens of the parents produce these antigens and also by interaction the "hybrid substance", a model is provided for a molecular explanation of heterosis. That is, certain genes as heterozygotes can accomplish the same effect as in the respective homozygotes, and an interaction product in addition.

Perhaps the most fundamental question to be answered in the genes for the cellular antigens act only to effect this recognizable product, or do they participate also in physiological processes. Authorities in population genetics have proposed that neutral mutants are likely to be eliminated from a population, unless they posses a selective advantage as a heterozygote. In this basis, the multiplicity of mutans effecting cellular antigens should be evidence for

some kind of significant effect of the causative genes, at least as heterozygotes. In man, for example, is the higher incidence of duodenal ulcer in persons with group O than in those with A, B or AB an index of some fundamental difference in function of the tissues of the digestive tracts of these types (see Race and Sanger[8] for references)? In chicken, certain genes in one of the systems effecting cellular antigens have been shown[23] to be associated with differences in mortality of the embryos, and certain heterozygotes in this series have an advantage over homozygotes in the expression of different characters[24,25]. These observations provide evidence of a physiological effect in these species apart from the antigens of the erythrocytes.

Early in this century, when the prevailing belief attributed immunological specificity solely to proteins, an eminent biologist discounted the idea of genetic control of the proteins by which species could be differentiated[26]. Other authors reported[27,28] that the proteins of closely related species, such as of the horse and the donkey, could be differentiated only with difficulty, if at all. Sometime later, however, segregation according to genetic expectation was observed of serum antigens, undoubtedly proteins, in the backcross offspring following crosses between species of doves[29]. Also, differences in the antigens of the serum of man were demonstrated by immunological technics[30]. The modern technics of studying proteins by their migration in a gel have revealed genetic control of proteins within species, a rapidly developing field of research. One can state with confidence that genetic diversity can be anticipated in each of the different proteins of all, or nearly all, species of higher animals.

The same question can be posed concerning the possibility of pleiotropic effects of the genes producing proteins that was raised for the genes effecting cellular antigens. That is, is the protein their main product, or are the different forms of the proteins also associated with differing degrees of physiological functions?

One definitive use of all the antigens will be to provide genetic for many kinds of genetic projects that will not be considered here. Only one will be mentioned — the genetics of somatic cells. It and other areas of genetics are to be considered in detail in subsequent sessions of this symposium.

Attention should be called to antigens of a lower form of life, the *Paramecium*[31]. These antigens are proteins and are found at the surface of the cilia. There are different antigenic types, under genetic control, with the unique feature that only one of the alternate forms is expressed at a time [31]. Their ability to change from one antigenic type to another in response to various stimuli, usually predictable, appears to be the only example presently known of the antigenic characters being influence by their environment.

Finally, although the antigens of bacteria provide models for some understanding of the cellular antigens of animals, mention will be made only of the antigens of the pneumococci. Prior to the demonstration that the immunolo-

gical specifity of the different types of the pneumococci depended upon the carbohydrates of the capsular wall[32,33], it was firmly believed that only proteins could impart this specificity. And, from studies on the transforming principle of the same organism came another outstanding discovery, namely, the first evidence that the gene substance itself was not protein, but deoxyribonucleic acid (DNA)[34].

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Paper No. 1043 from the Laboratory of Genetics, University of Wisconsin. The research from this laboratory to which reference is made was supported in part by Public Health Service Research Grant Al-01643, from the National Institute of Allergy and Infectious Diseases.

Mendel and Evolution

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The influence of M e n d e l ' s discoveries on our understanding of evolution is far too great and far-reaching for it to be possible, in a short lecture, to deal with all aspects of it. The theory of evolution rests on two foundations; one is D a r w i n, the other Mendel. They are of equal importance. Neither could provide the basis for an adequate theory without the other. I shall first sketch the ways in which Mendelism fills the gaps which Darwin's theories still contained I shall then pass rapidly over the main achievements of Mendelian evolutionary genetics in its classical days from 1920 onwards; and finally devote rather more time to discussing the new directions which evolutionary genetics seems likely to take in the next few years.

The main lack in Darwin's theory of evolution was his inability to provide any consistent and firmly-based account of heredity. He knew neither the nature of hereditary transmission, nor anything about the origin of new hereditary variation. Concerning hereditary transmission, he adopted the idea of blending inheritance which was current among most biologists at that time. It was soon pointed out, however, that a system of blending inheritance will lead to the disappearance of hereditary variation. When different variants interbreed, their offspring will be intermediate and a population in which cross-breeding occurs will soon be reduced to a uniform average type. No variation will be left on which natural selection can operate. This dilemma could be avoided if new variation is continually being created. It was in order to find some agent that would continually produce new hereditary variation that D a r w i n became attracted to the idea of the inheritance of acquired characters; if the environment itself causes new variants to appear, the loss of differences which blending inheritance brings about be of less importance.

The re-discoverers of M e n d e l almost immediately realized that the knowledge solved both of Darwin's problems. Inheritance is not by new blending; hereditary variation is carried by discrete, more or less permanent factors, which may mingle in hybrids, but which can then segregate again in their original purity. Cross-breeding does not, therefore, involve any necessary loss of variation. Moreover, the Mendelian factors, although very stable, were soon found to mutate occasionally, thus providing a source of new varia-

tion. It was only when the Mendelians added these two points to Darwinism that the theory of evolution acquired a fully convincing intellectual structure. Moreover, by pointing out that there is no inherent tendency for variation to disappear, and that in any case some new variation is appearing all the time, the Mendelian discoveries removed the temptation to invoke the inheritance of acquired characters to get over these difficulties, and left the question whether such inheritance does or does not occur as a purely factual matter to be decided on the weight of the evidence. As is well known, the evidence is strongly against the Lamarckian idea.

In the early years after the re-discovery of M e n d e l , problems connected with the contrast between discontinuous and continuous variation played a great role in biological thought. Darwin had considered that evolution is in the main based on small scarcely appreciable variations from the norm. Some early Mendelians, such as d e V r i e s , were inclined to attribute much greater importance to well-defined, discontinuous variants. In Great Britain, the question was confused by the unfortunate controversy between B a t e s o n , who had come to see the importance of Mendelism through his studies on naturally-occurring discontinuous variants, and W h e l d o n , a statistician whose technical methods led him to deal almost exclusively with continuous variation. As a matter of facts, the possibility of reconciling the two views had already been stated before the controversy reached its height. In the very first years of the century, the statistician U d n e y Y u l e , who was a Fellow of the same Cambridge College as B a t e s o n, had published a short paper in which he showed that a character which is affected by many pairs of Mendelian factors will exhibit the phenomena of continuous variation in just the form which the statisticians described. In the heat of the B a t e s o n - W h e l d o n debate, the paper was overlooked, but the point had actually been made that Mendelism is applicable to the kind of minor deviations from the norm which D a r w i n had believed to provide the basis for evolution. And in countries other than England, the application of Mendelian ideas to continuous variation proceeded steadily, particularly at the hands of plant breeders, such as N i l s s o n - E h l e in Sweden, working with wheat, and E a s t and other corn breeders in the United States. After the disappearance of W h e l d o n , and the rise of a new generation of statisticians, such as F i s h e r , the point became accepted even in England.

With this acceptance, the basis was complete for what one may call the classical period of Mendelian evolutionary genetics. There is no time now to do more than mention the main headings of this tremendously productive period of biology, whose content will I am sure be well known to all of you. There are perhaps three major divisions of the field. First, the analysis of the variation occurring in natural populations, a subject in which much of the leadership has been provided by bilogists of Russian origin. T c h e t v e r i k o v was

probably the first to point out that the phenomenon of dominance makes it possible for a great deal more hereditary variation to exist in a population than appears on a superficial examination. Apart from the vigorous Russian school within the Soviet Union, one may mention T i m o f é e f f - R e s s o v s k y , who did much of his work in Germany, and D o b z h a n s k y , who worked in the United States. A second major field of advance was in the observation of, and experimentation on, processes of natural selection which are actually occurring at the present day. I need only mention work on such topics as the inversions of *Drosophila pseudo-obscura*, industrial melanism in moths, insecticide resistance, and so on. Finally the third major field was the development of an extensive and well-knit mathematical theory by H a l d a n e , W r i g h t and F i s h e r and their followers.

This whole complex of experiment, observation and theory is one of the great triumphs of modern biology, and it is, as I have already said, of far too great a magnitude to be even summarized here. It would be, perhaps, a fitter tribute to Mendel's importance for the study of evolution, to forego any further attempt to evaluate his influence on the past and to consider what may be his role in the future developments of evolutionary thought.

Here I shall pay him what may seem a rather paradoxical compliment. I believe that the time has come when we need to recognize just in what way Mendel's genius operated; and that will involve the realization of the limitations as well as the achievements of his thought. The discovery of new fundamental entities in science, and the formulation of the rules of their behaviour, always involves a powerful act of abstraction from the complexities of more superficial levels. It is success in performing such feats of simplification that is the true mark of genius. But in the process something must be left out of consideration, namely the complexities which are not relevant to the matter in hand. M e n d e l was able to discover the existence of discrete hereditary factors just because he refused to allow himself to be diverted into considering the epigenetic mechanisms by which these factors produce the corresponding characters. He went straight from factor to character; everything in between, that is, the whole of development, was irrelevant to the problem of hereditary transmission with which he was concerning himself. But there is no reason to suppose, in fact every reason to deny, that development is irrelevant to the theory of evolution; and the same is true of several other matters which M e n d e l left on one side in his beautifully executed act of seizing on one deep-lying truth. The time seems to me to have come when we should attempt to bring some of these matters back again into our evolutionary theories.

In classical evolutionary genetics, the relation between one generation of an evolving population and the next was conceived of in very simple terms; the genotypes of generation n gave rise to those of generation $n + 1$ through a process of reproduction which involved Mendelian segregation, recombina-

tion etc., and the only factors of fundamental importance were mutation and natural selection (processes such as migration being sometimes influential, but not essential parts of the basic evolutionary mechanism). A moment's thought is enough to reveal how much has been omitted from this picture. In the first place, natural selection does not act directly on genes; it operates on phenotypes, that is to say on the results of the developmental or epigenetic activities controlled by the genes. Moreover, one must remember that the environment contributes to the character of the phenotype. The natural selective value of an organism may be affected by the environmental contribution as well as by the genetic. To put it in another way, an organism may be selected for the way in which its developmental system has reacted to the environmental stresses to which it has been exposed, just as a horse may win a race as much because it has been well trained as because of its hereditary constitution.

This point of view has already stimulated some new experimental approaches to well known evolutionary problems, and has resulted in the discovery of one quite novel type of phenomenon. For instance it has been shown that, as might be expected, the capacity of an organism to respond in particular ways to environmental stresses impinging on it during its development is a hereditary character, determined by its genotype. One can therefore successfully practise selection for the ability to produce a certain phenotype in response to some particular stress. Natural selection can certainly do the same thing. For instance, if *Drosophila* larvae are kept in media to which sodium chloride has been added in sub-lethal concentrations, the survivors have slightly enlarged anal papillae. If such cultures are kept for many (say 20) generations on gradually increasing concentrations of salt, natural selection not only brings about an improvement in the percentage of survivors, but has two effects on the enlargement of papillae. Firstly, the larvae in later generations show a much great teadiness to respond to the presence of excess salt during their development by producing enlarged papillae. Secondly in these selected generations, the size of the papillae is larger, at all concentrations, than it had been in the original stock. In fact, if an egg from a late generation is allowed to develop on normal medium (with little salt) it gives a larva whose anal papillae are larger than those produced by eggs of the original stock grown on salted medium. The enlarged papillae, which could be regarded as being a typical "acquired character" in the original stock, produced only under the environmental stimulus of the salted medium, has in the later generations become a typically "inherited character", produced even when the food is not salted.

This conversion, by selection, of an acquired character into an inherited one, is the novel phenomenon mentioned above. It is usually referred to by the name "genetic assimilation". I have discussed it at length in several publica-

tions (1) and will say more about it here, except to emphasize again that it is a strictly Mendelian process, depending on the operation of selective pressures on population genotypes. No genetic assimilation takes place if selection is not practised, or in situations (such as with inbred stocks) in which selection cannot be effective. The experiments which demonstrated these last two points also provide clear evidence against any direct inheritance of acquired characters. Genetic assimilation produces the same end-result as the inheritance of acquire characters, but by a Mendelian instead of a Lamarckian mechanism.

In studies on genetic assimilation and related problems, a beginning has been made in the investigation of the importance of the developmental processes of organisms for their evolution. There is another category of topics in "post-classical" Mendelian evolutionary genetics to which I should like to draw attention. These are subjects which biologists are only just beginning to think about, and very little work on them has yet been undertaken. An animal species, in its evolution, has to meet the challenges which natural selection by the inorganic or biotic surroundings will present to it in the future. There is no way in which the population at a given time is history can foretell what these future pressures will be; possibly it will find itself confronted with another Ice Age, or with a new parasite or predator. The species is, one might say, faced with the problem of deciding what evolutionary strategy it will adopt. Will it evolve into a form which has an extremely flexible developmental system, so that any variation in the environment produces a changed adult form? An example of such species would be those of *Daphnia*, in which the adults differ in nearly every pond and in all the main seasons of the year. An alternative strategy is that of the mouse, for instance, which is hardly modified in even the most extreme environments. Of course it is clear that a species does not have a "species intelligence" by which it can consciously adoopt a particular strategy; but in a large evolving, sub-populations may change along several of possible alternative pathways, and this will amount to the testing of various strategies, the most effective of which will emerge as the overall direction of the evolution of the species.

The mathematical theory appropriate for discussion of choices of strategy is that of Games Theory and Linear Programming. It seems likely that such methods will find many applications to the theory of evolution, not only in connection with the question of developmental flexibility or canalization, which has just been mentioned, but perhaps particularly in relation to animal behaviour. The classical theory did not sufficiently recognize that natural selection is not a completely external agent to which the evoliving animal is subjected, but is to a considerable extent itself an expression of the genotype on which it acts. Animals frequently choose the environment in which they spend their lives, and often modify it by their activities, in building nests, burrows and so on. In the general case, we have to face the intellectual difficul-

ties implicit in the fact that the organism's genotype causes it to select the type of environment which will then exert selection pressure on it. Some gene mutations may in fact at least partly escape from natural-selective competition with the older types because they cause their possessors to alter their habits in such a way as to exploit new habitats or food-stuffs. This is a feed-back relation of a rather subtle kind. The theory of such processes falls in the province of cybernetics. This branch of mathematics also has very obvious importance for the theory of developmental processes in general.

In the classical period of Mendelian evolutionary genetics, the form in which the general theory of the subject was elaborated was that of the statistics of variation, combined with differential, integral and finite difference equations. The present discussion leads to the suggestion that the next phase in the application of Mendel's principles to evolutionary problems will demand a theory worked out in terms of some of the newer types of mathematics, such as Games Theory and Cybernetics.

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Discussion Contributions

On the Chemical Theory of Heredity

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A short account of the genetic development shows the following concepts.

For M e n d e l the most important fact was the combination-computation, the basis of two paternal factors. But for the results he received, the factors corresponding to the physical appearance were not sufficient therefore he stated "Dominance (recessivity)". These cannot be deduced from combinations, but has to be added to them and goes beyond the factor theory. Also the assumption of a mediatorcell in crossing very different individuals cannot be included in the factor theory. Logically thinking M e n d e l knew this, but he was unable to continue his work in this field. He could not have thought of chemical genetic reactions, as biochemistry in our modern sense was non-existend. Not even the Swiss chemist F r . M i e s c h e r could find a suitable expression, though he stated nucleid acids to be the chemical basis of heredity already in 1872. After M e n d e l he should be regarded as the second founder of genetics.

After 1902, the year of the rediscovery of Mendel's rules, the gene-theory was based on the same combination concept with many ad hoc new factors. That this theory could not explain the change of dominance and other changes has already been observed by J a n k o w s k y when he stated the principles of a chemical heredity theory in 1934 and 1941.

When the chemical structure of nucleid acids were established, it was sure that the genes have a chemical basis and for about a decade a new theory on this has been expanded. Its principle is only partly chemical, partly it is based on logical non-chemical factors replacing gradually the morphological mosaic by physiological equilibriums (feed-back etc.). If here are still existing concepts of the gene-theory, they are due to historical development. This actual theory is not satisfactory, for the enormous amount of literature in this field shows as many contradictions as well as progress. The general assumption that one enzyme in every reaction would need about 200 000 enzymes, an appreciation of Dellbrückwhat, requires in his opinion a new theory. Therefore, J a n k o w s k y ' s chemical theory will be shortly explained as a contribution to the memory of Mendel's work.

Also the number of hypothetic factors is too high. First of all, we have to

establish besides the chemotactic powers between the gamets, analogical but not identical powers between the alleles whose mixture (compound) is the essence of amphimixis. These power can be only chemical (heteropolar, homopolar, covalente), even if the alleles are very similar molecules. This conclusion is based on the socalled cross-structure of the DNA and RNA with their electric charges. Consequently, the complementary bases-pairing has to be a chemical liaison. In this case, chance groups cannot be joined, but only certain determined ones, according to their own structure and those of the neighbour — groups with their electrostatic charges. This chemical concept does not need any matrix for doubling, their chemical powers are sufficient, just like in the growth of crystals, when suitable substances and the right environemnt are at hand. These substances and evironment exist in every cell and originate from nutritional material. This signifies that the growth is automatic, like in most chemical reaction proven by Kornberg's experiments with DNA and by tissue-breeding which is pointed out in the new results of E. Wolff with improved methods.

We cannot overlook the fact that heredity is not a new creation of substances but the growth of already existing ones. When these substances are gaining in volume, metabolites appear, creating special effects but alway in connection with the total mass.

The difference between the actual and Jankowsky's theory the latter principally confirmed by development, is that the first of based on the combination of different genes. This diversity of the latter is in our opinion also one basis of genetic processes, like in chemistry the variety of atoms. But the other basis, like in chemistry, is the chemo-physical reaction between the genes with its often different results. The divergence in the combination of genes and the theory above-explained correspondens to the difference between a physical mixture and a chemical compound. Today, nobody will assume the first, which is unable to explain the change of dominance and other changes or the growth. To explain the change of dominance, the presence of one gene is insufficient, there has to be some reaction with other genes. That is well known, that even a big molecule, through a change in position among a group (change of chemical constitution) will be altered and we have to reckon that in DNA and RNA even in the same species and races such differences will occur.

These reactions between the different DNA were first proved by the alteration of pneumococci and now by the experiences of Fahmy with pure DNA and the results of mutations. Also the lethal factors should, in our opinion, better be called lethal reactions, because these factors show changes in their effect which can only be explained by reaction with other factors. Chemical reactions are not only present in these special cases, but always because two different processes in heredity at the same time are impossible. They occur in most cases like the combinations under disguise of the true processes.

The proteins in the nuclei and plasma already existing can grow only in the same manner, since in many proteins a cross-structure has been verified. This growth can take place in nuclei and in plasma. An assumption of M- and T--RNA is not necessary. Lile with all these processes they end when a certain size is reached, in this case as a splitting of chromosoms and cells.

The most difficult matter, not only in genetics but also in chemistry, are the enzymes. In the enormous literature of this field there is a growing demand for fundamental changes. It is necessary to point out the fact that the enzymes are mostly substances of the catabolism of organs, that is to say, they are not existing at the beginning of the development and in general chemistry there is less use of enzymes. Therefore, the concept of the automation of growth could be explained by a process that preceds reactions regulating the manner of the following reactions. For chemists this is well known as they use automatic processes in industry, especially as metalic catalysts are different from biological enzymes. Geologists also know automatic processes as the origin of deposits.

The construction of the specific proteins does not explain heredity as a whole. We have to ask in which manner the proteins as the material achieve the differentiation of tissues, organs and organisms. That each chemical compound has a certain form, is not a sufficient explanation. How these intracellular powers, besides local influences of cells and organs, achieve supperimposed regulations among themselves is the most difficult part in genetics to be ascertained. Similar to the symetrical centre in crystals, S p e m a n n assumed a centre of organisation but he could verify it only in the first stage of development. But here is more probable a functional centre, not necessarily localized in on point, since living matters, in contrast to crystal, have many diversified parts. Therefore, we have to assume an automatic process in which the preceding stage regulates the following one. This corresponds with the above-menioned chemical reactions and shows the unity of connected, but different processes.

With more and more research in this field going on, the differences between the recent theory and the one explained above is diminishing, as newest studies of R . M a u r e r show. When he said that the cells do not always have all enzymes at their disposal but their synthesis is corresponding to their particulass need, like in micro-organisms which have a greater capacity to utilize nourishment if it is offered in larger quantities, then that formulation is nearly the same as the above-explained chemical and biological automation.

That this theory points to phylogeny may be mentioned on the side-line, since M e n d e l had the concept of development by crossing and this concept has to be included in the hereditary theory. For each crossing is a reaction between different DNA and in this connection the artificial breeding of ducks by B é n o i t is of great interest. Indeed among millions of crossing there might meet such DNA resulting hereditary descendants.

The idea of the development from the zygote to the different organisms represents a series of chemico-physical processes giving an up to now unknown unity to genetics. If many take the prognosis as the main thing, we can only repeat the former explanation that even chemistry, far more developed than genetics cannot forecast what is to come and in our opinion neither can genetics. Of course, details of these processes have to be investigated. Therefore, the theory of J a n k o w s k y based on the general principles of biology and chemistry shows a simpler concept than the ultimate one.

Session IV

SPECIAL APPLICATION OF GENETICS

CHAIRMAN: S. L. LUSH
VICE-CHAIRMAN: A. TAVČAR

Plant Breeding and Plant Hybridization

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As you know, human culture could not arise until agriculture started about 10 000 years ago. A necessary condition for agriculture is the production of cultivated plants from wild progenitors. This process has occurred at many different points of time. Most cultivated plants are extremely old, others are of more recent origin and still others predominantly remain at the wild stage.

The ways in which our cultivated plants and domestic animals have arisen and the differences between the properties of the wild original material and the domesticated races were first thoroughly discussed by D a r w i n in his famous book "Animals and plants under domestication" (1968). According to D a r w i n , the domestic races could arise due to selection acting on extremely strong genetic variation, occurring in all cross-fertilizing organisms. We still agree with D a r w i n that this mechanism is of extreme importance and that selection in a variable material may often lead surprisingly far (cf. S c h w a n i t z 1957). A good example of this is represented by *Brassica oleracea*, the oldest cultivated varieties of which were known in the Stone Age. New cale and cabbage varieties were produced by the Greeks and Romans, though varieties were not as strongly differentiated from each other as modern varieties.

Another good example showing what selection may accomplish in cultivated plants is represented by the production of sugar beet during the 19th century. The ultimate progenitor in this case is the wild *Beta maritima*, from which the first cultivated forms arose in the eastern Mediterranean area about 500 years B. C. These varieties were leaf vegetables similar to Swiss chard; later on white- and red-flashed salad beets were produced and during the 18th century it was possible to produce mangels. In 1847 M a r g g r a f discovered that the beet roots contained sucrose and at the beginning of the 19th century A c h a r d succeeded in producing the first real sugar beet. By continuous selection in the range of 100 years the cultivators managed to raise the sugar content from originally 6 or 7 per cent to more than 20 per cent, and in this way a quite new and important cultivated plant was created.

In spite of these good results we may consider that the epoch of real plant breeding did not start until the beginning of this century, when the science of

genetics had become firmly established. Very soon after the rediscovery of Gregor Mendel's results it was realized that the new knowledge concerning heredity and variation brought important results for practical plant breeding. As early as in 1901 and 1902, the Plant Breeding Institute of Svalöf, Sweden, had been visited by two of Mendel's rediscoverors, de Vries and Tschermak, who furnished the plant breeders at this station with information concerning the new laws of heredity. Especially Mendel's principle of recombination aroused enthusiasm among the breeders, as it clearly indicated the possibility of combining into one new variety different valuable properties from different parent varieties. Genetic recombination is still one of the cornerstones of plant breeding and is in general of utmost importance for the life of all organisms with sexual reproduction or other means of gene exchange. The prerequisite of recombination is the occurrence of those stable units of heredity which Mendel (1866) discovered and which later on were called genes.

In a now classical paper dated 1906 Nilsson-Ehle pointed out that artificial crosses represent the best method of obtaining a combination of various desirable properties. He especially stresses that crosses should be carried out with the definite intention of combining one or several valuable properties in one of the parent varieties with other valuable properties in the other parent variety. Crosses should not be carried out at random as had been the rule up to that time, merely to bring about a stronger degree of variation.

Nilsson-Ehle quotes a series of examples and points out that in the offspring of experimentally produced hybrids he had really obtained products combining the valuable properties of the parents. At the same time, however, he obtained other segregation products which represented a combination of the bad propertis of the parents. This was true, for instance, of crosses between the winter-wheat varieties Extra Squarehead and Grenadier, in which certain segregations combined the stiff straw of Grenadier with the good resistance to yellow rust of Extra Squarehead. Other products of recombination, on the other hand, were obvious failures, combining the tall and weak straw of Extra Squarehead with the susceptibility to yellow rust of Grenadier. From such examples it became clear that economically important properties in cultivated plants may be recombined.

In three papers published in 1908—1911 Nilsson-Ehle (1908, 1909, 1911) demonstrated that quantitative characters, such as size, earliness, resistance to disease, etc., are inherited in a Mendelian way, just as those qualitative characters, differences in flower colour, etc., with which Mendel and the early Mendelists had been working. The quantitative characters, however, are as a rule conditioned by a more or less high number of polymeric genes originally called ("gleichsinnige Faktoren"), which after recombination, when homozygosity has been attained, give rise to numerous constant gradations.

The realization that quantitative characters are generally conditioned by several or many with similar effects had also been gained by East (1910) in the U.S.A., who, at about the same time as Nilsson-Ehle, published results on quantitative inheritance in *Nicotiana* and maize.

For the further development of the new science of genetics the demonstration that quantitative characters are also inherited in a Mendelian way was of great importance. Thanks to this knowledge it also became possible to understand how the organisms could be so remarkably well-adapted to different environmental conditions. This was clearly pointed out by Nilsson-Ehle as early as in 1911 in a paper read before the Fourth International Congress of Genetics in Paris. Nilsson-Ehle (1911b) had observed that winter wheat varieties clearly showed different degrees of winter hardiness, representing adaptations to the climate in the area of cultivation. He also showed that winter hardiness was a complex character, depending on the actions of several genes. The same was true of such characters as earliness and certain cases of disease resistance.

This work on adaptation was extended to wild plants by Nilsson-Ehle's pupil Turesson (1922, 1923, 1925, 1930, 1936) who showed that genotypical adaptation brought about by selection in a material segregating for polymeric genes, is evidently of universal occurrence.

It should be pointed out that the concept of polymeric genes was clearly indicated in Mendel's brief information about his crosses between *Phaseolus vulgaris* and *Ph. nanus*. In F_2 of this cross there was a series of different flower colours, ranging from purple to white and at 31 individuals available only one plant had white flowers. This could be explained, says Mendel, by the assumption that flower and seed colour in *Ph. multiflorus* is composed of two or more independent colours segregating in the same way as in *Pisum*. In such a case, segregations in the ratios 15 : 1 or 63 : 1 would be expected. Such ratios were, indeed, established by Nilsson-Ehle in his material of wheat and oats and were of importance for the development of his theory of polymeric genes.

It is also of interest to point out that the principle of progeny testing which is of basic importance in all modern plant and animal breeding also goes back to Mendel. He knew that two plants may have just the same appearance though differing in genetic constitution, and that the only way to distinguish such individuals is to raise separate progenies from each of them. In the simplest case it may be a question of heterozygotes and dominant homozygotes for a single allelic pair, the similarity between the individuals in this case simply being due to dominance. In most cases the genotypical differences are more complicated, but the principle remains the same. External similarity between two individuals is no guarantee for genetical identity. This problem was worked out in greater detail by Johannsen (1903, 1909) and led to

the important concepts of genotype and phenotype. Though not knowing these terms Mendel had understood the essential distinction.

Mendel's as well as Johannsen's main materials were the strictly self-fertilizing species *Pisum sativum* and *Phaseolus vulgaris*. Also the oat and wheat material studied by Nilsson-Ehle was spontaneously self-fertilizing.

The knowledge that cross-fertilizers are in a constant state of hybridity and, therefore, always segregating is chiefly due to those American workers who analysed the genetic constitution of open-pollinated plants as well as inbred lines in maize. G. H. Shull started parallel cultures of self- and cross-fertilized families of maize in 1904 and described his first basic results in the years 1908 to 1911 (Shull, 1908, 1909, 1910, 1911a, b). Also E. M. East (1909) gave important contributions to the same problems. For our present survey it is of particular interest that Shull realized that in an ordinary field of corn the individuals are generally very complex hybrids, or in more modern terminology strongly heterozygous. In contrast to this, inbreeding after a number of generations resulted in homozygous lines with more or less reduced vigour and specific and constant properties. Shull also discovered that hybridization between homozygous inbred lines resulted in F_1 hybrids showing a very marked hybrid vigour or heterosis. He realized that the utilization of heterosis might be quite important in the breeding of maize, as the hybrid combinations differed from each other in degree of heterosis, some combinations being definitely superior to the original, non-inbred variety. Therefore, Shull (1909) states that the object of the corn breeder is not to find the best "pure line", but to find and maintain the best hybrid combination. He realized that this principle would have very great potential consequence for the practical grower of corn and possibly for the breeder of many other cross-breeding plants and animals. This almost prophetic vision should, indeed, become true, and the utilization of heterosis is now the most important principle in the breeding of all allogamous organisms. Also in some autogamous plants, such as the tomato, heterosis may be achieved and exploited by intercrossing specific homozygous biotypes. It has even been suggested that it might pay to transform wheat into a cross-fertilizing species with the help of cytoplasmic male sterility (Wilson and Ross 1961; Schmidt and Johnson 1963; Joshi and Dhawan 1965).

As you know, hybrid maize is at present of utmost importance for feeding the explosively growing human population of our earth (cf. Sprague 1955), and utilization of the same principle in some food crops, so far not high-bred in this way, may for some time bring additional help to the large starving human populations in India and elsewhere.

For the rational utilization of inbreeding and hybrid vigour the realization that quantitative characters are also inherited in a Mendelian way has been of considerable importance. Since this became clear, about 1910, it is easy to

understand that an unlimited number of different inbred lines may be obtained from allogamous populations and that F_1 — combinations between such lines have specific properties and show different degrees of heterosis.

Concerning the real causes of inbreeding degeneration and heterosis, research and discussions are still going on (cf. M ü n t z i n g 1945, 1961) and also the methods used are undergoing various changes. However, the most important methodological change was introduced by J o n e s long ago (cf. E a s t and J o n e s 1919) when the single crosses were largely replaced by double crosses, involving four different inbred lines instead of two. It was also J o n e s (1917) who eleborated the dominance theory of inbreeding. According to this theory inbreeding degeneration is caused by the occurrence of a large number of deleterious recessive genes present in the original population in a heterozygous condition and are only noticeable when they become homozygous after a period of inbreeding. Heterosis is obtained because the inbred lines have different sets of dominant vigour genes. Thus, after crossing, F_1 plants are obtained, in which as a rule the deleterious effects of the recessive genes from one of the lines are compensated by dominant vigour genes from the other line and vice versa. As to recent discussions of these problems, it should only be pointed out that there are several good reasons to suspect that the recessive deleterious genes, causing often inbreeding degeneration or perhaps always, represent small structural changes in the chromosomes rather than true so-called "point mutations" (cf. M ü n t z i n g 1961, pp. 200—206).

The early plant hybridizers before M e n d e l were chiefly interested in crosses between widely different parents, preferably belonging to different genera or at leaast to different species. Also M e n d e l carried outseveral species crosses which, however, were of little help to his theory of inheritance. In modern plant breeding work, species crosses are also utilized in different ways especially for two different purposes. The first one is to transfer genes or chromosomes for disease resistance from a wild species to a cultivated species lacking such resistance. This may be achieved by repeated back-crossing. In this way it is possible to acquire the resistance from the primitive species without losing the good characters of the cultivated variety.

In work of this kind, and in work with species crosses in general, it is necessary to combine the experimental work with cytological studies. Species have often different chromosome numbers, and even when the chromosome number is the same, the structure of the chromosomes is generally different. This is a field of which M e n d e l could know nothing but which is now of considerable importance. It has been realized that in work with the incorporation of genes from one species to another so-called substitution types may be obtained, in which one chromosome pair of the host is absent and is instead replaced by a particular chromosome pair from the donor (cf. J e n k i n s 1957). In other cases the transfer may be limited to the important gene only, or a short segment

of the chromosome carrying this gene. This may be accomplished by X-ray induced translocations (Sears 1956; Elliott 1957) or by exceptional crossing-over between the recipient chromosome and the alien donor chromosome. In wheat such crossing-over between wheat chromosome and alien chromosome is greatly favoured by a temporary removal of a particular gene, controlling meiosis and preventing crossing-over between chromosomes that are not strictly homologous (Riley, Chapman and Kimber 1959).

The second purpose of making species crosses in present-day plant breeding work is to produce allopolyploids containing the sum of the chromosome complements of the parent species. In this way quite new types of cultivated plants may be produced, or already existing cultivated plant species may be synthesized again. In the latter case, valuable genes may be included which are not present in the spontaneous material. Such is the case in rape, *Brassica napus* (2n = 38), which may be synthesized from crosses between *B. oleracea* (2n = 18) and *B. campestris* (2n = 20). Synthetic rape strains are available, which have a better winter hardiness and larger oil production that the best spontaneous rape varieties (Olsson 1960, 1963). Still better results may, however, be obtained from hybrids between the old spontaneous and the new synthetis varieties.

Thus, we are again back to Mendel's fundamental principle of genetic recombination. This principle is also utilized in other types of modern plant breeding work. In cases of autopolyploidy the new poducts must be hybridized and recombined in order to get a sufficient degree of genetic balance and differentiation. This is absolutely necessary when the species involved are self-fertilizing, but also in cross-fertilizing and hence heterozygous material, hybridization between different autopolyploid strains is favourable.

In cases of induced mutations in cultivated plants genetic recombination has also an important function. The new genes often tend to reduce vigour and fertility in the original material, but by recombination a better genotypical environment may be created which leads to a restoration of vigour and fertility. Hence, new mutant genes are only rarely of immediate importance in the variety in which they were produced, but are of greater economic importance after hybridization and recombination (cf. Hagberg and Persson 1963).

Though highly important in plant breeding work, all this represents only one special sector of the enormous, general biological significance of genetic recombination. Without this mechanism which leads to polymorphism and adaptation, evolution and species formation would have been impossible, and it is very unlikely that, for instance, our own species Homo sapiens could have arisen in the absence of genetic recombination. Mendel did not invent this mechanism but he detected it and clearly realized that a very great

hereditary variation could be created by reshuffling a very limited number of constant hereditary units. This was indeed of the greatest biological discoveries ever made, which will forever influence biological research and its practical application in the service of mankind.

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Plant Breeding and Induced Mutation*)

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(1) The genotype-milieu interactions of crop species and varieties necessitate a detailed information on genecological aspects in agriculture.

In agriculture of to-day as well as in horticulture, the milieu conditions rapidly and greatly change, owing in part to improved soil treatments, more efficient fertilizers, planned irrigarion etc. Greenhouse cultivation, with soil-free cultures, increased light and humidity, controlled temperature etc., will more and more replace open-air cultivation in numerous crop plants. In fact, space-saving and inexpensive types of greenhouse constructions are on the market. This state of things puts further pressure on the plant breeder, his methods, his planning of cultivaton. There is already now a demand for rather extensive recombinations of existing genes, for the induction of new genes and gene patterns, comprising changes in linkages and chromosome structures, as well as for a wider use of cytoplasmic inheritance.

(2) Karyotypes of crop species and varieties often display a peculiar organization of chromosomes: in size, structure, differentiation. There is a need for more precise information of how indispensable the prevailing, largely historically determined chromosome organization really is in relation to present and future gene functions and cell metabolism. To choose a specific example: how deeply connected with metabolic perfectness is the eccentric karyotype of the horse bean, *Vicia faba*? How far can it be rearranged without serious effects on cell and plant viability? A considerable reshuffling of chromosome organization can certainly be undertaken without loss of productivity, in barley, horse bean as well as in other species. If the present organization is of no special advantage functionally, or rather a disadvantage, how far do we wish to remodel the chromosomes of a species with regard to size, number, amount of heterochromatin, satellites and satellite regions, occurrence of tertiary constrictions, etc.? And then, to what extent are we able to increase the efficiency of genes, gene sequences and cytoplasmic constituents further by such means of chromosome remodelling?

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*) It is summary of problems discussed in the lecture at Symposium on the mutationa Process (Praha, August 9, 1965).

(3) To-day there are conflicting opinions concerning the relative role of mutations with great versus slight effects. In the writer's opinion this is a fight of the pope's beard. In fact, many species and varieties have become domesticated in the course of time by means of mutations causing discrete changes, conspicuous in their effects. According to the early work by N i l s s o n - E h l e (in 1913—1915 and previously) there is an abundance of genes, on the other hand, with small effects, working on essential features towards agricultural fitness (they were called "polygenes" by him). Type of species and variety, as well as choice of properties to be improved, decide which technique should be applied in the process of agricultural improvement: recombination of genes, back--crossing, F_2 heterosis, mutation, polyploidy. Furthermore, they also decide on the degree of phenotypic change required in the individual case: a discrete, often conspicuously changed property (according to the S e n g b u s c h model of lupine improvement) or a property more of the continuous type (according to the N i l s s o n - E h l e model), for instance effecting a production increase in wheat and oats.

(4) Mutations, both spontaneous and induced, are in general considered from a negative point of view. They are classified as lethal, destructive, detrimental, viability decreasing, in the homozygous as well as in the heterozygous state. In several publications the present writer has emphasized an opposite view, also with regard to lethal or semilethal mutations as for instance chlorophyll lethals in plants in the heterozygous state. Such lethals or semilethals are often "super-vital" when heterozygous, although in variable respects, varying with the kind of environment, with competition or without competition. That high-productive mutations in the homozygous state can be induced in many crop plants has been fully evidenced in recent years. Mutants involving slight as well as conspicious changes have been released into practice. They will no doubt be of considerable value in further recombination breeding, as has already been indicated by the work of Swedish and German plant breeders.

(5) New approaches to an effective screening of high-productive mutants should be worked out with regard to characters important in agriculture: productivity, lodging resistance, earliness, disease resistance, quality properties. With the avid of efficient screening techniques, spontaneous and induced mutations will, to be sure, be more and more considered from the positive point of view, both as regards their heterozygous and homozygous states. An illustration of such a procedure was given in the lecture. In röntgen series of barley, after selection for the so-called erectoides character, no less than 1,000 high--productive mutants may be isolated out of 10,000 X_2 spike offspring, using a dose of 10,000 r-units. This means that one progeny out of ten will contain a mutation, high-productive under conditions optimal to the parental strain. In fact, one out of eight induced mutations will in such a case turn out to be -highproductive, which does not mean, of course, that it is ready for agricultural release.

(6) Considering specific gene loci, like ert-c or ert-k in barley, high-productive mutants will be even more frequent. One out of two c or k mutants is equally productive from an agricultural point of view as its parental strain. Furthermore, the type of mutagenic agent (sparsely contra densely ionizing radiations, radiations contra chemicals) seems to be of importance for the further promotion of positive mutability. There is already sufficient evidence available that the application of different mutagens will lead to different types and positions of chromosome breakage. Chromosome breaks and gene changes imply different kinds of mutations. Consequently, the mutation process can be intentionally directed in various ways also in higher organisms.

(7) Finally, it is worth pointing out once more that plant breeding is not and has never been an appendage of genetics. Rather it is based on a synthesis of several biosciences. It falls within the limits of genecology, as this term was originally defined by T u r e s s o n . It deals with the artificial evolution of crop species, changing and accomodating them more and more precisely to human needs and demands. No doubt, in the starving world of to-day and of decades to come planned plant breeding will, as a branch of genecology, be in the centre of biology.

Interspecific Conversion and Formative Process in the Remote Hybridization of Plants

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Today, all the people the world over celebrate the respectful memory of a person who hundred years ago made his prominent contribution to biology. His findings are and will be one of the most important foundations for genetics and selection to understand many phenomena of heredity.

In view of this, I would like to share with you some of the ideas arising from our investigations on hereditary characteristics and symptoms in the remote hybridization.

Various opinions and views have been reported about the remoteness of forms and species of plants involved in crossing. Thus, forms which are close systematically but different in their geographic origin, are believed to be attributed to remote crossings. Forms with various genetic structures, both with compatible and incompatible characteristics and symptoms confined to the genetic code are attributed to the same. But everything stated above, certainly, fails to give a clear definition of this conception.

We think it true to understand the remote hybridization as the crossing of plants of various species and genera among themselves. This aslo includes crossing of cultivated plants with wild ones, grassy plants with tree — like ones.

The principal criterion of the methods of remote hybridization is the difficulty in the crossing ability of the parental forms and high sterility of F_I hybrids. Our experience shows that this field of investigation corroboratings laws discovered by G. Mendel at the same time supplements them.

The first law — invariable unity of form — remains valid in F_I hybrids originated by the remote hybridization. But this uniformity is usually broken in F_I since heterozygous species and forms of plants instead of homozygous ones are involved in crossing in the remote hybridization. Thus, by crossing homozygous forms of *Triticum* with *Agropyron*, a cross-pollinated plants which is always to a certain extent heterozygous in F_I, we see several variations in the morphological characters and physiological features of plants.

Still greater differences are observed in the hybridization of two heterozygous forms, e.g., *Secale* × *Agropyron*. In this case, F_I plants are considerably varied in their characters and features, e.g. in the form of the ear and its individual morphological characters, in the number of flowers in the spikelet, in the dura-

tion of vegetation etc. Strongly pronounced heterozygosis of both parents may explain this phenomenon. The same phenomenon was never obsereved in intraspecific crossing, since plants in this case do not have sharp differences in their characters.

The second law — splitting in F_2 — is valid in the remote hybridization. However, this law cannot by put in any, even approximate numerical ratio and it has essentially a new nature in the remote hybridization.

Mendel's term splitting can be used both for intraspecific and interspecific crossing with the difference that synthesis of new species, varieties and forms, side by side with splitting, takes place in the remote hybridization. Therefore, notion fixed in genetics about the formative process and the beginning of it in F_2 corroborates this idea by a sufficient number of facts.

Strictly speaking, the formative process dominates in the experiment and influences its final results: we can gain what we wish and eliminate what we do not want.

Any crossing results in the origination of new, however close intraspecific crossing results at the beginning of the formative process is of slight importance. Usually, new forms do not exceed the limits of a species. Quite the reverse, the remote hybridization permits the investigator to discover the formative processes of a wide diapason, in which new species and varieties appear; any other modern methods fail to receive the same results. This is quite understandable. Thus, by crossing *Triticum* to *Agropyron* i.e. a cultured plant with a wild one, we are trying to combine the characters and features which they gained along their different paths of evolution. It is well-known that cultured plants were produced by man. For thousands of years man kept changing plants to satisfy his own needs frequently to the detriment of the requirements of the plant itself. For this reason, cultured plants acquired in the course of centuries properties and characters necessary to man but not to the plants themselves. The wild flora accumulated over thousands of years properties and characters which only the plants themselves needed.

Different factors in the evolution of cultured and wild plants made part of them delicate, unable to live without assistance. The other became strong and resistant, able to grow without the help of man.

Thus, the remote hybridization occupies a particular position among the problems of geenetics and selection. By crossing plants and animals of various species and genera of various evolutionary — historical ways of development we change their nature itself. Devised methods of remote hybridization make it possible to introduce new plant and animal organisms and to transfer most valuable economic characters of wild plants to the cultured ones.

Therefore remote hybridization is essentially the only possible method combining in its hybrids (particularly, obtained as crosses of cultured plants to wild ones) two vegetable kingsdoms which appeared historically at different

stages and ways of evolution. In this case we deal with nucleus and plasma of completely different formation, owing to which new varieties, species and cultures appear in the formative processes and this cannot be achieved by any other methods of modern selection and genetics.

For instance, polyploidy and mutagenesis even stimulating most complex processes make changes only within structural textures of one species, i.e. as we say, all hereditary changes here go on by themselves.

To counterbalance it, hereditary changes (as a result of hybridization) in the

The Formation of Wheat Type Forms in the Hybridization of *Triticum Aestivum* with *Agropyron Glaucum*

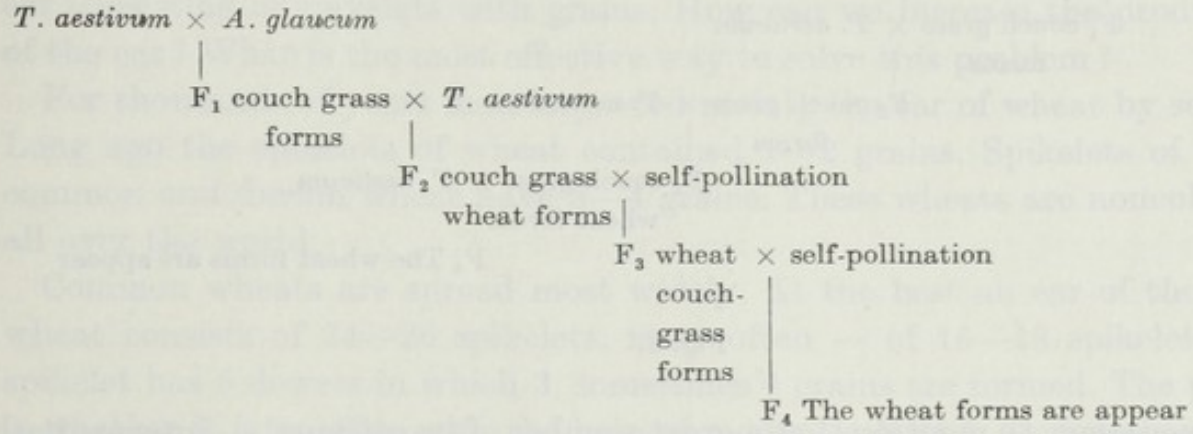

Fig. 1.

new hybrid plant go on at the expense of not one but two-three-four non-related species. Here, we found the fundamental difference in the importance of the remote hybridization when compared with other methods.

However, this conclusion is not a contraposition. Each method has its important meaning, e.g., without polyploidy it is impossible to overcome difficult cases of sterility often found in the remote hybridization.

Using this method in our wok we were able to overcome the combining inability of wheat crossed with *Elymus* and also the sterility of F_I of rye-couch--grass hybrids ets. Hence, application of all modern methods of genetics and selection will help to solve successfully the problems both of theoretical and practical importance.

I venture to draw your attention to some laws in the formative process discovered in our on remote hybridization.

General regularity observed by us lies mainly in the fact that in crossing non-related pairs the formative process obligatory passes the stage of the intermediate development of hybrids in generations. However, nature of this stage in each individual crossing will have peculiar characters. Let us take two examples of our work.

The first — crossing of *Triticum aestivum* with *Agropyron glaucum* v.

genuinum, in which the formative process usually proceeds as shown in Fig. 1.

We can also see from the pictures that the real wheat form of the ear appears only in F_4 plants. Thus, the abovementioned material clearly shows that the formation of the ear of wheat or couch-grass form is possible, providing obligatory stages of transitional — intermediate development.

The Formation of Wheat Type Forms in the Hybridization of *Triticum Aestivum* with *Agropyron Elongatum*

T. aestivum × *A. elongatum*
|
F_1 couch grass × *T. aestivum*
forms |
F_2 couch grass × *T. aestivum*
forms |
F_3 couch grass × *T. aestivum*
wheat forms |
F_4 The wheat forms are appear

Fig. 2.

It is necessary to mention that a great number of transitional — intermediate forms appear in any formative process, not taking into account whether it arises in nature or artificially. As a result of remote hybridization we always obtain a wide range of the transitional forms, most of which proved to be unadaptable to the given conditions.

Under experimental conditions temporary and constant species, varieties and forms appear, they refer to the transitional — intermediate stages of the formation of species, most of which perish because they become unable to stand ecological conditions. Everything stated corroborate Darwin's very important thesis about the breakage in the unbroken formative process in the organic nature, as a result of which isolation of species takes place.

We are able to observe all these phenomena in miniature, infinite facts confirm them. It is possible that species and forms lost by nature as well as well as those nonexisting might appear as a result of the formative process of remote hybridization. This is of particular interest to experimental botany, where the method of hybridization can be successfully used for phyllogenic investigations.

The second example — crossing of *Triticum aestivum* with *A. elongatum* in which the formative process has a somewhat other character (Fig. 2).

As we see, subsequent back-crossed generations do not have plants with the wheat type ears. Therefore, it is necessary to make additional 2—3 back-crosses to wheat to originate wheat forms.

Hence, in both cases wheat forms appear in F_4 with only one difference that in the first case this results after one back-cross and in the second case — after 2—3 back-crosses.

Studying the formative processes we investigate the laws of inheritance of individual characters of hybrid plant, co-ordinating our researches with the requirements of practice. Here the problem of the raising of crop yields and particularly of cereals — fundamental basis for crop production and animal breeding — is one of the most important problems of agriculture.

It is doubtful whether any other problem can compete by its importance with this vital problem.

Naturally, wheat is a leading cereal culture. Its main productive part is the ear consisting of spikelets with grains. How can we increase the productivity of the ear? What is the most effective way to solve this problem?

For thousands of years man improved mainly the ear of wheat by selection. Long ago the spikelets of wheat contained 1—2 grains. Spikelets of modern common and durum wheat have 3—4 grains. These wheats are noncultivated all over the world.

Common wheats are spread most widely. At the best an ear of the winter wheat consists of 24—26 spikelets, more often — of 16—18 spikelets. Each spikelet has 5 flowers in which 3, sometimes 4 grains are formed. The problem is whether it is possible with the help of modern selective — genetic methods to originate such wheats, the ears of which would consist if 30 and more spikelets each having 7—8 grains, on an average 4—5 instead of 3 grains which the wheat has. It is possible to originate such plants. We have already had theoretical prerequisites confirmed by our practical results.

Here is a picture of two ears. An ear of common wheat is on the left, one of wheat-couch-grass hybrid is on the right. It is not difficult to count the spikelets and grains. Both ears have 16 spikelets. Each spikelet of common wheat contains 2—3 grains, hybrid ears — 5—7 and even 8. The whole ear of the common wheat has 40 grains and that of the hybrid — 80. This means that it is possible to increase the yield.

We can see the gradual formation of the multigrained ear originated as a cross of wheat to couch grass in this picture. The couch grass ear is on the left, F_1 ear follows it, then from F_2 to F_6. It is clearly shown that the formation of the vigorous multigrained ear never met either in nature or by man.

All multigrained forms of wheat developed by us are now undergoing extensive tests and the first data obtained shows their importance for the increase of yield.

It is difficult to state now the limits of increasing the size of the ear, number of spikelets and grains. We dare believe the bounds are not limited as one may suppose. Therefore, it is, certainly, very interesting to grow under production conditions a variety of branchy eared wheat with an increased yielding capac-

ity. To solve this problem we used branchy forms of the couch grass. We crossed them with wheat and developed a number of new branchy forms of wheat. In contrast to spring branchy durum wheat our hybrids are common and winter ones. Our branchy forms of hybrid wheat have 25 grain in some twigs of the ear which were formed instead of the spikelet. Thus, we have developed completely new varieties of wheat — high-yielding, winter hardy, immune to various diseases.

I would also like to dwell on one more fundamental question. There is much argument in science about the principles of genetics and selection and their usage in solving various problems of practice. For example, whether it is possible to combine studied characters of the plants involved in the hybridization in a new plant. Numerous experiments show that it is possible with the help of hybridization to combine separate characters of both parents in one hybrid plant. We use the term "separate characters of both parents and combination of them in hybridization" relatively to a certain extent. All processes in hybridization which form new organisms integrate desirable characters in the process of development; however, these characters are absolutely new in essence as the whole hybrid organism itself.

Life appears and develops in an environment in which it finds necessary conditions for its existence and development. But life as a peculiar form of the motion of matter has its qualitative specificity — the character of inherent regularities. Revealing the study and use of these specific laws of development makes the essence of biology, its matter.

Sexual reproduction appeared during the relatively later stages of the development of living nature and being a progressive factor plays an important role in the evolution of organic world. One of the advantages of this factors is the possibility of hybridization in the bounds of species followed by hybridization between species and out of them.

It will not be an exaggeration to say that this new factor of hybridization raised evolution to a new and higher level, as an important condition for speeding up and enlarging the processes of species formation. While such factors were not in action, organisms and species changed and developed towards perfection under the influence of environemental conditions very slowly. A given species cannot obtain the characters, properties and peculiarities of other species, which they had achieved during evolution. As a result of this a new factor, on the basis of the laws of unity of organisms and environment in the process of evolution, was included as a new strong element leading to the creation of variation of forms and to a more active role of natural selection.

Nature with her abundance of plants still unused by man is one of the mighty reserves for remote hybridization. The vast natural vegetable resources may and must be utilized by biologists as unlimited initial material for their creative work.

Results of investigations carried out by the scientists in the Soviet Union and abroad corroborate this idea. At present, we have successfully crossed 3 species of *Elymus* to *T. aestivum*, *T. durum*, *Hordeum*, *Secale*, winter rye to *Agropyron*, wheat to hybrid couch grass (*A. glaucum* × *A. repens*), tree-like tobacco — *Nicotiana glauca* to a grassy plant — *N. rustica*, *N. glauca* to *N. alata* and many others.

Only as a result of the remote crossing of wheat to couch grass we have originated both new species and new crops, e.g., perennial wheat, grain-fodder wheat, a number of new varieties of wheat of intermediate type, branchy common winter wheat etc.

This work shows exceptional importance for investigation in the field of the remote hybridization and the hybridization of cultured plants with wild plants particular.

Genetic Research of Combination Breeding of Some Useful Characteristic through Hybridization of Some Hexaploids with Some Yugoslav Ecotypes of Tetraploid Wheat

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Introduction and problems

Of many papers dealing with the genetic research of the hybrids between hexaploid and tetraploid wheat only some connected with our researches should be mentioned: K. Sax, P. Mathis, H. Raum, A. Tavčar.

On the Yugoslav Adriatic coast and its islands many different ecotypes of *Triticum turgidum* and *Triticum durum*, as well as their natural hybrids, existed until some years ago cultivated by the farmers of these regions as natural populations.

Because of the very interesting and useful characteristics of these ecotypes we collected them for genetical studies of their morphological, physiological and cytological characteristics and for combination breeding with some of the hexaploids.

Research

Some of collected ecotypes of *Triticum durum* and *Tr. turgidum* have useful characteristics which could be combined through hybridization with some improved hexaploid wheats, in which some of the useful characteristics of the tetraploid are missing. Such characteristics are the greater number of spikelets, especially in some *Tr. turgidum* types, greater content of proteins in *Tr. durum* types, greater resistance to dryness of *Tr. durum* and *Tr. turgidum* and greater resistance of some ecotypes to some diseases, especially to *Puccinia graminis*. These mentioned tetraploid ecotypes have, of course, also some negative characteristics, such as, for example, very long stems, low winterhardiness and 28 chromosomes, which make the combination breeding with hexaploids somewhat difficult.

The purpose of our research was to combine through hybridization some of the useful characteristics of some of our ecotypes of tetraploids of *Triticum turgidum* and *Tr. durum* with improved varieties of hexaploid cultivated on a larger scale in our country, in order to create homozygous genotypes of *Tr. aestivum*, *Tr. durum* and *Tr. turgidum*, with the useful characteristics of the mentioned hexaploids and tetraploids.

The individual selection of the plants of the mentioned population, till desirable pure lines were produced, was made in the Arboretum Trsteno (near Dubrovnik) in Dalmatia.

The hybridization with some of the improved homozygous hexaploid winter wheat of continental regions was performed at the Department of Plant Breeding and Genetics, Faculty of Agriculture, Zagreb.

Of many of our species hybrids between hexaploids of *Tr. aestivum* and *tetraploids (Tr. turgidum* and *Tr. durum)* which we have made especially during the last 10 years we shall discuss only the results of the following ones:

Tr. aestivum — San Pastore × *Tr. turgidum* var. *Salomonis* (Pelješac)
Tr. aestivum — San Pastore × *Tr. turgidum* var. *melanatherum* (Lošinj)
Tr. aestivum — San Pastore × *Tr. durum* var. *Valencia* (Pelješac)
Tr. aestivum — Produttore × *Tr. turgidum* var. *Salomonis* (Pelješac)
Tr. aestivum — Produttore × *Tr. durum* var. *obscurum* (Pelješac)

Results and conclusions

The research involves the following characteristics:

a) height of the stem, b) length of the ear, c) number of spilets per ear, d) cold resistance, e) length of the veg. period, f) resistance to *Puccinia graminis* and g) cytogenetical studies on the sporocytes.

On the Tab. 1. to Tab. 5. are the data for the parents, F_1 gen., genetical variations in F_2 gen. in some of the mentioned characteristics (the number under the limit of variation indicates the number of the genotypes which have been studied in detail), and some of the interesting and useful characteristics selected from F_2 gen. and produce through farther selection to phenotypically constant genotypes in F_5 gen.

Our studies led to the following results and conclusions:

1. F_1 gen. between *Tr. aestivum* and tetraploids *Tr. durum* and *Tr. turgidum* is on the average intermediary in comparison to the parents concerning the length of the stem, length of the ear, number of spikelets per ear, colour of glumes, colour of awns, winterhardiness and resistance to *Puccinia graminis.*

2. The explanation of the segregation of the phaenotypes in F_2 gen. is due to the different number of chromosomes in the hybrids which varied from 28—30—35—40—42—56 and of the interaction especially of genes for quantitative characteristics very complicated.

3. The different number of chromosomes of the parents cause in segregating the formation of a small promille of pollen grain with 2 pores and 2n chromosomes, especially in the plants with 2n = 35 chromosomes. Other cytogenetic abnormalities in the sporocytes of the hybrids are in chromosome aberrations, for instance, in the formation of micronuclei, fragmentation, increase of number of chromosomes of the same genome, translocations and others.

Table 1.

Characteristics of parents, F_1 gen. and of some genotypes of F_5 gen. of *Tr. aestivum* San Pastore × *Tr. turgidum* var. *Salcmonis* (Pelješac)

Generation and variety	Stem length cm	Ear length cm	Spikelets number	Ear type	Glumes		Awns		Winter-hardin. 0—10	Pucc. graminis 0—10	Veg. period (+) (−)	Chromosomes 2n
					pubesc.	colour	length	colour				
P_1 S. Pastore	84·2±2·8	6·9±0·4	16·6±1·7	aestiv.	−	brown	0	0	5	5	0	42
F_1	112·4±5·7	7·4±0·5	20·7±2·2	interm.	+	brown	3·6±0·7	brown	4	4	+4	35
P_1 *turgidum*	122·4±4·5	9·7±0·3	23·3±2·1	turgid.	+	white	13·6±1·8	black	3	1—2	+6	28
F_2	Genetic variations in some characteristics											
	65—119 / 7	5—15 / 8	17—25 / 5	turg.	(+) (−)	white	6—14	white	2—7	2—5	−5 to	28—42
				aestiv.	(+) (−)			brown			+7	
				speltoid	(−) (+)	brown	7	black	4	4		
				compact.	(−) (+)							
F_5	Some interesting genotypes											
2792/1	59·8±3·6	7·3±0·2	15·4±1·3	compac.	+	white	9·7±	black	5	5	+4	40
2794/2	65·5±4·2	8·5±0·3	24·1±1·7	aestiv.	−	white	−	−	5	5	−5	42
2793/4	76·3±4·1	6·5±0·2	24·2±1·9	turg.	+	brown	14·3±	brown	7	4	−3	30
2788/2	83·4±3·9	5·6±0·3	19·6±1·8	comp.	+	brown	−	−	6	4	+6	40
2785/1	91·6±4·6	13·2±0·1	21·3±1·7	spelt.	+	brown	−	−	4	4	+7	40
2768/1	97·4±4·5	9·2±0·1	23·6±1·6	aestiv.	−	brown	−	−	5	2	−3	42
2765/1	107·5±5·2	10·3±0·2	21·4±1·4	aestiv.	+	white	6·8±	white	6	4	+6	42
2779/1	117·6±5·7	7·5±0·2	23·3±1·8	aestiv.	−	white	11·2±	black	7	2	−4	42
2782/1	72·4±4·2	10·5±0·3	19·4±1·7	aestiv.	+	white	−	−	5	3	−5	42

Table 2.

Characteristics of parents F_1 gen. and of some genotypes of F_5 gen. of *Tr. aestivum* San Pastore × *Tr. turgidum* var. *melanatherum* (Lošinj)

Generation and variety	Stem length cm	Ear length cm	Spikelets number	Ear type	Glumes		Awns		Winter-hardin. 0—10	Pucc. gramin. 0—10	Veg. period (+) (−)	Chromosomes 2n
					glabrous	colour	length	colour				
P_1 S. Pastore	84·2±2·8	6·9±0·4	16·6±1·7	aestiv.	—	brown	0	0	5	5	0	42
F_1	112·0±4·4	9·2±0·8	19·3±2·3	interm.	—	brown	7·2±1·5	brown	4	5	+5	35
P_1 *Tr. turg.*	144·8±4·5	11·2±1·5	23·5±2·1	turgid.	—	white	14·7±2·2	white	2—3	6	+7	28
F_2	Genetic variations in different characteristics											
	78—141 / 7	4·5—13·5 / 5	15—24 / 4	eastiv. interm. turgid.	—	white / brown	0—15 / 8	white / brown	1—7	−3—7	−3 to +6	35—42
F_5	Some interesting genotypes											
4117/4	82·4±5·7	6·2±0·4	19·3±2·4	compact.	—	brown	6·4±0·4	brown	4	4	+3	40
4119/1	85·5±5·2	9·4±0·7	16·2±1·9	interm.	—	brown	8·5±0·3	brown	3	5	+3	38
4104/2	81·3±4·8	10·2±0·9	14·5±1·3	interm.	—	white	7·3±0·5	white	3	3	+2	38
4105/1	84·6±5·6	10·5±0·8	16·7±1·8	aestiv.	—	brown	8·3±0·7	brown	3	3	−1	40
4138/2	99·7±6·1	10·2±0·6	23·4±2·1	aestiv.	—	white	—	—	4	1—2	−2	40
4124/1	106·5±5·9	10·3±0·5	18·4±1·5	aestiv.	—	brown	6·5±0·4	brown	6	2—3	+3	42
4126/2	113·3±6·4	9·5±0·3	21·7±1·7	aestiv.	—	brown	—	—	5	3	+2	42
4137/2	123·5±7·5	9·7±0·4	22·4±2·0	interm.	—	white	8·4±0·4	white	3	0	−1	38
4139/4	127·1±6·9	13·5±0·9	24·1±2·2	speltoid	—	white	6·5±0·2	white	4	1—2	+2	42

Table 3.

Characteristics of parents F_1 gen. and of some genotypes of F_5 gen. *Tr. aestivum* San Pastore × *Tr. durum* var. *Valencia* (Pelješac)

Generation and variety	Stem length cm	Ear length cm	Spikelets number	Ear type	Glumes		Awns		Winter-hardin. 0—10	Pucc. graminis 0—10	Veg. period (+) (−)	Chromosomes 2n
					pubesc.	colour	length	colour				
P_1 S. Pastore	84·2±2·8	6·9±0·4	16·6±1·7	aestiv.	−	brown	0	0	5	5	0	42
F_1	109·5±4·7	9·7±0·6	19·8±1·5	interm.	+	brown	8·5±1·2	white	4	5	+3	35
P_1 *Tr. durum*	129·2±4·1	11·4±1·3	24·6±1·9	durum	+	white	18·4±2·3	white	3	3	+4	28
	Genetic variations in different characteristics											
F_2	90—117 6	8—13 4	20—26 3	aestiv. durum speltoid compact.	(+) (−)	white brown	0—13 13 0—9 0—6	white brown	3—7	2—7	−3 to +4	28—42
	Some interesting genotypes											
F_5												
3533/1	90·3±6·6	10·2±0·6	26·1±1·3	speltoid	+	d.brown	9·3±1·5	brown	6	4—5	+3	40
3532/2	90·6±6·2	12·5±0·9	21·6±1·6	aestiv.	−	brown	−	−	2	2	+3	42
3529/1	93·4±7·1	9·4±0,7	21·2±1·4	interm.	−	brown	−	−	7	4	+2	38
3529/19	110·2±6·8	9·6±0·8	23·4±1·8	aestiv.	−	brown	9·5±1·8	brown	6	3	+3	42
3531/2	115·3±7·4	11·5±0·5	21·5±1·6	durum	−	white	9·7±1·4	white	8	4	+4	40
3534/2	116·5±6·7	9·1±0·6	21·6±1·2	aestiv.	+	d.brown	10·1±2·1	brown	7	3	+4	42
3535/2	84·2±4·7	5·8±0·8	20·3±1·8	compac.	−	white	5·9±1·1	white	6	4		40

Table 4.

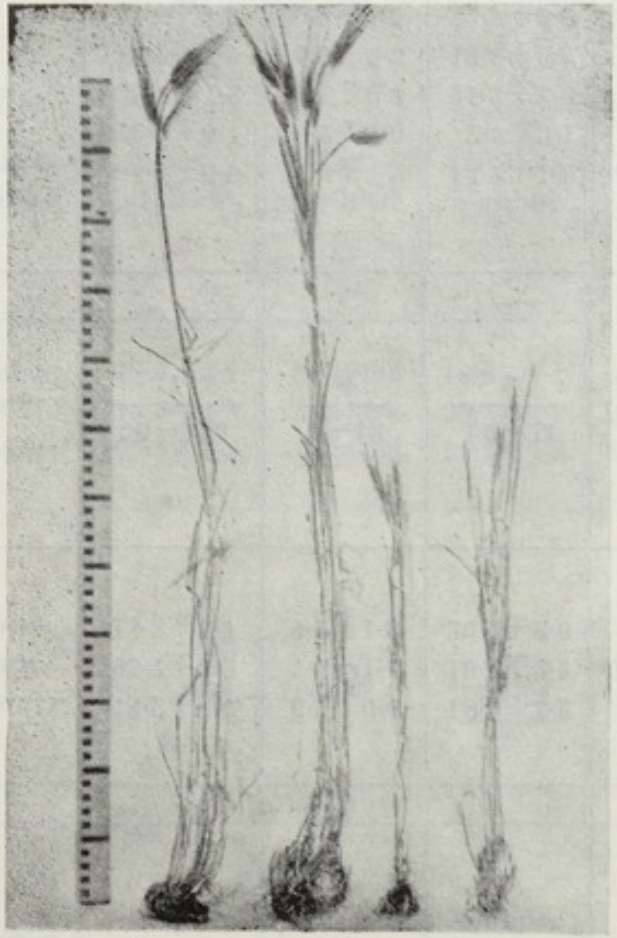
Characteristics of parents, F_1 gen. and some genotypes of F_5 gen. of *Tr. aestivum-Produttore* × *Tr. turgidum* var. *Salomonis* (Pelješac)

Generation and variety	Stem length cm	Ear length cm	Spikelets number	Ear type	Glume		Awns		Winter-hardin. 0–10	Pucc. graminis	Veg. period (+) (−)	Chromosomes 2n
					pubesc.	colour	length cm	colour				
P_1: *Produtt.*	78·2±2·7	6·7±0·5	18·8±1·2	aestiv.	0	white	0	0	4	4	−	42
F_1	115·6±4·8	6·8±0·4	20·7±1·5	interm.	+	brown	7·6±0·8	black	6		+4	35
P_1 *turgidum*	137·5±5·8	8·2±0·3	23·1±1·8	turgid.	+	brown	12·7±1·6	black	3	2	+7	27
F_2	Genetic variations in characters											
	75–140·2 / 8	6–8 / 3	17–24 / 7	aestiv. turg. spelt. comp.	+− +− −+ −+	white brown	7–13 / 5	white brown black	3–7 / 4	1 to 6 / 3	3–7 / 4	28–42
F_5	Some interesting genotypes											
4188/2												
4164/1	98·6±5·8	8·2±0·5	21·5±1·6	aestiv.	0	brown	0	0	4	2	+2	40
4167/4	104·2±6·4	9·5±0·7	22·3±1·2	turgid.	0	brown	0	0	4	1	+3	40
4178/4	101·3±7·3	9·7±0·6	25·4±1·4	aestiv.	+	white	7·5±1·3	white	5	1–2	−3	42
4179/3	109·6±6·8	11·3±0·8	21·3±1·3	aestiv.	+	brown	6·8±1·0	black	4	2	+2	42
4180/2	113·5±6·3	10·8±1·1	23·2±1·6	spelt.	0	white	8·5±2·1	white	6	3	+3	40
	74·4±5·3	5·5±1·0	21·4±1·8	compac.	0	brown	6·4±1·5	black	4	3	+3	42

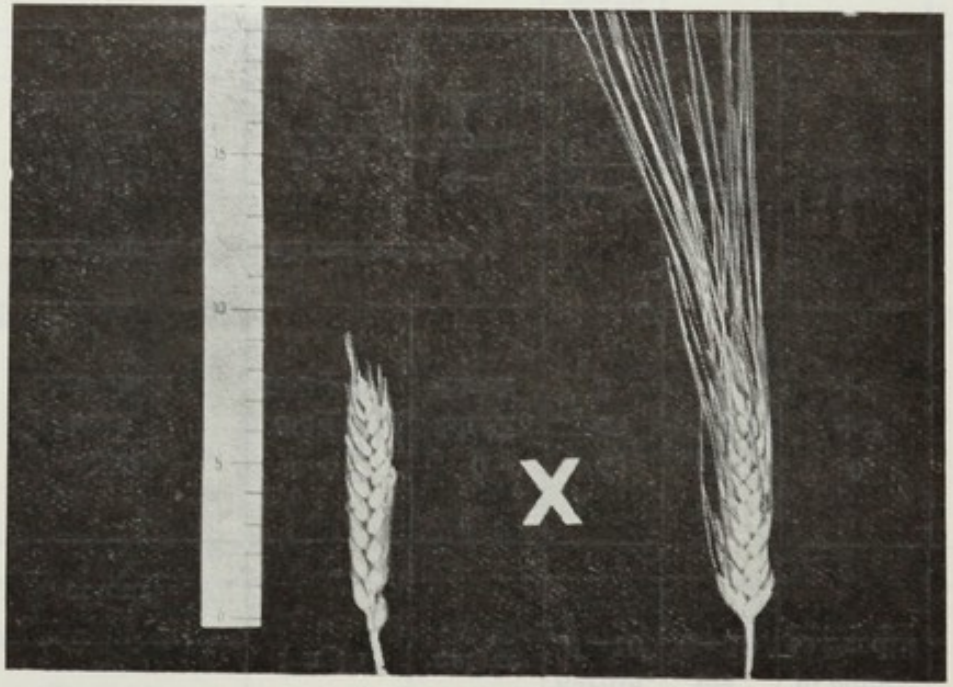
Table 5.

Characteristics of parents, F_1 gen. and some genotype of F_5 gen. of *Tr. aestivum- Produttore* × *Tr. durum* var. *obscurum* (Pelješac)

Generation	Stem length cm	Ear length cm	Spikelets number	Ear type	Glumes		Awns		Winter-hardin. 0—10	Pucc. gramin. 0—10	Veg. period in comp. to Produt	Chromosomes 2n
					glabrous	colour	length	colour				
P_1: Produtt.	78·2±2·7	6·7±0·5	18·8±1·2	aestiv.	white		0	0	4	4	0	42
F_1 gen.	95·7±3·2	7·6±1·4	19·4±2·2	interm.	blue		5·4±0·7	black	4	5	+2	35
P_1: *durum*	118·5±3·7	9·2±1·3	20·2±2·6	durum	blue-black		10·2±2·1	black	3	6	+4	28
					Genetic variations in some characteristics							
F_2 gen.	70—135 / 7	5—12 / 4	14—23 / 6	aestiv.	white blue blue-black		5—14 / 4	3—6 brown black	3—6 / 4	3—7 / 3	1 to 5 / 3	28—42
					Some interesting genotypes							
	66·4±5·9	5·8±1·2	18·2±1·6	compac.				white	4	4	+3	42
	78·3±6·1	6·2±1·0	2·7±2·1	aestiv.	white		7·5±1·1	black	5	5	0	42
F_5 gen.	82·6±7·2	8·5±0·6	21·3±1·8	durum	white		8·9±0·7	white	4	5	+4	28
	113·2±8·3	6·9±0·8	19·8±2·0	interm.	blue		7·6±0·8	black	7	4	+3	30
	125·6±8·6	10·6±1·5	23·7±2·2	spelt.	white		12·8±1·2	black	6	6	−2	42
					black		14·6±1·4					



a



b

Fig. 1. a) Parents: Produttore (left), *Tr. turgidum* (right). Centre: Genotypes of extreme length of the stem of F_8 gen. b) Ears of the parents: Produttore (left), *Tr. turgidum* (right).

Fig. 1. c) and d): Ears of some genotypes of F_s gen.

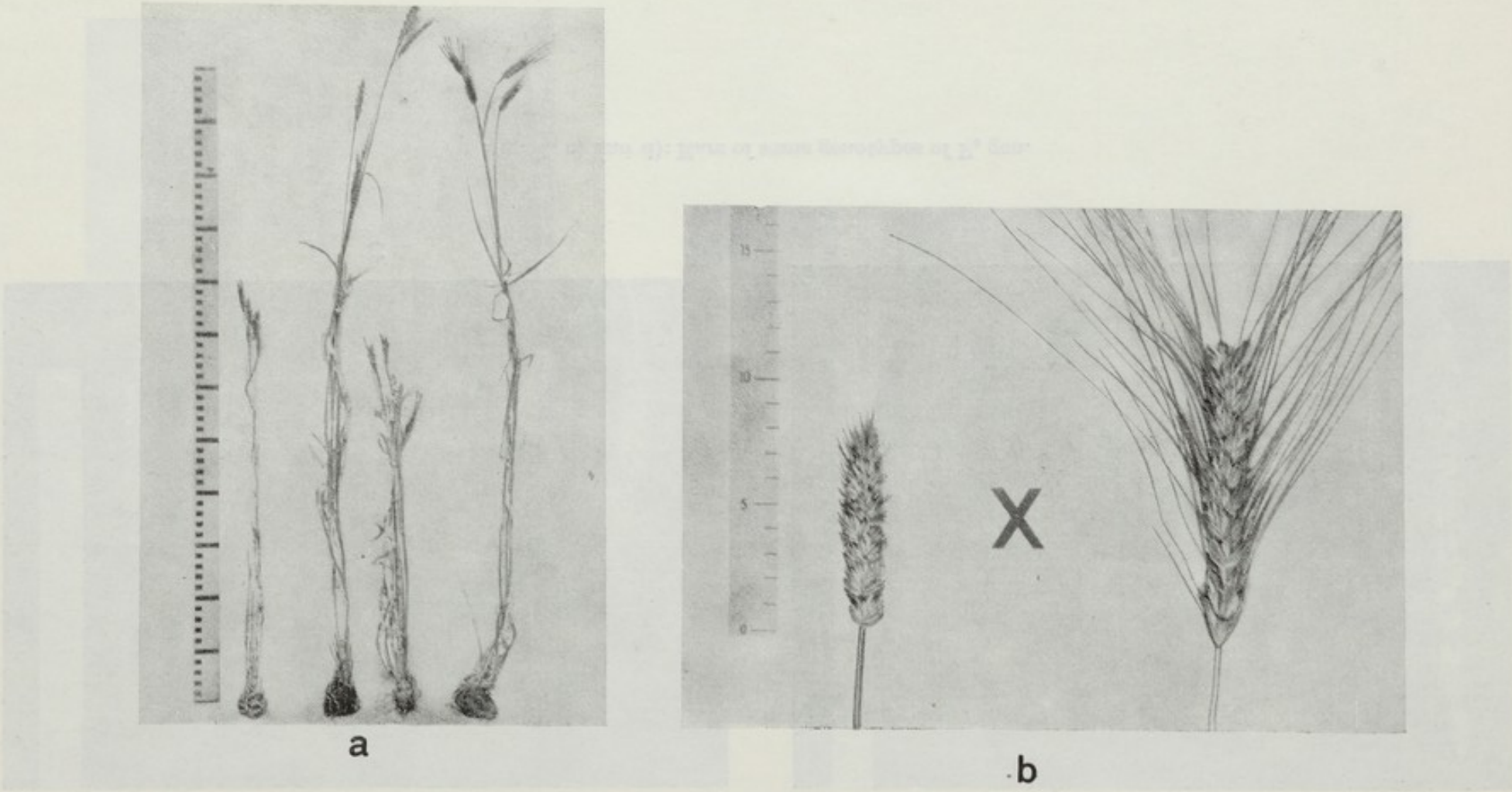


Fig. 2. a) Parents: San Pastore (left), *Tr. turgidum* (right). Centre: Genotypes of extreme length of the stem of F_5 gen. b) Ears of the parents: San Pastore (left), *Tr. turgidum* (right).

Fig. 2. c) and d): Ears of some genotypes of F_5 gen.

4. Of F_2 and F_3 gen. plants with combinations of the useful and interesting characteristics of the hexaploids of the improved varieties of *Tr. aestivum* and of tetraploids of *Tr. durum* and *Tr. turgidum*, as well as of new types, due to the interaction of different genes of the parent, selected and to the F_5 gen. reproduced to phaenotypically equalized forms, many are very promising for further breeding, such as shorter stem as in the parent of *Tr. durum* and *Tr. turgidum*, greater number of spikelets per ear and better quality of kernels, as in parent of *Tr. aestivum*, shorter veg. period and greater cold resistance, as of the parents of *Tr. durum* and *Tr. turgidum*, and greater resistance to *Puccinia graminis*, as of the parents of *Tr. aestivum*.

5. Our studies demonstrate the importance of the ecotypes of *Tr. durum* and *Tr. turgidum* for combining breeding with *Tr. aestivum* for the creation of winter varieties: varieties of *Tr. aestivum*, *Tr. turgidum* and *Tr. durum* for continental regions.

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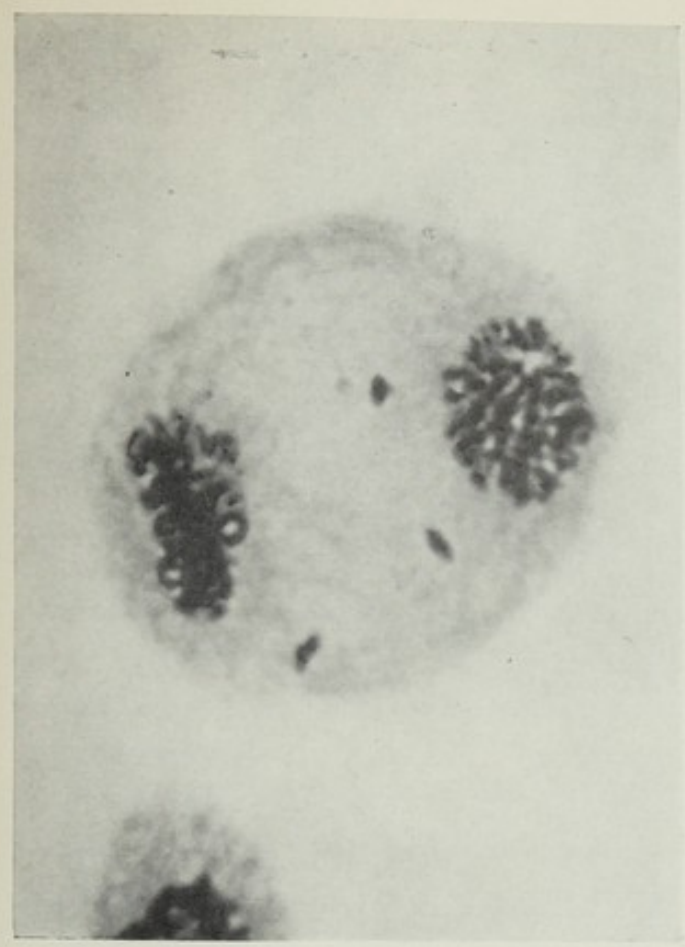

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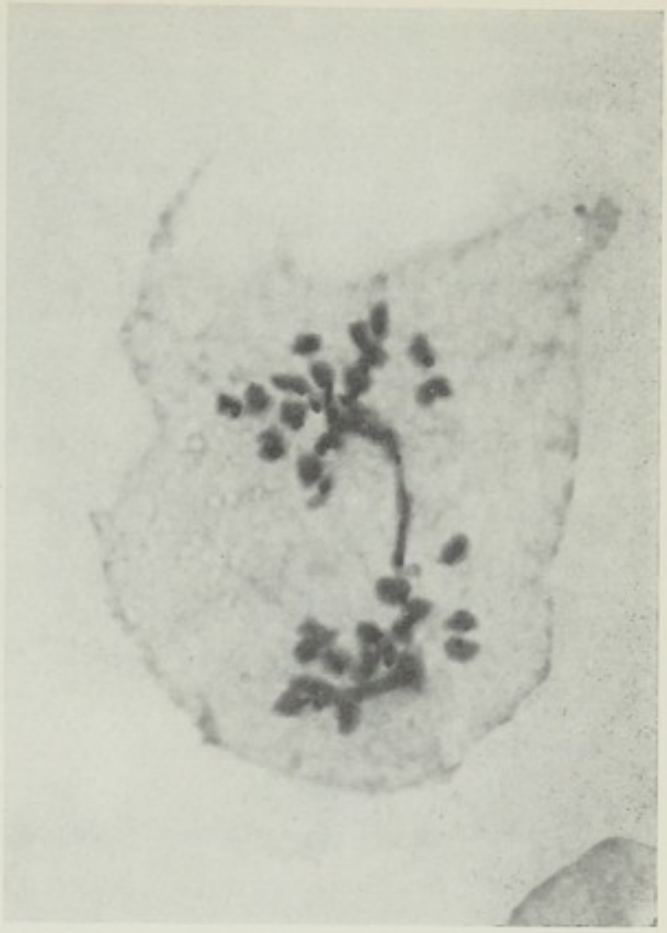

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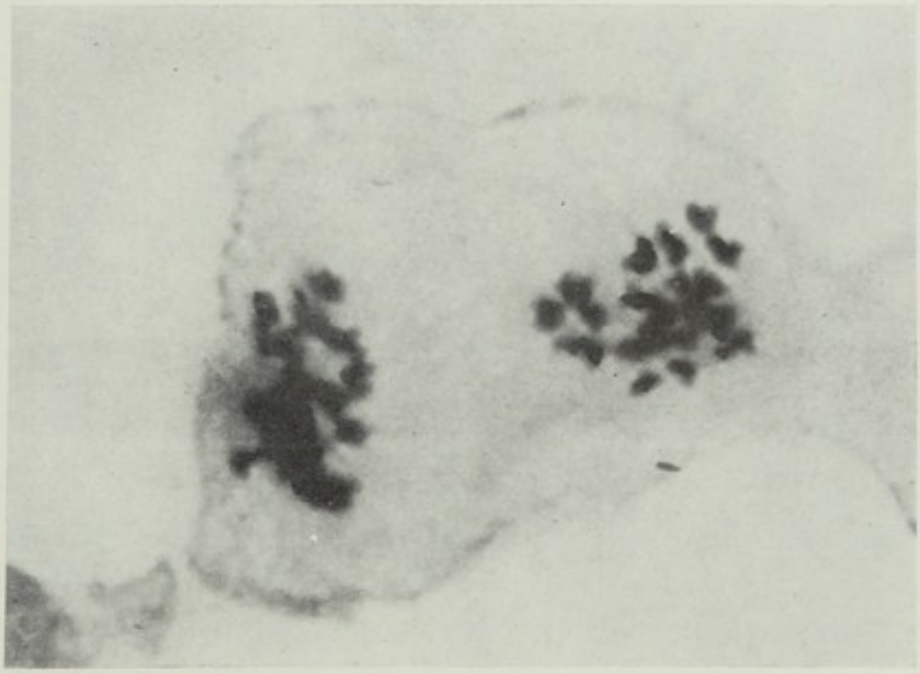
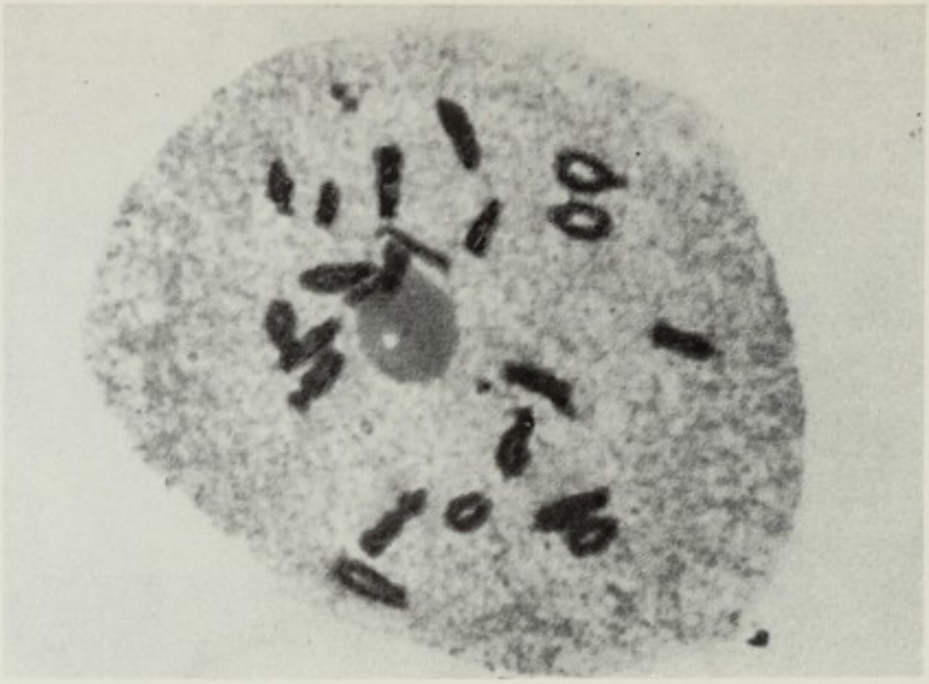


c

Cytological abnormalities in some genotypes of F_2 and F_3 gen.: a) 3 fragments of chromosomes; b) chromosomes bridges, 14 and 14 chromosomes; c) anaphase with 21 and 21 chromosomes; the cells of b) and c) were in the same anther.



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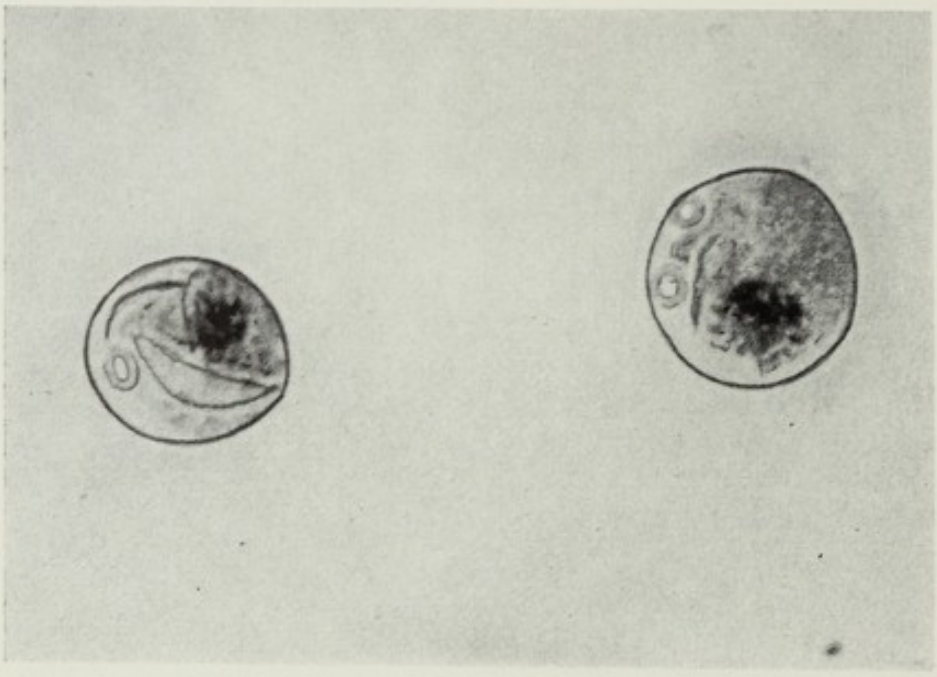

e

d) diakinesis with some fragments; e) one smaller pollen with one pore and n chromosomes, and one larger with 2 pores and $2n$ chromosomes. — d) and e): San Pastore × *Tr. turgidum.*

Mendelism and Animal Breeding

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In this centennial year of Mendel there is very little new about his contribution to animal breeding that can be added to what has already been said in the course of the last fifty years. But there are, perhaps, different ways of repeating these evaluations, especially if Mendelism rather than Mendel personally is taken as the point of departure.

Mendel's keen mind, his all-around scientific interests, his consuming curiosity about nature, are all too well known to require extensive documentation, at least under the topic assigned to me. His ventures into animal breeding were few. It has been reported that he kept white and grey mice in his room and probably made crosses between them. More authenticated are his extensive bee hybridization experiments undertaken, at least in part, in an attempt to establish a generalization of Mendelian laws embracing animals as well as plants. From Iltis's account, it may be surmised that it was the incomplete state of knowledge of sex determination in *Hymenoptera* that hindered this purpose. But irrespective of the material he worked with, there are two facts about Mendel which come to mind immediately should we want to explore the contribution of Mendelism to animal breeding.

Mendel

The first one of these is that Mendel's success in demonstrating the basis of formal genetics was based on his deductive approach to the problem. As Fisher pointed out over a third of a century ago, given three simple assumptions: 1) particulate inheritance, 2) structural geminal material, and 3) equal contributions by the two parents, deduction of the laws of heredity by any abstract thinker would be inevitable. Yet why was Mendel the only one of his day to make these assumptions, and why did his results, certainly not requiring any great intellectual effort to understand, go unheeded by a whole generation of biologists?

One is tempted to speculate that the deductive approach was characteristic of physical scientists and philosophers rather than of naturalists. It is, perhaps,

an ironic coincidence, but also possibly of deeper significance, that two of the really monumental breakthroughs in the study of heredity, Mendelism and the molecular biology revolution, were brought on by men whose primary training and original basic interests were not biological. At least with respect to the first, so it appears from Mendel's biography. And the argument that the ready acceptance of Darwin's equally deductive derivation of the theory of natural selection is evidence against the view that such means of arriving at knowledge are not foreign to biologists, is not a strong one. With but a few exceptions in the persons of Huxley, Haeckel, and others, the immediate readers of The Origin of Species who were its enthusiastic supporters were as likely as not physical scientists such as Lyell, philosophers or sociologists such as Spencer, and not naturalists such as Agassiz. Furthermore, of course, Darwin's deductions were not of a mathematical nature.

The second point is that Mendel clearly visualized the basic principle of multifactorial inheritance on which most improvement of plants and animals is based. This is shown from his comments following the description of the experiments on color inheritance in beans: "Whoever studies the coloration which results in ornamental plants, from similar fertilization, can hardly escape the conviction that here also the development follows a definite law, which possibly finds its expression in the combination of several independent color characters".

Clearly the extension of the idea that a continuous color range would be produced by a series of independently assorting hereditary units to other quantitative traits would have required only a short step from this formulation. But, in considering animal breeding, it is Mendelism and Mendelians rather than the prelate himself that must be the object of discussion.

Early Century Mendelism

The initial decades following rediscovery of Mendel's laws were characterized not only by the enthusiasm of the first converts but, as is well known, by the great bitterness in the debate between the two schools of thought on the nature of hereditary transmission. I need not dwell here on the controversy between the Mendelians and Biometricians which generated much light and even more heat. It is true that data from domestic animals were drawn upon by the polemicists of both sides, as it happened in the major confrontation of Hurst and Weldon regarding color inheritance in horses. But very little of the evidence adduced referred to polygenically determined traits of economic importance which we now generally associate with animal breeding.

The American Breeders Association, the ancestor of the present American Genetic Association, which pursued the study of the phase of evolution dealing

with plant and animal improvement, (called by some early proponents the science of thremmatology), held its first meeting in December, 1903. De Vries was the opening speaker and though Mendel was mentioned, it was only at the second meeting 14 months later that Castle prementioned examples of Mendelian bahavior in animals, and such Mendelizing trast as polling in cattle and wool color in sheep were considered.

It seems that it was the domestic fowl that first played a major role in the history of Mendelism as related to economic improvement of animals. It was, I think, Raymond Pearl, curiously enough a man with one foot in each camp, who made the first attempt to outfit a character of this sort with a simple Mendelian straightjacket. The trait, egg production in chickens, soon became a favorite subject for exercises of this type on both sides of the Atlantic.

Pearl's paper appeared in 1912. This fact led me to examine two animal breeding textbooks published in that year, in order to verify whether simple Mendelian schemes were already being invoked as panaceas for selection of livestock. One, a British volume (by J. Wilson) contained considerable emphasis on the application of Mendelism to livestock breeding, and even expressed optimism about its use in the improvement of quantitative characters.

The other, Marshall's American text, was much more reserved. Out of 290 pages only 20 were devoted to Mendelian inheritance, but much of that space was taken up by the discussion of the mutation theory of De Vries and other extraneous matters. Indeed, the author opined that "Although the results of Mendel's work have been freely spoken of as promising to revolutionize practical breeding it now seems that the matter is still chiefly of scientific interest". The curious dichotomous attitude that breeding and science cannot be combined is still, of course, reflected by many breeders of larger animals, though clearly in poultry improvement the only surviving practitioners are those who have relied on genetic methods in their operations.

In reality it is impossible to determine with any precision just how much the knowledge of genetics, either of the simple monogenic variety or of the complex mathematical type, has contributed to the rising levels of production. On the occasion of the fiftieth anniversary of the rediscovery of Mendelism, Lush presented a long series of graphs showing changes in yield in different classes of livestock in the course of the post-Mendelian era. Though much has been learned about the measurement of genetic changes under experimental conditions, concurrent changes in nutrition, sanitation and other aspects of management, make it nearly impossible to arrive at any reasonable partitioning of gains attained in the field. Hence the best Lush could say is that in his opinion "a large part of these truly astounding changes made in animal productivity over the last 20 to 50 years is genetic".

I think that most of us will be inclined to agree with this formulation without being able to make it any more precise. However, the point I want to make here is that the impact of the introduction of Mendelism to animal breeders came largely through their discovery of the fact that phenotype and genotype are not equivalent, and not through the direct application of Mendelian ratios to breeding procedures.

I want to emphasize this in another way, since I believe that it involves the most important one of the contributions that genetics has made to the practice of animal breeding. It is only through the understanding of the process underlying Mendelian phenomena that two very vital problems puzzling to the breeders of bygone days could be solved. The first one dealt with the question why animals with identical pedigrees differed in their hereditary endowment. Mendelian segregation supplied the answer. The second question was why animals identical in performance would transmit vastly different potentialities to their offspring. The first exercises in Mendelism gave one answer to this problem by invoking dominance. Later multiple factors came to supplement it, and, still later, methods of statistical partitioning of variability into genetic and environmental sources gave a fuller reply.

There were also steps in the wrong directions that came as a result of Mendelism. For one thing, the temptation to explain the inheritance of physiologically complex processes in terms of single gene variation, was no doubt overpowering and many, or even perhaps the vast majority of early Mendelians dealing with animal breeding, fell victim to it. One may ask how much harm was actually done by the essays of geneticists to fit data on the inheritance of economic traits to one, two or three gene distributions. From the standpoint of practical breeding probably not very much, if the damaging effects due to the seeds of distrust in genetics implanted in disappointed breeders by poor advice based on such naive considerations are discounted. Otherwise, since some morphological characters (e.g. presence or absence of horns, color) and many lethals behave for all practical purposes as if determined by single gene pair differences, Mendelian advice may have been useful. Other instances, where many gene pairs had to be invoked, were so complicated that artificial interpretations in the form of arbitrarily assumed interactions between several loci would in any case have no very serious practical consequences.

The more serious damage which the overenthusiasm of early Mendelian studies produced was probably in the academic field. Here the ready acceptance of formal schemes which often had to be of completely unverifiable complexity, prevented full exploitation of experimental material which was gradually becoming available to research institutions. In addition, training in the older tradition produced resistance to acceptance of new ideas, a reluctance to undertake a rigorous preparation in mathematics, lack of understanding of statistical principles and various other barriers to progress. Although the

continental European schools of animal husbandry have been the worst offenders in this respect, we in the United States have also had our share of obstructionists, fortunately now reduced to a relatively few diehards. I must, of course, insist at this point that I do not claim that the current notions involving the application of population genetics to breeding are the final word on the subject. But in the meantime, the type of approach to animal breeding developed by the quantitative geneticists, while firmly established in some classes of livestock, is still not accepted by many breeders of large animals.

The Rise of Mathematical Genetics

It was the idea of particulateness of inheritance that permitted development of the quantitative theory of selection. In essence, the basis for these developments lay in simple or beanbag Mendelian genetics. In one of the papers written by Haldane just before his premature death, he defended this approach to evolutionary theory against Ernst Mayr's chalenge formulated in his monumental book on animal speciation. When the legacy of such genetics to modern animal breeding theory is considered, no defense seems to be necessary, except against its overzealous supporters of the nineteentwenties and thirties, now mostly gone, and from a few relics of those days, who either will not or, possibly, cannot understand even the elementary quantitative method— of studying heredity.

The fact that it was the mathematical school of beanbaggers that laid the foundation of modern agricultural genetics is, of course, not in dispute. Even if it cannot be said that such a powerful breeding tool as the introduction of hybrid vigor into agricultural practice should be credited to this source, the efficient exploitation of this essentially Mendelian phenomenon still derives from the work of the mathematical school.

Starting with simple Mendelian algebra, the three architects of quantitative genetics, Fisher, Wright and Haldane, have laid down the foundations of the current theory of plant and animal improvement, with the superstructure of animal breeding planning erected by Lush and his school, and of biometrical genetics highlighted by Mather and his followers, based directly on them.

Haldane, in referring to the three main lines of developemnt of this theoretical framework, with typical whimsy, christened the first two, respectively, the Halieutic (from the Greek equivalent of Fisher) and Tectonic (from the Greek for Wright), while modestly alluding to the third one as "my own". If feel that the eponymic triad should be completed, identifying the line of Haldane's mathematical tool design with his name. Unfortunately, deriving from the Teutonic "half-Dane", it is for obvious reasons not directly translatable either into classical Greek or into Sanskrit, which, I suppose, he would

have preferred. The closest equivalent (for which I am indebted to Dr. H. Sharat Chandra) is Ardhauthareyan (from Ardha, — half and Uthareya, — originating from the North). Though I have little hope that this neologism will live any longer than the two proposed by Haldane, my intent in suggesting it is as serious as was his. I only feel sad that we shall never know what his response (possibly in the form of a quotation from Dante) to my suggestion would have been.

But to return to the more immediate topic, it was the development of Mendelian algebra that permitted a quantitative approach to animal improvement, allowed the possibility of advance evaluation of selection results and thereby eliminated much of the guesswork in and folkloristic attitude towards breeding. Perhaps a brief review of some of the concepts underlying current breeding programs, which developed essentially from the simple bases of Mendelian heredity, is pertinent here.

Bases of Current Breeding Practice

The first of these refers to the concept already alluded to: the partitioning of phenotypic variance into its component genetic and environmental portions. It was the application of statistical methods to the Mendelian scheme of transmission that made this operation possible. In consequence, determination of the heritability of economic traits now presents the first order of business in devising a breeding program. Instead of the pre-Mendelian recipes for success in breeding based on percentage of blood, linebreeding, and similar other vague notions, a quantitatively assessed distinction between performance and genetic endowment is possible. Whereas it is likely that in pre-Mendelian days selection between breeders may have played a greater role in animal improvement than selection by breeders within their on flocks or herds, today this may only be true at the level of economics rather than of biology.

It must, of course, be realized that we still do not know everything that we need to know about selection. The prediction range for gains based on computations involving heritability is a reasonably short one. A priori estimates of the changes to be expected from one or another scheme of selection and mating are usually fairly reliable for unimproved traits. But estimates for populations in which a high level of average performance has been reached, often prove to be erroneous. Whether this indicates deficiencies in the general theory of selection or a change in the parameters entering the computations is not always clear. In any case, the possibility of even short-term predictions has undoubtedly increased the efficiency of breeding operations and has placed sib and progeny testing, pedigrees, and individual performance into their proper places in the scheme of things.

Even more sophisticated developments of selection theory have led to the

construction of selection indexes both as aids in the improvement of single traits and, of possibly greater significance, in multiple-objective selection. One may wonder how Bakewell would have fared, had he been forced to work with the multiplicity of characters of relatively low heritability that a modern breeder has to take into account if he is to survive in competition with others. For example, to use the class of stock most advanced with respect to quantification of selection criteria, the chicken, we find that a breeder concerned with egg production has to consider fertility, hatchability, percentage of cull chicks, early mortality, mortality to 60 weeks of age, broodiness, body size, age at first egg, rate of production, egg size, specific gravity of eggs, egg shape, albumen score, shell texture, shell color, and incidence of blood spots in his selection program.

It seems abundantly clear that independent selection for each of these traits, without reference to their heritabilities, their economic values and correlations between them, could not be carried out in any rational way. Selection indexes based on Mendelian inheritance can, on the other hand, with the aid of computers, lead to objective and fully repeatable choices of the parents of the next generation. If they sometimes fail to produce the expected gains, their deficiencies must be looked for in the same causes as those involved in the simple mass selection predictions.

Still a further extension of basic Mendelian theory lies in the choice of mating system and the somewhat more theoretical problem of genetic balance. Both of these issues are intimately tied up with the problem of heterosis which, in spite of extensive studies, in many ways still remains a problem. Though hybrid vigor was observed and used somewhat haphazardly in pre-Mendelian days, it was only with the firm establishment of Mendelian principles that the beginnings of a theoretical foundation for this phenomenon appeared. It is doubtful that it would have occurred to many early poultry breeders that unattractive, weak and poorly laying inbred birds would be capable, through judicious selection of mates, of producing offspring of high quality. Whatever theory of heterosis is accepted, be it based on linked dominant genes, on real or pseudo-overdominance, on genotype-cytoplasm interaction, or on physiological considerations, underlying it must be one or another aspect of Mendelian inheritance and Mendelian algebra. It may be true that we are still foundering in attempting to interpret the basis of heterosis because we are too committed to the classical forms of mathematical genetics. Perhaps a revaluation of the whole subject based on a molecular approach (e.g., is it clear that substitution of nucleotide pairs for the 1920—30 concept of a gene would produce identical results regarding the micro-evolutionary processes?) will be necessary before we fully understand heterosis. But the fact that the technique of its utilization, rooted in Mendelism, has contributed immensely to current standards of production in several classes of animals, is patently clear.

Similarly, the ideas regarding genetic balance, both on the individual and population levels, derive from Mendelian considerations. Whatever the role of genetic homeostasis may be in natural populations or in man, its manifestations in relatively inbred domestic animals seem to be well established. However, it is likely that the eventual explanation of this and related phenomena will have to come not from studies on animals of economic worth, but from *Drosophila* with its exquisitely analyzed system of Mendelian markers. Indeed, as Haldane has noted, livestock breeders, with few exceptions such as autosexing in chickens and similar trick breeding in silkworms, have not availed themselves of the full arsenal of techniques used by *Drosophila* workers. I suspect that this as yet is not possible to any extent. But when the polygenic traits of the various economically useful animals are more fully analyzed in terms of their physiological and biochemical components, it is possible that trick Mendelian breeding will come into its own.

Where Do We Stand?

The history of science has been said to be the history of errors corrected. Mendelism in application to animal breeding has, indeed, overturned many of the delusions, fallacies and misconceptions of the earlier practitioners of the art. Indeed, it was Mendelism that introduced the first elements of science, including predictability, into livestock improvement. So far the period of time in which it had an opportunity to contribute to breeding practice has been very short relative to the length of the inter-generation interval of the larger animals. How much of an ingredient of such operations our present quantitative methods will remain in the future cannot be foreseen. With the rapid advances to be expected in what Lederberg has called euphenics, and with eventual possibilities of genetical engineering in prospect, it is not unlikely that the application of current selection and mating principles will become obsolete. But Mendelism as an explanation of the fundamental mechanism of inheritance is not likely to be discarded soon.

Fisher in 1936 in reference to Mendel said that it is clear "that since 1900, in spite of the immense publicity it has received, his work has not often been examined with sufficient care to prevent its many extraordinary features being overlooked, and the opinions of its author being mis-represented. Each generation, perhaps, found in Mendel's paper only what it expected to find; in the first period a repetition of the hybridization results commonly reported, in the second a discovery in inheritance supposedly difficult to reconcile with continuous evolution. Each generation, therefore, ignored what did not confirm its own expectations".

I think that today we should not be open to this charge. The first two decades

of this century were devoted by animal geneticists to to furthering understanding and to elaboration of Mendelian principles. The twenties and the thirties saw the development of quantitative Mendelian theory. The forties and the fifties represented the era of enthusiastic application of these to animal breeding. In the mid-sixties, I believe, a somewhat more cuatious appraisal of the level of our knowledge and of the power of our genetical tools, than such as I myself made in 1950, is warranted. But be that as it may, it seems to me that this reservation applies more to the future than to the evaluation of the past or particularly to Mendel's own work.

Let me then conclude by a reference to what a famous Brno biologist said of his illustrious predecessor. I speak of Dr. Jaroslav Kříženecký, whose absence from our proceedings today is a cause of profound regret to all of us. I have never had the good fortune of meeting him in person, but we have exchanged reprints since long before World War II, and corresponded at length in the difficult days that followed it. I have always admired the breadth and thoroughness of his publications on animal breeding. In looking over my file of his works, I find, in addition to theoretical studies, papers on milch cows, on perch, on geese, swine, chickens, rabbits, guinea fowl, pigeons, and ducks; on endocrinology, reproduction, selection, growth, statistics, physiology, egg quality, development, marketing, nutrition, incubation; in short, on every major aspect of the zootechnical sciences. It was a cruel fate that prevented him from attendance at our symposium which was so dear to his heart. My remarks on Mendelism and animal breeding could be, it seems to me, concluded most appropriately by quoting Dr. Kříženecký's own words spoken (in Czech) nearly thirty years ago at another international meeting held in this country. In evaluating the import of Mendel to the agricultural sciences, he said:

"Mendelism made it possible to unite explicatively a series of isolated facts interpreted earlier casuistically through various imaginative concepts, into a uniform system of general concepts... Specifically, Mendelism affected systematic research and the collection of facts and data, and thus paved the way towards our understanding of the hereditary transmission of qualities in plants and animals. This alone represents an enormous, concrete contribution to our knowledge and to our means and ways of breeding better animals and plants."

Mendel and Human Genetics*)

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Mendel left no records concerning studies in human genetics. His biographer Iltis, however, states that Mendel had shown persistently great interest in hereditary phenomena in man and in anthropological and medical problems. He studied the records of old Brno families for aspects of inheritance and, in his own kindred, made careful observations of peculiarities in hair form, hair color, and body size in successive generations. Regualrly he took measures of body dimensions of his growing nephews and he often attended autopsies in a hospital. Had Mendel's time not gradually been completely absorbed by his duties as abbot of his monastery, it might be surmised that he would have reported on his observations on man, expanded them and, with the insight gained from his experiments on peas, been able to clarify problems of human inheritance in such a way as to be counted a direct founder of human genetics. But it hardly changes the situation that Mendel did not make a specific contribution to that field. His basic discoveries in plants could be applied to man without requiring new insights.

Human genetics had a slow growth. This has been ascribed to the difficulties which man with his long life span, his small families, and the absence of scientifically controlled matings offers to genetic analysis. It has also been ascribed to the dampening effect on bona fide research which resulted from class and race prejudice within the eugenics movement. Undoubtedly both of these aspects had some influence, but perhaps most important was the fact that for decades the best minds working in genetics were interested in the general phenomena of inheritance, not in their expression in specific species. "If you want to study the genetics of rabbits", it has been said informally some forty years ago, "study rabbits. If you want to study genetics, study *Drosophila!*". Replace the word *Drosophila* for a still earlier period by pea *(Pisum)*, fowl, sweet pea *(Lathyrus)*, or gypsy moth *(Lymantria)*, and by bread mold *(Neurospora)*, colon bacterium *(Escherichia)*, or bacteriophage for

*) This paper appears also in Proceedings of the American Philosophical Society, vol. 109, 1965.

a subsequent one, and it becomes understandable why human genetics remained peripheral to the center of genetic advance.

Beyond such influences on the development of a field, its history may depend on extrinsic phenomena, such as the state which related areas have attained. Mendel's paper can serve as an illustration. The reason that it remained without influence for thirty-five years and then, on its "rediscovery", was immediately recognized in its importance, depended primarily on what had happened during the intervening period. This period had included the discovery of chromosomes and their behavior in cell division and gametogenesis, an intensive study of biological variation, and the formulation, by Weismann, of a conceptual framework for a theory of heredity, development, and evolution. The time was ripe for Mendelism.

One additional element should be mentioned which influences the growth of knowledge. This is the limitation of individuals and communication between individuals which leads them to recognize only slowly the significance of new findings, whether made by others or by themselves. The development of human genetics furnishes examples for such delays, as will be shown in the following pages.

There are many interweaving threads in human genetics. A few main strands will be followed here in artificial separation from one another. The discussion will halt at the time when human genetics became of age, at the end of the period between the two World Wars.

Pedigree analysis

Careful descriptions of pedigrees and the establishment of empirical rules of inheritance of specific traits preceded the recognition of Mendel's work (Fig. 1, center). Already the Talmud gave evidence of knowledge concerning the mode of transmisson of hemophilia, and Nasse, in 1820, gave a specific formulation of it. Maupertuis and Réaumur, in the middle of the eighteenth century, each described in admirable detail a pedigree of polydactyly. The discovery of red-green color blindness in an English boy (Whisson 1779) was accompanied by the realization of its occurrence in other members of his family and of its hereditary nature. This was followed by other studies of "Daltonian" color blindness and, one hundred years later, by Horner's codification of the empirical facts of transmission. In 1814 the physician Joseph Adams wrote a penetrating Treatise on the Supposed Hereditary Properties of Diseases, in which the modern reader can discern many of the features of both general and specifically human genetics now familiar to us. Sedgwick, in 1861, assembled extensive data "On Sexual Limitation in Hereditary Disease", and Huntington, in 1872, accurately described

the mode of transmission of a hereditary chorea which now carries his name. In an impressive memoir, "Upon the Formation of a Deaf Variety of the Human Race", Alexander Graham Bell, in 1883, showed the hereditary basis of many instances of deafness and emphasized the fact of preferential marriage between deaf mutes. All these studies, however, remained separate and mostly without further consequences. Even when the rules of inheritance of a trait were clearly described, no underlying causes were recognized, so that the level of the discussions rose only slightly above that of casuistics. This became different as soon as Mendel's work was rediscovered. When Garrod began to study the biochemistry of alkaptonuria and became aware of its familial occurrence, Bateson suggested that it might well be a recessive Mendelian trait (1902). A year later Farabee (1903a), described a Negro kindred with several occurrences of albinism as evidence for the recessive nature of this trait. During the winter of 1901—1902 Farabee had attended Castle's lectures on inheritance at Harvard University in which the latter interpreted albinism in mice as being due to a recessive allele. In 1903 (b) Farabee filed his doctoral dissertation, which contains a description of a large Pennsylvania kindred with brachydactyly and demonstrated convincingly that the trait followed the transmission of a dominant gene (or "character" as it still was called). Ever since, in a steady stream, innumerable pedigrees have been published, largely concerned with abnormal and medically significant traits. Variations within the normal range were likewise interpreted in Mendelian manner, eye and hair colors being the first two examples (G. C. and C. B. Davenport 1907, 1910; Hurst 1908). A third example concerns the human A—B—O blood groups which were discovered by Landsteiner (1900, 1901). Their inherited nature was recognized by von Dungern and Hirschfeld, and a two gene-pair hypothesis was proposed. We shall return to this topic. Mendelian segregation became also apparent in racial crosses as for various anthropological traits in the Rehoboth hybrids between Caucasians and Hottentots in South Africa (Fischer), and, for skin color, in the Negro-Caucasian hybrids of Jamaica (Davenport 1913). This was of general significance since the belief in a non-Mendelian "blending" inheritance in racial mixtures had been particularly strong.

The recording of a single pedigree or a few pedigrees for a given trait was expanded into monographic treatments of all its known incidences. Pearson's monumental Monograph on Albinism (1911—1913) and the series of many volumes entitled The Treasury of Human Iheritance which was founded by him in 1912 and still continues publication, as well as Cockayne's Inherited Abnormalities of the Skin and its Appendages, furnished abundant data not only for the conclusions of their authors but also for independent investigators in need of facts.

The enthusiasm of many workers was both a boon and a danger in the early days of genetics. Hurst, for instance, the student of eye-color inheritance, was "a tireless worker and full of ideas, but over-apt to find the 3 : 1 ration in everything he touched" (Punnett 1950). Only gradually did a truly critical attitude toward pedigree studies evolve. The first one who saw the methodological problems posed by analyses of pedigrees was the physican

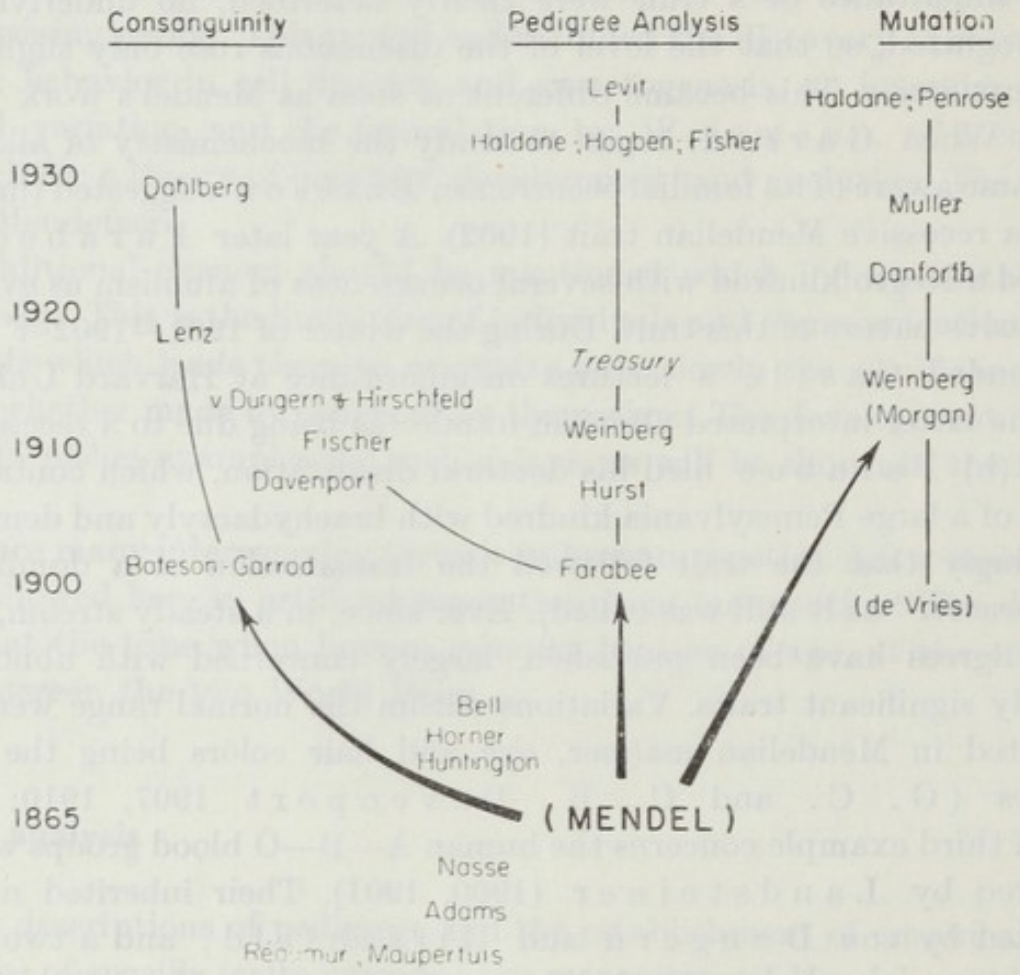

Fig. 1. Trends in the history of human genetics: pedigree analysis, consanguinity, and mutation
In this figure as well as in the similar figures 3 and 4, the selection of names of investigators does not lack arbitrariness. While the inclusion of persons can probably be defended in most cases, absence of names can often be excused only by the attempt not to overload these schematic presentations. Names in parentheses refer to individuals not directly concerned with human studies. The word "Treasury", in italics refers to a specific serial publication (see Bibliography under K. Pearson, ed.).

Wilhelm Weinberg. Beginning in 1908 with a paper on the demonstration of inheritance in man, and particularly in a publication of 1912 on methods and sources of error in studies directed toward Mendelian proportions in man (1912a), he devised means of correcting for various types of ascertainment. The fact which had concerned Bateson (1909) and for which Garrod showed an intuitive though not explicit understanding, namely, that the frac-

tion of albinos in segregating sibships from normal parents is higher than the fraction 1/4 expected from Aa × Aa crosses, became comprehensible as the necessary deviation from Mendelian expectation when it remained uncorrected for biases introduced by family selection. Little further progress in this area was made for twenty years; then Hogben (1931), Haldane (1932a), Fisher (1934), and others began to apply their rigorous minds to the problems of pedigree analysis. During this period also it was recognized generally that the manifestation of many genotypes varies from person to person. The bearing of incomplete penetrance on the problem of dominance in man underwent an important analysis by Levit (1936).

The knowledge of Mendelism early made possible a new interpretation of the effects of consanguinity (Fig. 1, left). This age-long problem had been actively followed in the nineteenth century, with the pioneering inquiry by Bemiss (1858) deserving specific mention. Again, the facts gained remained without a rational foundation. When, however, Garrod (1901) noticed that in three out of four sibships containing alkaptonuric individuals the parents were first cousins or otherwise closely related, Bateson (1902) furnished the expalnation. He reasoned that a person who carries a rare recessive gene would have a low chance to marry an unrelated person who also carried this rare gene, but a high chance, in case of consanguinity, to have his spouse be a carrier who had inherited the gene from a common ancestor. It seems to have occurred to no one to provide a quantitative expression for this relationship until Lenz's article in 1919. Then, beginning in 1927, Dahlberg refined the mathematical treatment of consanguinity which in recent years has become a central issue in the study of the genetic load of populations.

The problems of this load will not be a topic of this account, but a brief reference is indicated to the mutations which compose a highly important part of it (Fig. 1, right). Mendel did not make a direct contribution to the problem of the origin of different varieties of a gene, of its alleles. On the other hand, de Vries was led to his rediscovery of Mendel's paper by his earlier studies of genetic changes in the evening primrose. Morgan, of course, who first discovered as well as analyzed mutations in *Drosophila*, came to genetics via Mendel and de Vries. The epochal success of his former student, Muller, in "Artificial Transmutation of the Gene" (1927) by means of x-rays, was used by him immediately to call attention to the possibilities of radiation-induced damage to human genes. It was not the first time that mutations in human genes had been considered by modern investigators. Weinberg, in 1912 (b), noted the tendency of last-born children to be more frequently affected by dwarfism than would be expected by chance. He suggested that, if more exact analysis should indeed show this to be the case, this would speak for mutation from normal to dwarfness increasing in frequency with age of the parents. Danforth, in 1923, actually estimated

human mutation rates, assuming an equilibrium between mutational input and selective outgo of unfavorable genes. His pioneering paper remained without consequences and the same method had to be re-invented, in 1935, by Haldane and Penrose (see Gunther and Penrose).

Population genetics

Mendel himself was the first who, on the basis of his particulate theory of inheritance, attacked a problem not only of the genetics of individuals and their progeny, but also of a whole population. After having established the 1 : 2 : 1 ratio for homozygotes of one kind: heterozygotes: homozygotes

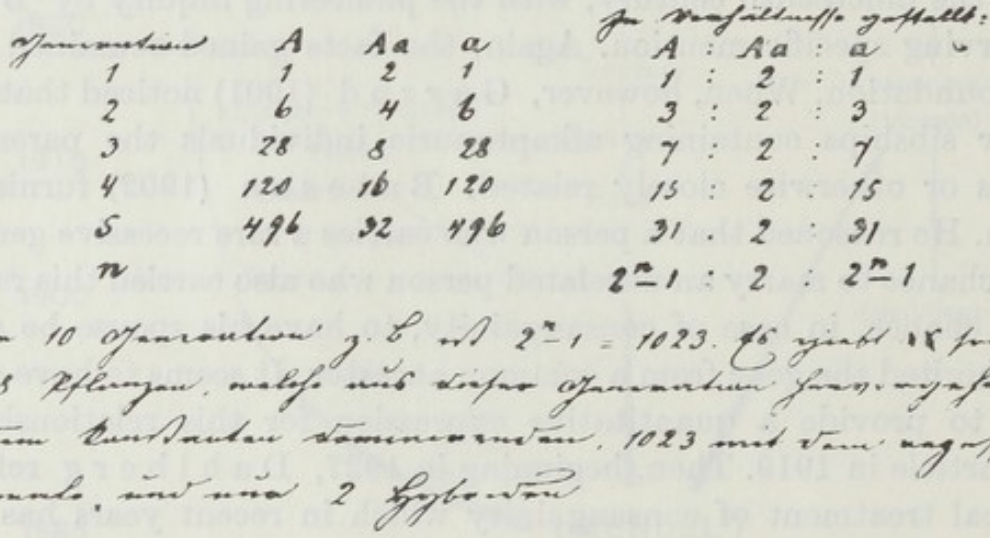

Fig. 2. Mendel's analysis of a problem in population genetics. From pages 37—38 of the facsimile of Mendel's manuscript of his "Versuche über Pflanzen-Hybriden" reprinted in L. Gedda, Novant'anni delle leggi Mendeliane (Instituto "Gregorio Mendel," Rome 1956).

of the alternative kind in the F_2 generation of his crosses, he asked what ratios would be found in the further generations of the F_2 population. Peas are self-fertilizing plants, and Mendel found that in this instance the proportions of the three genotypes change from generation to generation. He obtained an algebraic expression for this change, yielding the proportions $(2^n - 1) : 2 : (2^n - 1)$ where n is the number of generations beginning with the F_2 (Fig. 2).

Most organisms do not reproduce by selfing, a fact which is obvious for species with separate sexes. It was natural, therefore, that the question arose concerning the proportions of genotypes in various generations of crossbreeding forms, but the way in which this came about and the slow steps by which it was answered make a fascinating chapter of genetics (Fig. 3, left).

Before 1900, beginning with Galton and deepened by Karl Pearson, a biometric school had developed in England which formulated laws of inheritance of a statistical nature. Basing their work primarily on measure-

ments of human stature, the biometricians determined correlation coefficients between groups of parents and children, and between other groups of related individuals. Galton (1897) derived from his data a "Law of Ancestral Heredity": "The two parents contribute between them, on the average one-half... of the total heritage of the offspring; the four grandparents, one-quarter..., and so on". Pearson (1904) modified Galton's specific conclusions but upheld its basic tenets. It was the assumption of genetic

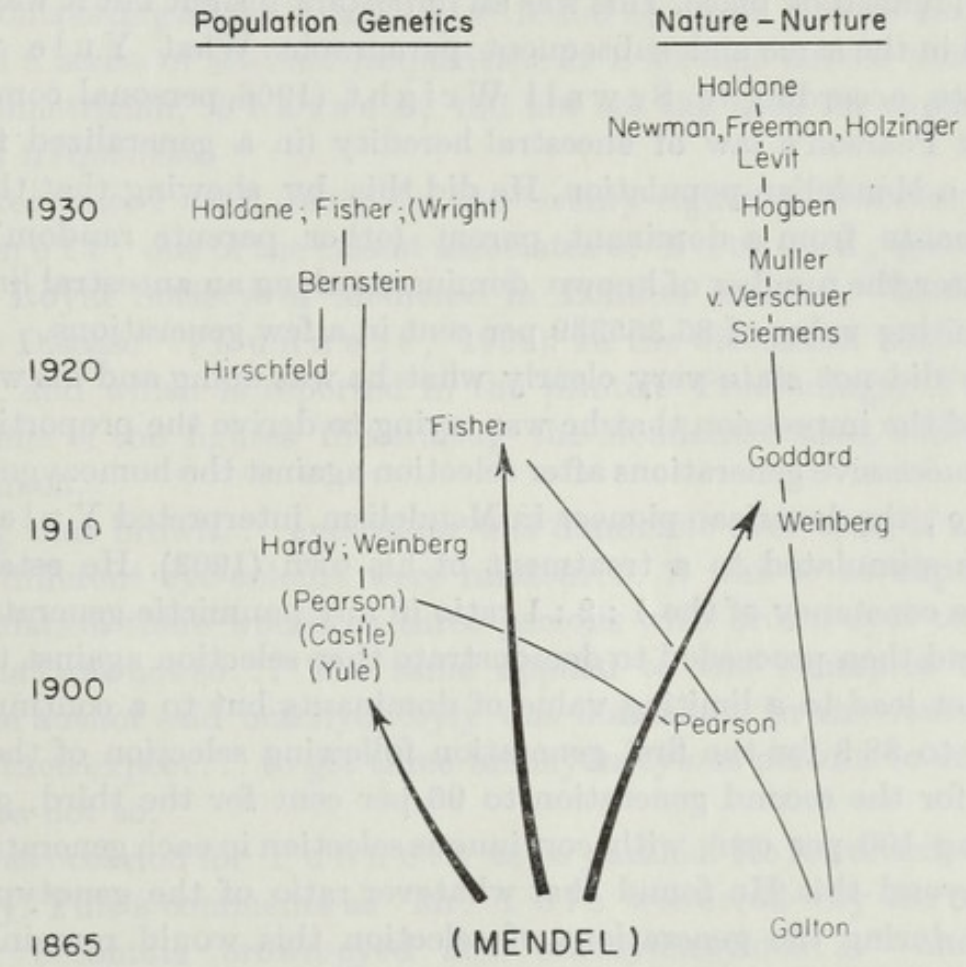

Fig. 3. Trends in the history of human genetics: Population genetics, and nature-nurture.

contributions of the preparental ancestors which disturbed the Mendelians. Mendel's law of segregation centered on the purity of gametes. A homozygous recessive parent, even if derived from two heterozygotes, would only transmit his own recessive genes, uncontaminated with dominant ancestral influences. Likewise, a homozygous dominant parent with earlier recessives-bearing parentage would transmit only his own dominant genes, free from recessive ancestral contamination. Bateson insisted that Mendel's law of segregation and the law of "ancestral heredity" could not both be applicable to the same class of cases. The biometricians, on the other side, either felt that there was no inconsistency between the two, or that Mendelian genetics was not applicable generally. The basic conflict between Galton's and

Mendel's laws led to a violent controversy in which the standard bearers were W e l d o n for the biometricians and Bateson for the Mendelians.

In 1902 the statistician Y u l e published a discussion on Mendel's Laws in which he took Weldon's side, though he was "inclined to agree with Mr. B a t e s o n as to the p o s s i b l y very high importance . . . of Mendelian phenomena". In his paper he correctly derived the fact that an F_2 generation would preserve its 1 : 2 : 1 ratio in all later generations, provided that random mating between all individuals took place. This was an important insight but it was lost in what followed in the same and subsequent paragraphs. What Y u l e wished to demonstrate, according to S e w a l l W r i g h t (1966, personal communication), was that Pearson's law of ancestral heredity (in a generalized form) applied in such a Mendelian population. He did this by showing that the proportion of dominants from a dominant parent (other parents random) was greater the greater the number of known dominants along an ancestral line, approaching a limiting value of 85.355339 per cent in a few generations.

Y u l e did not state very clearly what he was doing and his wording easily produced the impression that he was trying to derive the proportion of dominants in successive generations after selection against the homozygous recessives. C a s t l e , the American pioneer in Mendelism, interpreted Y u l e in this way, and was stimulated to a treatment of his own (1903). He established once more the constancy of the 1 : 2 : 1 ratio in any panmictic generation following the F_2 and then proceeded to demonstrate that selection against the recessives would not lead to a limiting value of dominants but to a continuous increase from 75 to 88·8 for the first generation following selection of the dominants, to 93·7 for the second generation to 96 per cent for the third, gradually approaching 100 per cent with continuous selection in each generation. C a s t l e went beyond this. He found that whatever ratio of the genotypes had been reached during the generations of selection this would remain constant in future generations once selection had been discontinued. "In general, as soon as selection is arested the race remains stable at the degree of purity then retained . . ." Thus, he had discovered an equilibrium law not only for the 1 : 2 : 1 ratio but for the infinitely large class of all ratios resulting from selection against recessives. With this successful defense of Mendelism against Yule's presumed position, C a s t l e returned to his breeding experiments, little aware of the gold which he had found in the still undefined area of population genetics. His paper remained largely unnoticed and even Y u l e seems not to have responded to it in printed form. When, twelve years later, N o r t o n provided P u n n e t t (1915) with a table on the effect of selection against Mendelian genes and, a further two years late, P u n n e t t (1917), with help from the mathematician H a r d y , wrote a note in which he showed the slow progress to be expected from the elimination from reproduction of supposedly simple homozygous recessive feebleminded individuals, they essen-

tially followed Castle's steps (1903) but did not know that they had a predecessor.

Within a year after Castle, and obviously without knowing of his findings, Pearson himself proved the stability of the 1 : 2 : 1 ratio ina panmictic population. He also derived the results of panmixis when more than one pair of alleles were involved but always still based on an initial F_2 generation.

In modern terms, Pearson considered only the case of equal frequency of the two contrasting alleles A_1 and A_2 or (A and a), while Yule and Castle included a series of selected frequencies. It is strange indeed that the outstanding biometrician, Pearson, did not see the need for expanding the study to all frequencies.

The matter rested until 1908. On the twenty-eighth of February of that year Punnett, one of the closest associates of Bateson, gave a lecture before the Royal Society of Medicine in London entitled, "Mendelism in Relation to Disease" (Punnett, 1908). In the discussion which followed the lecture, and which is reported in the printed Proceedings, Yule referred to some of the figures illustrating the Mendelian cases, which puzzled him very much.

Assuming that brown... eye-colour was dominant over blue, if matings of persons of different eye-colours were random... it was to be expected that in the population there would be three persons with brown eyes to one with blue; but that was not so... The same applied to the examples of brachydactyly. The author said brachydactyly was dominant. In the course of time one would then expect... to get three brachydactylous persons to one normal, but that was not so.

Now it was occasion for Punnett to be puzzled. He reworded, somewhat inaccurately, Yule's comments as "Mr. Yule wondered why the nation was not slowly becoming brown-eyed and brachydactylous..." and replied, "So it might be for all he knew, but this made no difference to the mode of transmission of eye-colour or brachydactyly." Punnett, however, did not feel content with his own comment. On his return to Cambridge he at once sought out G. H. Hardy, whom he knew well, for they acted as joint secretaries to the Committee for the Retention of Greek in the Previous Examination and also used to play cricket together (Punnett, 1950).

Knowing that Hardy had not the slightest interest in genetics I put my problem to him as a mathematical one. He replied that it was quite simple and soon handed me the now well-known formula $pr = q^2$ ("where p, $2q$ and r are the properties of AA, Aa, and aa individuals in the population varying for the A-a difference". See footnote p. 9 in R. C. Punnett 1950.). Naturally pleased at getting so neat and prompt an answer I promised him that it should be known as "Hardy's Law" — a promise fulfilled in the next edition of my Mendelism.

The essence of Hardy's finding is the constancy of the distribution of the three genotypes after the second generation whatever the values of p, q and r may be, that is, whatever the frequencies of the two alleles may be. Specifically, Hardy showed through two examples that the proportion of brachydactylous persons, if the trait is dominant, will have no tendency whatever to increase, and if it were recessive, would have no tendency to decrease. It may be added that, while Hardy pointed out that he had considered only the very simplest hypothesis possible, he had actually trated, for the first time, the problem of genetic drift which was to become so important in Wright's later work. There is a postscript to Hardy's one-page note according to which Yule would accept its substance "as a satisfactory answer to the difficulty that he raised". It has been said that Nature yields answers only to correctly formulated questions. Hardy's solution to Yule's difficulty shows that wrong questions may sometimes be also fruitful.

I have wondered occasionally whether the statistician Yule's original question was asked seriously or rather with tongue-in-cheek in order to embarrass the Mendelian lecturer. Apparently this suspicion is quite unjustified. The question rather shows how a distinguished statistician could miss the general concept of allele frequencies which appeared so obvious to Hardy who could find nothing more subtle to apply to it than "a little mathematics of the multiplication-table type". Hardy's note was published in Science. "The reason why it appeared... (there) is that Nature at that time was extremely hostile and refused to to publish anything tainted with Mendelism". (R. C. Punnett, Feb. 5, 1950 in letter to the author.)

Hardy's Law remained known under this designation until 1943 when it was realized that, independently of Hardy and indeed at least six weeks prior to Hardy's involvement in genetics, Weinberg had presented the equivalent formula before the Society for Natural History in Stuttgart (Stern 1943). The publication of his paper also preceded that of Hardy's (Weinberg 1908). Weinberg came to it as a biologist and physician who had embarked on a wide-ranging mathematical treatment of problems of human genetics. His approach was less abstract than that of the mathematician Hardy. The idea of allele frequencies is not explicitly expressed by either Weinberg or Hardy, since both start with frequencies of genotypes. Instead of Hardy's three interrelated parameters p, q and r, Weinberg uses only two, m and n, which represent the frequencies of the two initial homozygous populations AA and aa and thus actually allele frequencies. He expresses the result of panmixis for the first time in the now familiar form:

$$m^2AA + 2m \cdot nAB + n^2BB \text{ (where } A \text{ and } B \text{ are alleles).}$$

The names of both the discoverers are now attached to the population formula: The Hardy-Weinberg Law.

In 1909 Weinberg generalized the theorem in terms valid for multiple

alleles, and investigated polyhydrid populations in which he recognized their essentially different method of attaining equilibrium. Since that time the concept of allele frequencies and the formula for equilibrium in case of panmixis in Mendelian populations have been the foundation for population genetics in general.

A very impressive application of an expanded Hardy-Weinberg formula was made by Bernstein (1924, 1925). This mathematician had earlier become interested in human genetics and had interpreted population data on variations in singing voice and direction of hair whorl as found in different populations in terms of allelic differences of single pairs of genes. His evidence consisted in a fit of the proportions of phenotypes to the $p^2 : 2pq : q^2$ expectation (where p and q correspond to Weinberg's m and n, and not to Hardy's terms). Bernstein then turned to a population genetic analysis of the frequencies of the four blood group types O, A, B and AB. Numerous records of racially variant blood-group frequencies were available, beginning with the discovery of this phenomenon by L. and H. Hirschfeld.

As noted earlier in this paper, a genetic interpretation of the blood-group variations had been given. It assumed the existence of two pairs of alleles, *A-a* and *B-b*. When Bernstein compared the expectations for the blood-group frequencies according to the dihybrid Hardy-Weinberg formula with the observed proportions, he found significant and consistent differences. He concluded that the blood-groups were not inherited in the hitherto accepted fashion and searched for a different interpretation. He thought of a triplealleliс system of a single locus, applied the appropriate equilibrium formula, and found excellent agreement between expectation and observation in frequencies in diverse populations. This Bernstein regarded as proof of his multiple allele theory, notwithstanding the fact that the limited amount of published pedigree data contained cases not in conformity with expectation from the theory. Later the apparent exceptions could be ascribed to various sources of error, and Bernstein's interpretation has long been fully established.

It may be permitted to record an incident which illuminates the newness and the power of the population genetics approach in the analysis of modes of inheritance. In the spring of 1933, Bernstein gave a seminar at the California Institute of Technology in which he reported on his mathematical approaches to human genetics with emphasis on blood groups. In the discussion, T. H. Morgan commented in his quizzical manner that Bernstein's approach was interesting, but could the solution not just as well have been obtained from pedigree analysis? Bernstein, as I remember it, replied that it could but that it wasn't!

Weinberg had early shown (1909, 1910) that the biometricians'

Law of Ancestral Heredity was fully compatible with a Mendelian interpretation if it included significant contributions to variance of non-genetic type as well as considerations of polygenic inheritance. The latter had become famous since Nilsson-Ehle's analysis of continuous variation in the color of wheat grains, but this concept of multifactorial inheritance had been fully conceived by Mendel, who had used it to provide a tentative explanation for continuous variation in flower color as observed in the F_2 crosses between two species of beans. In countries other than England the controversy between the biometricians and the Mendelians had never played an important role. Weinberg's demonstration, therefore, made no impression on non-British geneticists and was apparently missed by the British school. Only in 1918 did an analysis by R. A. Fisher lead to a generally accepted Mendelian interpretation of the pre-Mendelian findings of Galton, Pearson, and their school. The subsequent rise of higher population genetics, beginning with the work of Haldane, Wright, and Fisher in the 1920's, cannot be a topic of this survey, even though it has exerted a fundamental influence on human genetics.

Nature and nurture

Mendel was aware of variability in gene expression due to environmental conditions, specifically as regards the flowering time of his plants. He also noted that some characters do not permit a sharp and certain separation but exhibit continuous variation. For his main studies he deliberately selected such traits as appeared in the plants "clearly and definitely", a virtue in experiments whose purpose was to clarify the basic ways of hereditary transmission. Unfortunately, it led some of his intellectual descendents to reverse the argument. They would classify in alternative ways what was not clearly and definitely distinct, and they account for the alternatives in terms of single gene pairs.

Among the many examples of this procedure, one of the best known was Goddard's attempt to explain all feeblemindedness as due to a single homozygous recessive gene (Fig. 3, right). We now know that such types of feeblemindedness do indeed exist, but that they make up a small minority of all afflictions of this type. Of the majority, some are caused by birth injuries, others are due to complex and poorly understood polygenic types of inheritance, still others by perhaps even more complex and poorly understood social influences which help to push and individual below the arbitrary line separating low normality from "feeblemindeness" (or "mental retardation" as contemporary nomenclature prefers to call it). Perhaps most important, there are complex and poorly understood interactions between genetic and non genetic

agents which assign a person to his place in the continuous array of mental performance.

It was the nature-nurture problem which played such an important role in Galton's early creation of human genetics in pre-Mendelian terms. In this pioneering work the influence of the environment on many traits particularly those involving mental abilities and achievement, was clearly realized in a general way. On the other side, Galton (1908) concluded "when the nurtures of the persons compared were not exceedingly different" that under these circumstances "the evidence was overwhelming that the power of nature was far stronger than that of nurture".*) Based on this conviction, Galton founded the eugenics movement, which attracted many well-meaning but often class-prejudiced adherents. When Weinberg began his population genetics work, he became the first investigator who partitioned the total variance of observed phenotypes into genetic and environmental portions and therewith reconciled the two independent doctrines in genetics originated by Mendel and Galton (Weinberg 1909, 1910).

Galton made use of the similarities and differences between twins to judge the relative importance of hereditary versus environmental agents in human variation. In the nineteen-twenties twin research by Siemens and von Verschuer became a widely practiced area for the study of normal and particularly of medically significant traits. A particularly broad approach to twin genetics was organized sometime later by Levit but was soon terminated by extrinsic events.

The interpretation of the findings of the investigators who studied twins depended on the fact that identical twins have identical genotypes, while non-identical twins are genetically different. Since twins of both kinds are usually raised in the same home, it was often assumed that the environmental influences on pairs of identicalt wins were of the same degree of similarity als those on pairs of non-identicals. Additional parameters were desirable, such as those provided by cases where twins had been reared apart in different homes, or where children had been adopted away from their biological parents, or where groups of children from different parents had been raised in the relatively uniform environment of an orphanage. Muller (1925) described in detail the first case of identical twins reared apart, with emphasis on mental attributes, Barbara Burks compared foster-parent — foster-child resemblance in mental scores and achievement with that of true-parent — true-child resemblance, and Evelyn Lawrence studied the children in an orphanage. This type of analysis culminated in Twins: a Study of Heredity and Environment, a joint work by Newman, the

*) A penetrating treatment of the nature-nurture problem with special reference to Galton is given in A. Weinstein 1933.

biologist, Freeman the psychologist, and Holzinger, the statistician.

While such fundamental studies went on, the unscientific literature on class and race genetics, with its ultimately tragic consequences, exerted an inhibitory influence on wider participation in research in human genetics. Some of these interrelations have recently been traced by Dunn and Haller. But while many biologists stayed away from human genetics, other outstanding investigators with deep interest in the social consequences of science entered the field as scientists. They dissected unproven or false opinions, and made contributions of their own which strengthened human genetics as an objective discipline. As eminent examples of influential critics we may cite Hogben with his book on Nature and Nurture (1933) and Haldane with Heredity and Politics (1938), and both, in their research reports, as creators of new tools and concepts.

Cytogenetics

It was historically impossible for Mendel to have been directly involved in cytogenetic problems. When he wrote his paper in 1865 chromosomes had not yet been discovered. He did refer to the factors which were responsible for the traits he observed as cell-elements. He did establish the basic fact — although he communicated it only in two letters to Nägeli (3 July and 27 September, 1870) — that a single pollen grain is sufficient to fertilize an egg cell. And he carried out crosses involving plants with separate sexes — again reported in a letter only (27 September 1870) — whose results suggested to him that perhaps sex is inherited in a way similar to that of other segregating characters.

If Mendel had nothing to do with cytogenetics, Mendelism, of course, was one of its two pillars. Very briefly, therefore, the earlier history of human cytogenetics will be sketched here (Fig. 4). It was Flemming, the pioneer student of mitosis, who first estimated the number of chromosomes in human tissue cells and believed it to be close to 24. This was corrected by von Winiwarter (1912), who counted 47 chromosomes in male and 48 in female cells. Painter, eleven years later, confirmed Winiwarter's findings except that he saw 48 chromosomes in both sexes. It is now known that the true somatic chromosome number in man is 46, a fact established by Tjio and Levan only in 1956, well beyond the period which our survey covers.

The relation of specific chromosomes to sex determination had first been discovered in insects. It was assumed that sex chromosomes also exist in man. The uneven number of chromosomes seen in cells of the human male by von Winiwarter indicated an XX = ♀, XO = ♂ mechanism, but Painter

demonstrated clearly that while women have indeed two X-chromosomes, men have one X- and one Y-chromosome. Morgan as well as Wilson recognized in 1911 that the type of transmission of red-green color blindness could be understood on the basis of color vision genes located in the X-chromosome. In 1922, Castle, and Enriques suggested that the Y-chromosome

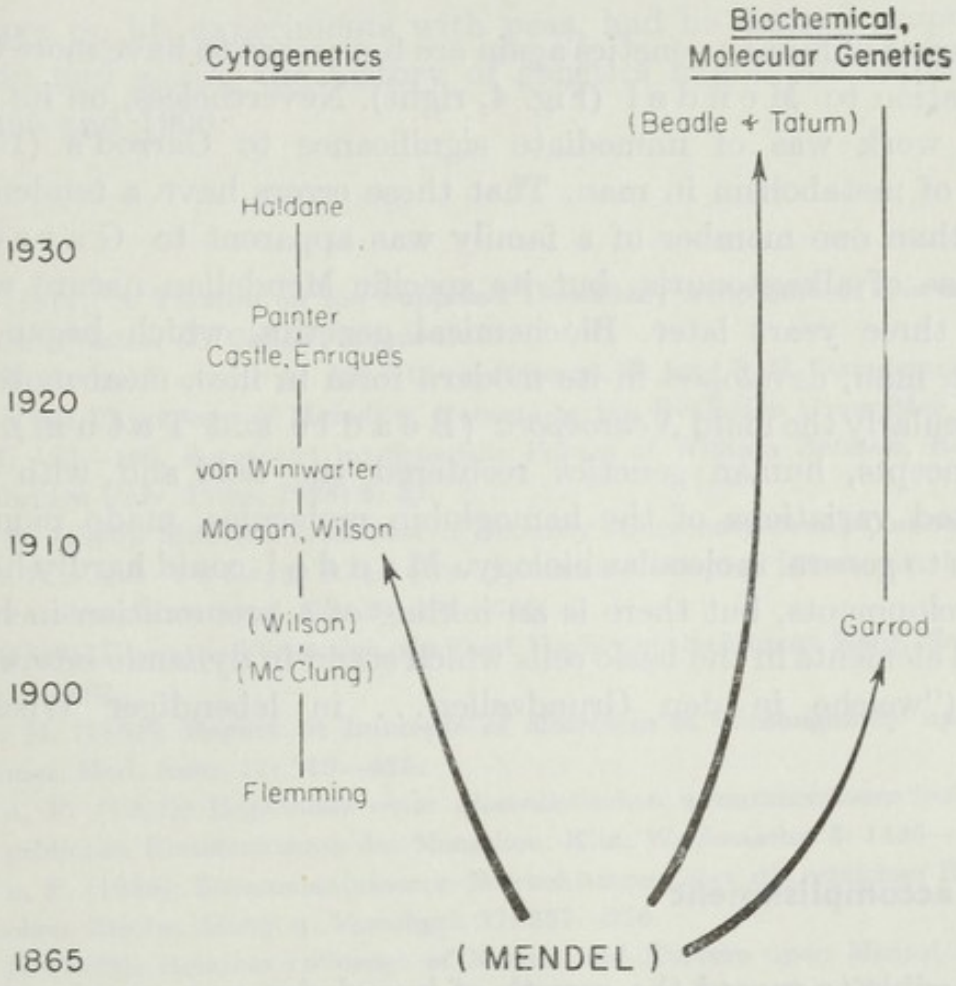

Fig. 4. Trends in the history of human genetics: cytogenics, and biochemical molecular genetics.

was the bearer of a gene for webbed toes whose transmission in a certain family seemed to follow the male line exclusively. But while the nature of the X-chromosome as carrier of numerous X-linked genes has been firmly established, the existence of Y-linked inheritance apart from determination of male sex is still under discussion.

Chromosomal abnormalities as causes of unusual transmission of human traits were first suspected in a family with a defect of color vision independently by T. H. Morgan and several other geneticists, among them Haldane (1932b; for further references see Stern and Walls 1957) who prophetically advocated in such cases the chromosomal study of leukocytes from exceptional individuals. Suggestions concerning a chromosomal abnor-

mality as the cause of Down's syndrome (mongolism) were also put forward in the nineteenthirties, but their validity was not proven for a quarter century, until after the correct chromosomal number of man had been discovered.

Biochemical and molecular genetics

These areas of human genetics again are too recent to have more than a slight direct relation to Mendel (Fig. 4, right). Nevertheless, on its rediscovery, Mendel's work was of immediate significance to Garrod's (1902) studies of errors of metabolism in man. That these errors have a tendency to occur in more than one member of a family was apparent to Garrod in 1899 in the case of alkaptonuria, but its specific Mendelian nature was only recognized three years later. Biochemical genetics, which began with these studies on man, developed in its modern form in flies, meal moth, silkworm, and particularly the mold *Neurospora* (Beadle and Tatum). Stimulated by its concepts, human genetics reentered the field and, with its analyses of inherited variations of the hemoglobin molecules, made pioneering contributions to general molecular biology. Mendel could hardly have foreseen these developments, but there is an inkling of a premonition in his reference to the cell elements in the basic cells which stand in dynamic interaction to one another ("welche in den Grundzellen... in lebendiger Wechselwirkung stehen").

Mendel's accomplishment

It is possible to regard the growth of knowledge as a superpersonal accomplishment of the Human Mind. In such a view there is little place for heroes and hero-worship. Each investigator contributes only what some other one would also have been able to contribute. And if specific personality has given a special touch to the discovery, such a feature is nothing but an ephemeral phenomenon. From the point of view of eternity this may well be true. Yet the Human Mind exists only in individuals. Those alive who search for knowledge can gain guidance and inspiration from their predecessors. Mendel's accomplishment is unique not only for its pioneering success but also for the way in which it was attained. With hardly any prior experience in original studies, for eight years Mendel systematically bred and crossed his plants. Without prematurely talking or writing about the facts he discovered, he thought about them — we do not know for how long. When his search had led him to see the principles which stand behind his observations, when he had made the synthesis between the many bare facts and the few generalities,

when he, the physics teacher at the local high school, had found their formulation by means of simple theorems of chance combinations, he wrote a single paper of forty-eight neatly handwritten pages. It is indeed justified that today, after a century, we look up to his example as an ideal of scientific accomplishment. This evaluation is not changed by the fact that the very qualities which make Mendel admirable as a person were at least in part responsible for the neglect of his discoveries. Had he not been content with writing only a single paper on his experiments with peas, had he instead propounded his theory again and again, the history of genetics might not exhibit its void between 1865 and 1900.

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The Use of the Mendelian Unit of Inheritance in Gemellology

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One hundred years after Gregor Mendel's discovery of the laws of Genetics one of their fields of application, that of Gemellology (i.e. the study of twins) is on the verge of some very significant developments: a series of international meetings will be hold in the coming months to study the problem of international cooperation and standardization of twin researches.

This represents the recognition of the world-wide importance of this branch of science, the foundations of which were barely being laid one century age. The study of twins was not introduced by Mendel: it can be said, in fact, that at least in human gemellology the real founder was Sir Francis Galton. The two scientists were contemporaries, but while Mendel was intent on his work leading to the discovery of the laws of Genetics, Galton explored the various fields of application of the same laws, which he ignored but invoked.

The study of twins represents a method of research that affords a discrimination between the effects of tendencies received at birth and those resulting from the particular circumstances of life; as such it can be used in any branch of applied genetics, but its role is especially valid in human genetics, where the experimental method is not available. This explains why human genetics, with its emphasis on gemellology, has found this method to be conditioned by the concept of hereditary units introduced by Mendel.

As long as heredity was studied in undivided form, science hardly progressed beyond common knowledge, which had always felt and stressed the principle of biological inheritance. Only when Mendel realized the opportunity and possibility of breaking down total inheritance into single units (which he considered as mathematical units) did it become possible to identify independence, segregation, dominance, recessivity and, generally speaking, the dynamics of these units resulting in the mathematical interpretation of heredity.

The use of the mendelian unit of inheritance is always fundamental in twin methodology, but its necessity and convenience become increasingly obvious when applied to those specialized areas of human genetics that are called Medical Genetics and Clinical Genetics. In Medical Genetics, where the degree of concordance of any given condition is differentially appraised among

monozygotic and dizygotic cotwins in order to provide an estimate of the role and the mechanism of hereditary transmission and where the reliability of any sample conditions the validity of any conclusion for the general population, the use of the mendelian unit of inheritance is widespread. Out of the many instances of such use we want to mention two examples, both of which are referred to the field of immunohematology in which the application of Mendel's laws was early, clear and rigorous.

The first example is the well known importance, for the diagnosis of zygosity of same-sexed twin pairs, of immunohematological findings. Blood group data, with the increase in the number of separate systems and factors, afford in many cases a definite exclusion of monozygosity, while providing significant indications of monozygosity when all factors are coincident. The importance of the breakdown into individual units of the blood group factors involved is even more obvious when we refer to family studies, often affording the passage from the phenotype to the genotype, with the inherent possibility of discrimination on a deeper level.

Our second example of the use of mendelian units of inheritance in twin research is represented by the so-called "Azygotic test" introduced by Gedda and Brenci in January, 1962. This test makes it possible to ascertain how closely a given twin sample reflects the situation found in the general population, in order to provide an estimate of the reliability and applicability of any conclusions the given sample may have indicated. The test is based on the selection of one or more factors, the mode of inheritance of which must be already clearly established, in order to compare its experimental distribution in the sample with the theoretical distribution in an ideal population. Such a comparison, based on chance inheritance of parental traits in dizygotic twins as against the implied identicalness in monozygotic twins, enables researchers to verify whether the two types of zygosity in the sample are in the same proportion as in the general population, providing a numerical estimate of the potential difference.

In their original paper Gedda and Brenci based the demonstration of the method on the simplest possible case, i.e. on the model of a diallelic monomeric trait with penetrance 1—0; we will refer now instead to the well known pair of erythrocytic antigenic factors, M and N. The mode of inheritance of these factors has clearly been shown to correspond in mendelian genetics to the model of a diallelic monomeric trait with penetrance 1—1: this model is generally refered to under the name of codominance and is studied in any course of general genetics through the classic example of the *Mirabilis jalapa*. Such a model has in our case the great advantage of full coincidence between phenotypical and genotypical classes.

The sample we chose for our example consists of 525 twin pairs on which blood group tests have been carried out. The tests had been carried out for

different purposes connected with different studies made by the various departments of our Institute, but a large percentage of the tests was intended to verify the tentative diagnoses of monozygosity as made according to Gedda's test of equivocity.

Without reporting our findings concerning other blood group systems (which could be similarly treated but whose models are generally more complex) we refer to the Table illustrating the distribution of twin pairs in the different phenotypical classes. It must be kept in mind that the terms "first twin" and "second twin" identify respectively the first and second in the order in which they were tested, without reference to order of birth. (Table I.).

Tabl. I.

Second Twin	First Twin			
	M	MN	N	total
M	103	37	9	149
MN	33	221	16	270
N	10	16	80	106
total	146	274	105	525

An examination of the Table confirms in the first place the independence of the behaviour of "first" and "second" twins, but the most relevant finding concerns the increase in the frequencies of the classes of concordance as compared to the frequencies in the same classes in a theoretical distribution based on random coupling. It is just on the basis of such difference, due to the necessary concordance of monozygotic pairs, that the method affords a quantification of the proportion between monozygotic and dizygotic pairs in the sample.

Considering, in fact, that the classes of discordance are composed of dizygotic pairs only, we can easily calculate the percentage of dizygotics in our sample. If we identify by P_m, P_{mn} and P_n the individual frequencies in the M, MN and N classes respectively in our material, it is clear that pairs belonging to the classes of discordance represent the sum of the frequencies ($2\,Pm \,.\, Pmn + 2\,Pm \,.\, Pn + 2\,Pmn \,.\, Pn$) in the random distribution represented by $(Pm + Pmn + Pn)^2$. It follows that the number of dizygotic pairs (N) is obtained by the formula:

$$N = \frac{D}{2\,P_m \,.\, P_{mn} + 2\,P_m \,.\, P_n + 2\,P_{mn} \,.\, P_n}$$

where D is the number of individuals in the classes of discordance. Since in our material the values of P_m, P_{mn} and P_n are respectively .28, .52 and .20, while D = 121, we have:

$$N = \frac{121}{2(.28 \times .52) + 2(.28 \times .20) + 2(.52 \times .20)} \cong \frac{121}{61} \cong 198\,.$$

Since the total number of pairs in our material is 525, the percentage of dizygotic pairs is thus 37·71%. Considering that in the general population the percentage of dizygotic pairs over total twin pairs is about 70%, we can now estimate the deviation of our sample from the standard population pattern of zygosity, introducing if necessary the proper corrections if the same sample were to be used for different studies, or utilizing the same sample as a term of reference in order to apply the same method to a different set of traits.

We wish to point out that the material we have chosen for this example, purposely including an abnormally high number of probably monozygotic pairs, receives from the application of the test a confirmation of such deliberate selection which, in turn, supports the reliability of the method based on the use of the mendelian units of inheritance.

Such use appears to be possible and advisable also in Clinical Genetics, especially through the application of the Clinical Twin Method, introduced by G e d d a and illustrated at the XI International Congress of Genetics at Scheveningen in 1963. The test is based on the principle that any morbid picture may be broken down into individual factors which, separately or collectively, may be treated by mathematical analysis.

The subdivision of a disease into individual factors, which is carried out by the traditional branches of medicine, leads in the first place to an obvious division of the same factors into two main groups: essential factors ("sine qua non") which condition the morbid picture itself, and non-essential factors, the presence of which is more or less frequent but never indispensable.

The individually different frequency of the various factors making up the second group allows us to apply estimates of probability whenever we find a given morbid picture affecting a pair of monozygotic twins. In each individual, in fact, the different factors in the second group can reveal different combinations with different probabilities according to the respective frequencies. In the case of monozygotic twin pairs, however, the clinical pictures of the cotwins tend to a superimposability of such a degree that it could be due to chance with such a low level of probability as to lead to the rejection of the hypothesis.

Rejection of the null hypothesis necessarily entails the operation of a causal factor responsible for the high degree of concordance; the factor involved should be related to the structure of the test, i.e. with the fact that concordances are found in a pair of monozygotic twins whose identical genotype obviously tends to result in an identical bahaviour.

It is clear that other factors, besides genotypical identicalness, may contribute to the tendency towards an identical bahaviour; among such other factors we may mention the total concordance as to age, or the generic concordance as to environment from endouterine life onwards. Yet the increase in the number of individual factors analyzed ought to succeed in revealing even small differences of environmental influences, if concordance were to be

ascribed to environmental factors only. Besides, accurate anamnestic investigations generally reveal environmental differences (placentation, infant feeding etc.) which ought to limit rather than an increase superimposability.

In order to identify the highest possible number of units of inheritance and of environmental influence to be used for research purposes, the Mendel Institute has been carrying out for years the systematic registration of normal, pathological, individual, familial and environmental traits concerning the 10,000 twin pairs in our "Gemelloteca" or Twin Register. We have also devised our own coding system, whereby this wealth of information is transferred onto IBM punch cards. This enables us to apply the most modern methodologies, extending the application of mendelian genetics, through gemellology, to human genetics, medical genetics and clinical genetics.

Discussion Contributions

Manifestation of Mendel's Laws in the Hybridization of Polyploid Species Forms

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By crossing *Tr. timopheevi* with *Tr. vulgare* and *Tr. durum* with *Tr. vulgare* and following colchicine induced doubling of the chromosome number, Zhebrak obtained new species forms of wheat with 70 chromosomes not occurring naturally. Segregation in the hybrids was accompanied by the elimination of a proportion of chromosomes and stable species forms with 56 and 42 chromosomes respectively were arising. Their genetical individuality was demonstrated by their poor tendency to give hybrids with each other as well as with other wheat species. As to the morphological characteristics of the new species forms they have appeared intermediary with respect to the species of origin, being however genetically more closely related to the common wheats, especially those with 42 chromosomes.

A considerable difference between the results of reciprocal crosses has obviously been due to some cytoplasmic factors.

In the analysis of hybrids, twenty different characters were investigated most of them quantitative in nature.

The first generation of hybrids displayed either dominance of one parent's character or the intermediary type of inheritance in full accord with the first Mendel's law. Crossing of the 56 chromosome forms with each other wheat as well as with other wheat species resulted in semisterility or nearly complete sterility in the first generation. Among the 42 chromosome forms, one could be distinguished by its genetical individuality. The degree of sterility and other characters in the first generation did not differ in the reciprocal crosses; it was thus not critical for them whether the maternal form was that with 56 or 42 chromosomes. This indicates a certain role of nucleus in the inheritance of the characters under investigation; however, the increase of chromosome number did not prove advantageous in this regard.

The segregation of phenotypes in the F_2 generation corresponded to that predicted according to the second Mendel's law. In addition to the transgressive segregation characteristic for the quantitative characters, mono- and di-factorial segregation was observed.

The features specific for the polyploid forms did not turn out advantageous in the F_2 generation either.

Simulation Studies about Selection Processes in Finite Random Mating Populations

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I am glad to be able to speak about the further application of Mendel's laws. They are the simulation studies of selection processes, the so-called Monte Carlo studies, by means of electronic computers. It is possible to create diploid model organisms (zygotes) with an arbitrary number of loci, arbitrary degrees of recombination (linkage) and different interaction of non-allelic loci (epistacy). According to the basic results of Mendel's laws in such populations it is possible to simulate reproduction and selection. These studies are very helpful in judging the theory of polygene inheritance. At present, the genetic model of the polygene inheritance is very simple and no more than an extension of the one-locus case to the polygene situation. The model requires no linkage, no epistacy, and that infinite populations are investigated. These are very strong assumptions which a priori do not hold good in the real populations. Estimates of genetic variances in breeding populations, received by experimental plans (as proposed by Comstock and Robinson and Kempthorne and Curnow), are frequently biased, because the promisses are unrealistic.

By creating model populations by simulation it is possible to judge the degree of bias due to linkage and finiteness. Therefore, selection processes in 6 combinations of parameters: 5, 20, 50 loci and each of this with and without linkage were compared. Each of the 6 combinations was subjected to 15 generations of selection with 20 runs ($r = 0{\cdot}5$) and 5 runs ($r = 0{\cdot}005$). The hypothesis $H_0 : \mu_i = \bar{P}_i$ for each of the 15 generations in all 6 combinations was proved ($\mu_i = m(p_i^{-2}\,AA + 2\,\bar{p}_i\bar{q}_i\,Aa + q_i^{-2}\,aa)$; $\bar{P}_i$ = mean over the runs of the means of populations at each generation; m = number of loci). Complete dominance was assumed. The following results support the assumption that it is possible to overcome the effect of finiteness by linkage. Without linkage, 5 loci: H_0, 20 loci: H_1, 50 loci: H_1; with linkage: 5 loci: H_0, 20 loci: H_0, 50 loci H_0. Increasing the number of loci without linkage the effect of finitenes also increases ($\alpha = 0{\cdot}002$), whereas this is not the case with linkage.

Furthemore, similar types of populations (A, B, C) were simulated with different mean degrees of dominance ($\bar{a} = 0{\cdot}5;\ 1{\cdot}0;\ 1{\cdot}5$). In each level 15 genera-

tions of selection were studied. There were significant differences in progress for selection by truncation (5/50). Increasing the degree of dominance, the genetic gain per generations was significantly reduced.

At present we examine the bias of additive genetic variance by epistacy and/or linkage by simulation studies of biparental analyses (Exp. I. by Comstock and Robinson).

Inheritance of Rust-Resistance in Some Aestivum Crosses as a Trigenic Character

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The mode of inheritance of resistance to race 15B of *Puccinia graminis tritici*, black rust of wheat, as studied in several inter-aestivum crosses. In one cross, resistance was provided by a Kenyan variety, K.58, while the susceptible parent was an Indian Variety, Pusa 4. The F1 was susceptible. In F3 278 lines were studied, with 20 seedlings each.

Of these, 38 lines were found breeding true for resistance. Sixty-one had all susceptible individuals, while 179 were segregating into resistant and susceptible individuals. These segregating lines moreover, showed arked difference in their behaviour, some giving a preponderance of resistant seedlings, others giving a preponderance of susceptible ones.

These results were found to be explainable best on the hypothesis that K.58 carries three factors for resistance, AABBCC, while P.4 carries the alleles; that the three factor pairs are independently inherited, are of equal effect and cumulative, any four dominant factors conditioning resistance.

On this supposition, 10 lines out of 64, carrying 2 pairs of dominant factors in homozygous condition will breed true for resistance; likewise, 10 lines out of every 64 will breed true for susceptibility. The remaining will segregate into resistant and susceptible individuals in various proportions.

Since each individual line comprised only about 20 plants, Warwick's correction factor for small samples was applied. The observed results were found to be in fair agreement with the calculations, P value lying between 0·50 & 0·70.

In another cross between the same resistant Kenya parent and Pusa 120, similar results were obtained. Out of 99 F3 lines of K58 × P120 cross studied 13 were found breeding true for resistance, 26 breeding true for susceptibility and 60 segregating. Applying the same trigenic hypothesis, and correcting for small numbers, P value between 0·50 and 0·30 was obtained.

It was further noticed in born the crosses that while the susceptible seedlings, presumably possessing 0, 1, 2 and three factors for resistance, appeared equally susceptible, the resistant ones could be differentiated with rather less difficulty as showing 0, 1 and 2 type reactions, presumably associated with 6, 5 or

4 factors for resistance. This observation, unfortunately, could not be checked up by further study.

The study was made at the University of Minnesota; breeding behaviour was checked by Professor H. K. Hayes and the reaction types by Professor E. C. Stackman.

Mendelian Factors of Photoperiodic Response in Poppy

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In an assortment of several poppy varieties, and in a periodical seeding experiment of five varieties, there was a single accession named Madurovic which excelled in unusual earliness and flowered even if seeded in the late summer, in spite of the shortening photoperiods. Thus, this variety "M" could not be characterized by a "critical seeding date" after which the reproductive phase was delayed and bud initiation did not begin until autumn frost destroyed the plants. The transition to reproductive activity was determined by direct observation of the growing point. Those data were published some years ago (Sárkány-Andrásfalvy-F. Riedel 1959).

Six poppy varieties were examined in a greenhouse at different photoperiods. The treatments applied are the following:

1. natural short days of the winter months,

2. and 3. those natural days supplemented by electric bulb light to 15 and 24 hours respectively.

The results of this experiment are shown in the three subsequent figures. On the first nodi of plants are expressed as function of time. The three

The onset of reproductive development expressed in numbers of nodi of poppy varieties (in a greenhouse experiment of photoperiodic treatments)

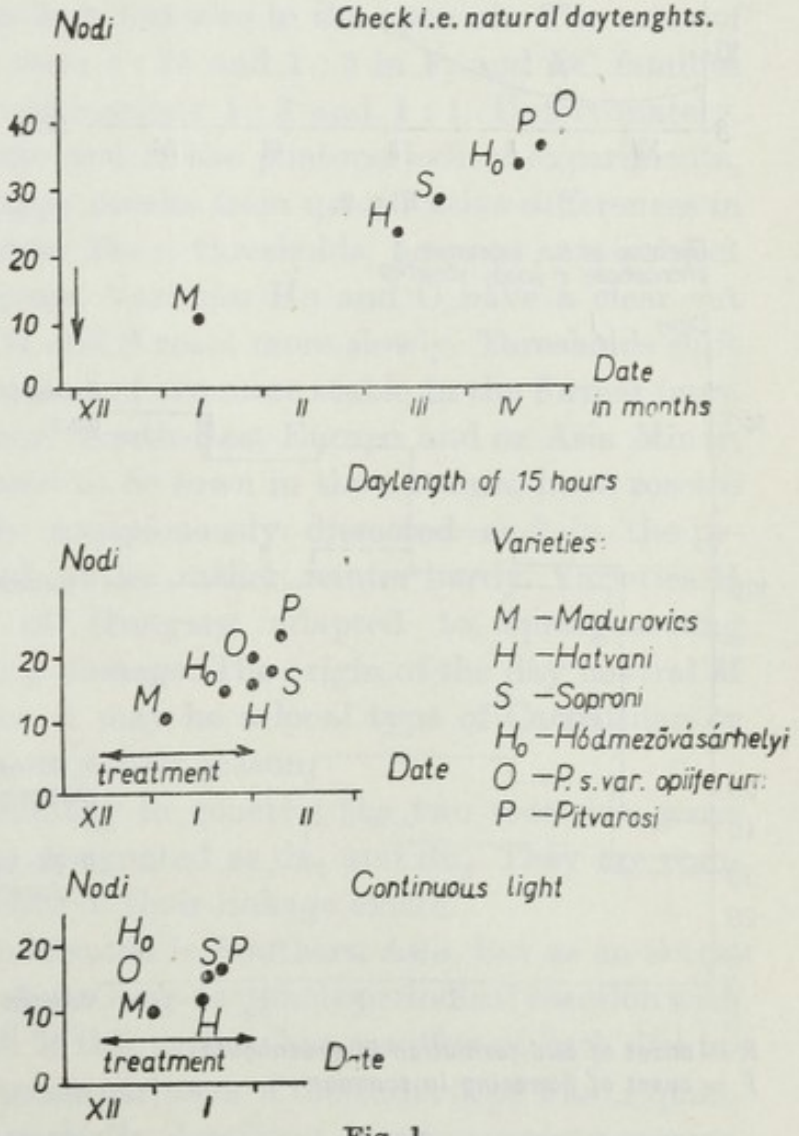
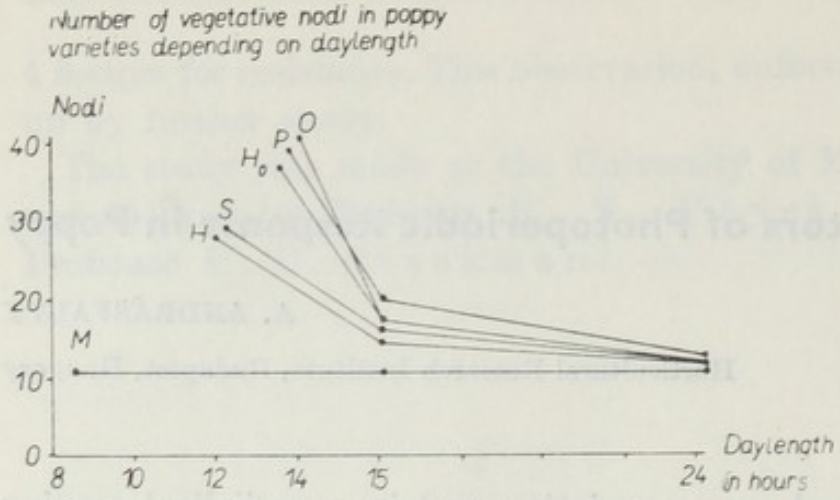


Fig. 1.



The beginning of bud development of poppy var-s according to natural daylengths

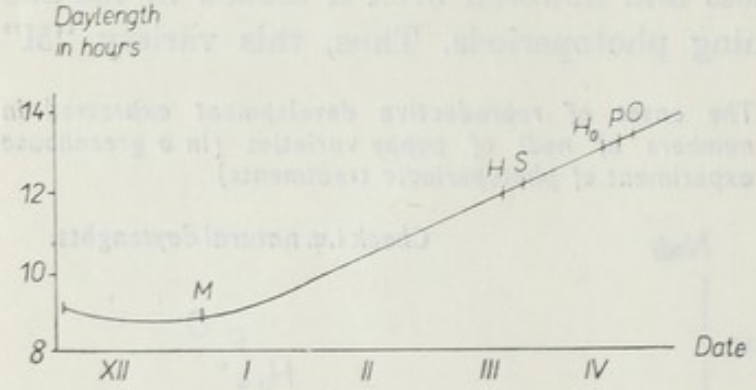
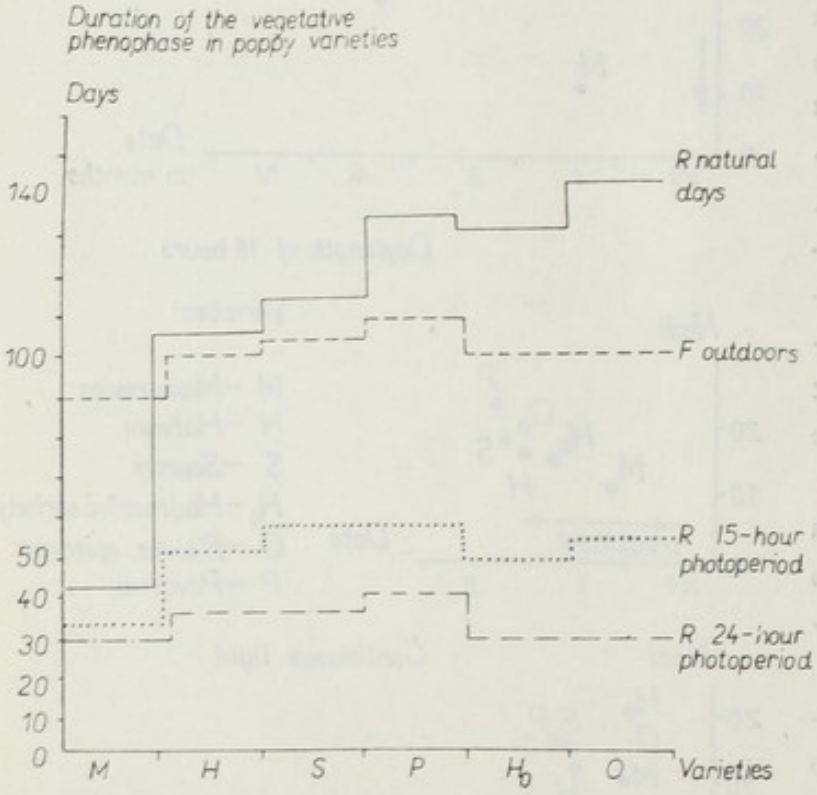


Fig. 2.



R = onset of bud formation in greenhouse
F = onset of flowering in summer

Fig. 3.

treatments caused essentially a different distribution of the beginning of bud initiation in the varieties. Variety M was not influenced by photoperiod in respect of the number of vegetative nodi, whereas a short delay may attributed to lower light and termal energy supply in the check treatment. Ho and O varieties coincident with M in continuous light initiated buds considerably later at 15 hour photoperiods, and even later than the variety O as the last in natural daylengths. Varieties H and S were less early at continuous days than the three former ones, almost coincident with them at 15-hour days, but in natural days H and S were second and third in earliness. Variety P was always about the last.

Fig. 2 shows the relation of daylength and bud initiation date as well as of daylength and number of vegetative nodi. It is remarkable that daylengths at which transition occurred were relatively short, because of the simultaneously increasing plant size and daylength inductive thresholds are not immediately comparable, that is they should be spread such more on an equal age basis.

The lengths of vegetative phenophases compared in different treatments and varieties may be related to the duration of the period from seeding to flowering of a usual culture in open air at the normal season on Fig. 3. The relation of the varieties to each other in flowering date of the open air seeding is very much like to that of the bud initiation date at continuous or 15-hour photoperiods, whereas in the short day treatment varietal differences are much more pronounced and altered.

Repeating the photoperiodic experiment in the next year in a somewhat less-heated greenhouse and applying 14 hour-instead of 15 hour-periods, our results changed considerably. Continuous light had about the same effect as before, but 14-hour periods and natural days did not validate the proofs of the first experiment. The conspicuous earliness of variety M was manifested quantitatively only at 14-hour periods, but no indication of day neutrality may be detected at short days. This phenomenon will be discussed later. Crossing experiments of the M variety with eleven others proved that this typical day-neutrality being completely recessive in F_1 was always easy to be scored in the assortment of varieties and segregating F_2 and BC generations because of its extreme earliness not only at short days but also in the open air. The rates of segregation in eight combinations were 1 : 15 and 1 : 3 in F_2 and BC families respectively and in three other combinations 1 : 3 and 1 : 1. Unfortunately, those three varietes were not represented in the photoperiodical experiments.

The other type of earliness in poppy results from quantitative differences in long-day requirement, i.e. thresholds. These thresholds, however, are subject to shifting in a characteristic manner. Varieties Ho and O have a clear cut photoperiodical reaction, whereas H and S react more slowly. Thresholds shift more by plant age in the latter ones and are more stable in the former ones. Varieties Ho and O originated from South-East-Europe and or Asia Minor, where as a general practice they used to be sown in the autumn, have rosette leaves developed in short days, are conspicuously dissected and in the periodical seeding experiments proved to be rather winter hardy. Varieties H and S are commercial varieties of Hungary adapted to spring sowing with little danger of frost heaving damage. The origin of the day neutral M variety could not be found exactly, it may be a local type of Carpathian or Alpine region adapted mainly to a very short season.

According to the rules of terminology in genetics the two recessive genes of day neutrality in poppy may be designated as dn_1 and dn_2. They are complementary in action and no evidence of their linkage exists.

Other very types of poppy are cultivated in Southern Asia, but as an accession from India they may have a definite long-day photoperiodical reaction with very low thresholds. In crosses with M this variety has manifested both dominant alleles of long-day reaction. Extreme earliness of the India type was of quantitative nature and intermediate or partially dominant in other variety-crosses.

The relation of geographical distribution and photoperiodical reaction of poppy varieties has been studied by Vesselovskaya (1933). She stated that southern varieties flowered very early and remained dwarf under the high latitudes of Minsk. Bremer and Weiseth (1962) made similar observations on a range of horticultural plants. Definite day neutrality has been reported in pea by Reath and Wittwer (1952) but lower temperature (50° F) made the formerly day neutral variety show typical long-day reaction. The mechanism of day neutrality and long-day reaction in pea was discussed by several authors. Barber (1959) used Sn/sn notation established by Wellensiek; and postulates the existence of a colysanthin (i.e. an inhibitor of flower formation) as a product of the dominant allel, whereas Haupt (1958) holds that a flowering stimulus is located in the cotyledon of the "early" varieties. A further example of a day-neutral strain of long-day species is lettuce. In this case, day neutrality causes extreme delay of reproductive activity contrary to pea and poppy even on long-days, thus long-day day neutrality reaction determined by a single T/t locus (Bremer and Grana 1935) has a reversed effect. Rapoport and Wittwer (1956) did not any alteration of day neutrality at 60° and 70° F. Experimental data in poppy of Mika (1955) suggests that temperature effect has a delicate optimum curve. Poppy plants held at 8-hour photoperiod differentiated buds at lower temperature (7—24° C) with 53 nodi, whereas they remained vegetative at higher temperatures (15·5—29° C) even with 98 leaves, whereas day neutrality reaction seems to have a minimum temperature threshold analoguous with pea.

According to Kopetz (1956), day neutrality is an extreme case of thresholds out of the range of photoperiod in a particular environment experienced. Thus, a quantitative approach of the day neutrality phenomenon may be justified.

Some indication exists on the vernalisation requirement of poppy (Lecat 1955), and if suppositions of analogies with pea and cereals are correct, the more clear-cut long day reaction of Ho and O varieties may be linked with the adaptation to autumn sowing and winter hardiness, i.e. some vernalization requirement so far not investigated.

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The Leptosome and Eurysome Types of Animals as a Phenomenon of Convergency

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The problem is related to the inheritance of the leptosome or eurysome types in our domestic animals, as well as to the question of convergency, not only between different breeds of and within the same breed of animals, but also between various species.

The leptosome and eurysome constitutional types have long been discussed in animal breeding. The Norwegian geneticist Wriedt has touched upon the problem of hereditary factors for the above types of animals in his book on inherited differences between trotter and race-horses (the eurysome and leptosome type). He believed at first that these differences were due to a wide range of hereditary factors. However, his later observations led him to suspect that the difference between these two types of horses, i.e. the leptosome and eurysome type, was due to a number of hereditary factors. Later on, he stated that all the characters of a trotter are dominant to those of a race-horse. While we paid attention to the difference between the leptosome and eurysome types in various breeds, other investigators reported that these typs are also to be found within the same breed. Ivanova-Bahitov reported of matings between the leptosome and eurysome types in cold-blooded horses. They found a clear segregation of these types. Zorn observed various types in ponies some of which resembled a cold-blooded horse (eurysome type) and the other a warm-blooded horse (leptosome type).

Similar observations were made in other species of animals. Cross-breeding experiments with various breeds of sheep (McKenzie-Marshall, Ritzman-Davenport) showed that multifactorial inheritance and not a simple Mendelian segregation is involved. Results from crossing the milk and beef breeds (Jersey, Holstein, Aberdeen Angus) indicated that the F_1 generation was more or less intermediate between the original parental breeds, and no great variation showed up in the F_2 generation (Cole, Johansson). Klatt was concerned with crossing the distantly related, extreme breeds of dogs, and the forms of growth determined by inheritance in relation to an identical size of animals was of sepecial interest to him. He distinguished two main factors, the "size" and the "form of growth".

Our investigations were conducted along a different line. At the moment we

have abandoned the biometrical findings on different characters under study, and our observations are based on visual examination of the conformation in general. A few years ago we have emphasized that inspection of the appearance and an exact characterization of the morphological features might be very useful (Schotterer). This we transmit to the establishment of typical forms of animals that are studied in the process of inheritance. Hereby we are judging, in general, the conformation of the leptosome or eurysome types independently of the size. In this case, the size is considered as a quantitative character and the conformation as a qualitative character.

1. The leptosome and eurysome types in Bosnian highland horses

Among the various kinds of the Bosnian highland horses two extreme types can be distinguished, i.e. the leptosome nad eurysome type. Upon breeding this kind of horses (in the stud-farm Borike near Sarajevo), we used a stallion of the eurysome type and by breeding for many years (approximately 5 generations with an average generation interval of 9 years) we produced a studline M. In addition to this line, another stallion of not so distinct eurysome type produced a second line B. The original breeding animal of the line M (stallion 7 M) of the eurysome type transmitted his typical constitution to all of his offspring so that we assumed that a dominant inheritance must have been involved. It has been observed that the eurysome types were produced only by mating the eurysome × eurysome or eurysome × leptosome types, but never by mating the leptosome types to each other. Similar confirmatory observations have been made by Ivanova-Bahitov.

Of all the offspring about 56% belonged to the stud-line M, 32% to the line B, whereas the rest of 12% of animals were of different origin. It must be emphasized that during 5 years of breeding a large number of matings between the descendants of the two lines were made and thus the line M and B became related to each other. Therefore, the eurysome types of animals were widely distributed in the line B.

Table 1 shows the way of extending the eurysome types through the stallion 7 M on to the progeny of the other line which were then reinforced by in-breeding.

2. Crossings between the eurysome and leptosome types

Cross-breeding experiments with the leptosome types of the Arabian horses and the Lipizzan horses (approximately 40 matings) provided further data on the inheritance of the eurysome types. As a practical example let us cite reci-

procal crosses between the Arabian or Lipizzan mares and Bosnian highland stallions of the eurysome type and vice versa. The offspring from matings of highland stallion × Arabian mare and vice versa were of the highland horse type at birth already and in later life they became more and more similar to highland horses, i.e. the eurysome type. Reciprocal crosses between

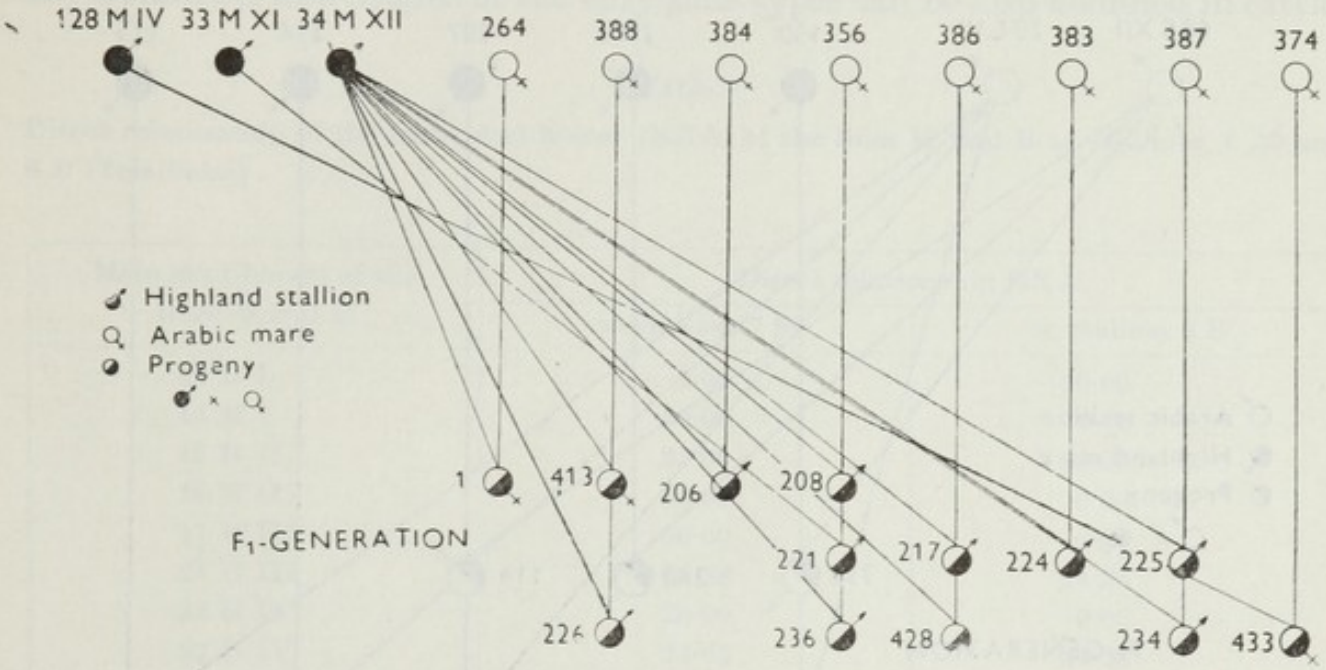

Fig. 1.

the Lipizzan stallion × highland mare and highland stallion × Lipizzan mare produced the offspring carrying the characters of eurysome highland horses. The offspring of all crosses were larger than highland horses and smaller than the other parental line (Figs. 1 and 2).

Back-crosses of the F_1 generation to the highland breed produced the offspring of distinct eurysome highland type.

All these investigations and observations pointed out that a monofactorial, possibly two-factorial inheritance of the eurysome type was involved. It must be emphasized that the size is inherited independently of the eurysome type. We underline again that the animals produced by these crosses and back-crosses were larger than the Bosnian highland horses, but the over-all picture shows more or less obvious eurysome types which were strongly influenced by environmental factors so that we can speak of a conditionally dominant inheritance of this character.

At the beginning of this paper it has been emphasized that the leptosome and eurysome types are to be found not only between different breeds of animals, but also within the same breed. It is interesting to see the mode of inheritance of these characters in other species of animals. We have already spoken about this, but other investigators believe that a multifactorial inheritance may be

involved. Let us illustrate this in cattle where the milk and beef breeds are distinguished. In a cross-breeding experiment with 85 animals between Aberdeen-Angus bulls and Tirolese Grey- and Brown-Cattle cows the F_1 generation shows a certain uniformity which is more striking in the eurysome Aberdeen-Angus breed. A similar uniformity was observed in the hybrids between

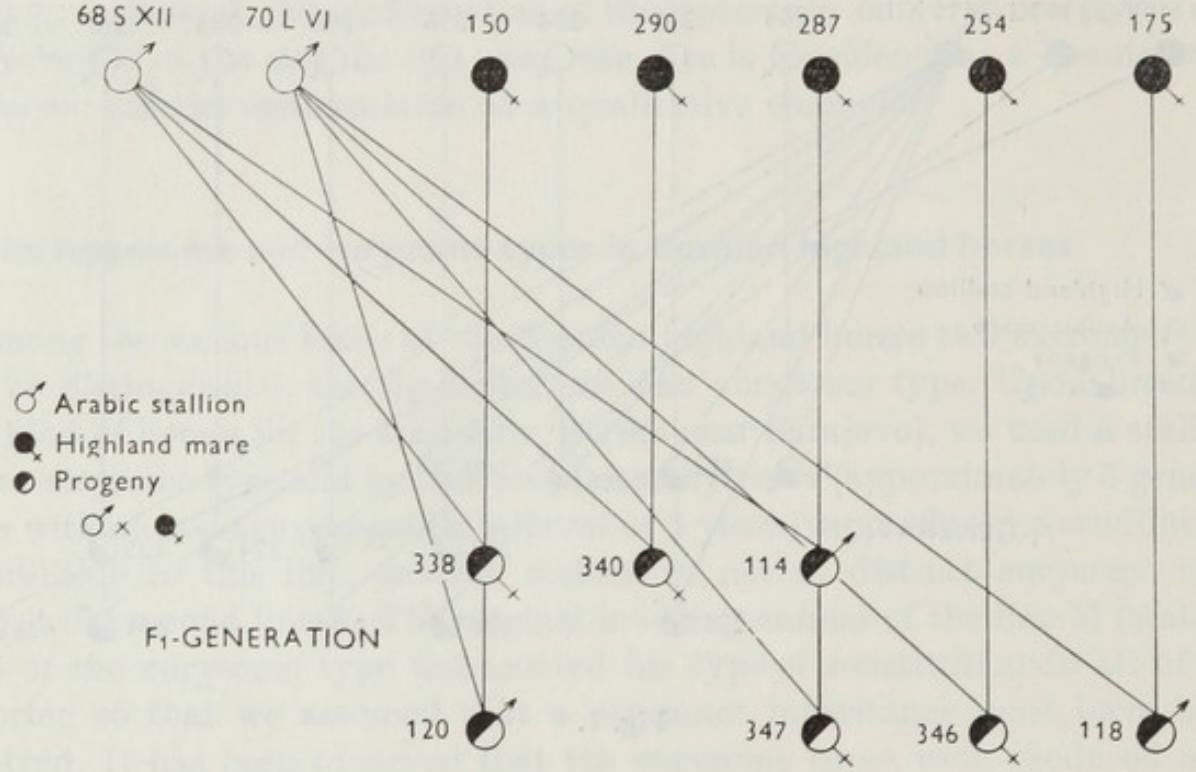

Fig. 2.

Hereford bulls and Buscha cows. The beef-type was observed especially in animals which are bred for meat (Animal Breeding Institute for Agricultural Research, Sarajevo). Similarly to horses, a conditionally dominant inheritance of the eurysome types as compared with leptosome types can also be assumed in cattle in this instance. These observations show that a phenomenon of convergency is involved in the leptosome and eurysome types in various species of animals, which is related not only to the personal appearance and metabolism, but also to the inheritance of these characters.

Summary

Observations that have been made on the Bosnian highland horses showed that the eurysome types are inherited dominantly. The matings between the leptosome and eurysome types of horses confirmed a conditional dominance. All the investigations indicated that a monofactorial, possibly two-factorial inheritance of the eurysome type was involved. It must be emphasized that

the size is inherited independently of the eurysome type. The two characters are also found in other dometic animals. A cross-breeding experiment with Aberdeen-Angus bulls and Tirolese Grey-Cattle and Brown-Cattle cows showed that there was a certain degree of uniformity in the F_1 generation which was, however, more striking in the eurysome Aberdeen-Angus breed. Conditionally dominant inheritance of the eurysome types can be also assumed in cattle.

Table 1

Direct relationship of the main stud-horses (RXA) of the lines M and B to stallions 7 M and 8 B (Telalbašič)

Main stud-horses of the lines M and B	Direct relationship RXA	
	to stallion 7 M	to stallion 8 B
13 B I	0·00	50·00
14 M I	50·00	0·00
15 B II	25·00	50·00
16 M II	50·00	0·00
17 M III	50·00	0·00
21 B III	36·38	24·25
22 M IV	25·00	0·00
23 B IV	24·63	24·63
25 M V	25·00	0·00
26 M VI	25·00	0·00
27 B V	24·60	24·25
28 M VII	24·60	0·00
29 M VIII	24·60	0·00
30 M IX	25·00	0·00
31 M X	29·84	12·50
32 B VI	28·88	18·06
33 M XI	12·50	0·00
34 M XII	12·50	0·00
36 B VII	25·62	17·89
37 M XIII	35·06	11·83

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The Variation of Penetration in Heterozygote Polydactylic Mice

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During preliminary genetic study the results of crossing polydactylic with hemimelic mice or their crossing with normal mice proved that polydactylic mice are of heterozygote genotypic constitution (+/he), hemimelic mice of homozygote constitution (he/he). This brought ourselves to hypothesis that four basic series of crossings (only four, males he/he are sterile) should give the following results:

1. +/+ × he/he —— +/he (all polydactylic),
2. +/hex × +/+ ——— 1he/+ : 1+/+ (polydactylic : normal),
3. +/he × +/he ——— 1+/+ : 2+/he : 1 he/he (normal : polydactylic : hemimelic),
4. +/he × he/he ——— 1+/he : 1 he/he (polydactylic : hemimelic).

But we obtained descendants of normal appearance theoretically not assumed (test 1 and 4) or in higher than expected frequency (test 2 and 3). By a series of crossings we could test the descendants of normal appearance and deduce that hemimelic mice are of genotypic constitution he/he (recessive homozygote) and polydactylic mice as well as normal overlaps individuals of constitution +/he, i.e. heterozygote.

The penetration of polydactyly is incomplete according to the presence of normal overlaps individuals; the penetration of hemimely is absolute.

We tried to determine the possibility of role of the genetic environment in various normal lines used by crossing during our research. For this study we took into consideration four normal lines: the French line MO/Ko and three American lines, i.e. RAP/Ko, C3H/Li-Ko and C57BL/6Ko. A total of 8 801 mice was distributed as follows: 3 361 RAP/Ko, 3 689 MO/Ko, 1 174 C3H/Li-Ko and 577 C57BL/6Ko.

We could prove the following influences:

1. The influence of the genetic environment. It was constant in any type of crossing. For example in a series of crossing between normal males and hemimelic females the penetration is strong in C57BL/6Ko and RAP/Ko 48,4 % and 36,6 %), weak in C3H/Li-Ko (19,4%) and very weak in MO/Ko (4%) environments.

2. The influence of polydactylic parents and of normal overlaps. It arose as

a result of crossing with normal females. In any genetic environment the penetration is statistically lower in case that one of the parents has not expressed the phenotype.

3. The influence of degree of expression of phenotype in parents. It is evident as in RAP/Ko as in MO/Ko environments. The penetration is strong by crossing of two parents with the expressed phenotype (polydactylic), weaker if the phenotype is not expressed one of them (polydactylic × normal overlaps) and weakest if both parents are heterozygotes with an unexpressed phenotype (normal overlaps × normal overlaps). Besides the penetration is stronger in descendants of both parents showing bilateral polydactyly than indescendants of both parents showing the left and right polydactyly.

4. The penetration in the first generation (F_1) is significantly weaker in RAP/Ko and C3H/Li-Ko environments than in descendants arosed by back crossing (F_b), but there is no difference between these penetrations in MO/Ko and C57BL/6Ko environments. For the explanation of these differences we were brought to an idea about the effect of modificating genes favouring the arising of anomaly which cumulation could be quick in RAP/Ko and C3H/Li-Ko environments and statistically unrecognizable on the level of C57BL/6Ko and MO/Ko environments.

5. The influence of sex of normal parents was detected by crossing between normal and heterozygote polydactylic individuals. The weakest penetration was observed in descendants arosed by crossing normal males × polydactylic females, unilateral left or right. This is especially evident in MO/Ko environment.

The Expressiveness and Specificity of Polydactyly in Mouse

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The genetic study of the longitudinal hemimely proved that hemimelic mice behave as recessive homozygotes (he/he) with absolute penetration. Heterozygotes (+/he) have either an expressed phenotype (polydactyly) or not (normal overlaps); the penetration is therefore incomplete.

Polydactyly attacks exclusively the preaxial ray of the distal segment of hind limbs. Our study comprised 1 836 polydactylic or heterophalangic mice of four genetic environments: 401 MO/Ko, 238 C3H/Li-Ko and 183 C57BL/6Ko.

Polydactylic individuals had either unilateral left or right, or bilateral anomaly. In the genetic environment MO/Ko the unilateral anomalies are equally frequented as the bilateral ones (1 : 1); on the contrary in the rest of three environments predominate bilateral anomalies (2 : 1). Among unilateral anomalies can be observed that the right leg is cought oftener than the left one, that is in three genetic environments: RAP/Ko, MO/Ko and C3H/Li-Ko. It is not so in the genetic environment C57BL/6Ko.

Among bilateral anomalies concordant forms (both legs are cought in the same way) and discordant forms (both legs are cought differently) can be distinguished. These two forms are equally distributed in C3H/Li-Ko environment; on the contrary concordant forms predominate in MO/Ko environment and discordant forms in RAP/Ko and C57BL/6Ko environments.

The more accurate examination shows that polydactyly assings a very considerable phenotypic diversity. According to the genetic environment 5 to 10 different types are distinguished. Light and intermediary forms: hyperphalangia of the 1st finger, skeleton or total hexadactyly with or without hyperphalangia of the preaxial ray of the 1st finger; serious forms: skeleton or total hexadactyly with separated hyperphalangia of two rays of the 1st finger and various forms of heptadactyly joined or not with hyperphalangia.

We could therefore prove the relation between the stage of seriousness of the anomaly and the manner of its expression, more or less in three genetic environments, i.e. RAP/Ko, C3H/Li-Ko and MO/Ko. In these three environments can be stated that in average here occur more serious forms in individuals with bilateral anomaly than in individuals with unilateral anomaly. In C57BL/

/6Ko environment, on the contrary, is an independent stage of seriousness and manner of expression.

Finally, if unilateral or bilateral discordant anomaly is the matter, there is no relation between the stage of seriousness and of laterity.

Genetic Method in Animal Breeding

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The discovery by G. Mendel of the laws of inheritance which led to the conception of corpuscular heredity has created a solid foundation for the elaboration of methods in synthetic plant and animal breeding.

One of the demonstrative examples of the application of Mendelism in animal breeding can be the work with fur animals, particularly coloured mink breeding.

Nowadays, 25 mutant genes (I8 loci) are known in mink; various combinations of them give an enormous variety of colours.

The first stage in the genetic synthesis of new colours is the obtaining heterozygous forms for colour genes in which the breeder is interested. Further it is necessary to obtain progeny from the back cross of F_1 heterozygotes with one of the parental forms and, subsequently, to cross the coloured offsprings. With such a scheme, the yield of less valuable standard-coloured heterozygotes is essentially reduced, and a scrupulous selection of coloured minks by the fur colour allows to display a considerable influence upon the quality of new colours.

According to these premises, work on creating pearl minks on the basis of the "Swedish palomino" (t^p) colour gene has been carried out. The obtained pearl minks, new for the U.S.S.R., diverge into two groups: 1) light smoky-blue fur with a beige tint and red eyes (ppt^pt^p). 2) a darker blue-beige colour of the fur and dark eyes (ppt^pt^p). The influence of the gene of aleutian colour (a) upon the eye colour helps in the choice of couples among the pearl minks. By their fertility and viability, the new pearl minks are close to the saphire ones (ppaa).

The fur colour genes in minks possess a wide pleiotropic effect. The mutant forms of minks differ in body weight, relative weight of the organs, bone length; they are characterized by a reduced viability and fertility.

We have shown that the coloured but heterozygous mink females possess a better fertility in comparison with the corresponding homozygous ones, i.e. heterozygosity for certain fur colour genes results in heterosis. In connection with this a scheme of coloured mink breeding has been proposed, taking into account the advantages of heterozygous females, e.g. (ppAa), and allowing at the same time to carry on the selection for fur qualities within definite groups.

According to this scheme, coloured heterozygous females are obtained and then crossed with the males which are homozygous for all the mutant factors present in the females' genotype. The application of this scheme considerably enlarges the possibilities of coloured mink breeding.

Genetic analysis of the recessive mutations widely used in mink breeding: silver blue(pp) and white "hedlung"(hh) colours have led to the discovery of pseudoalleles in minks. In this connection a new genetic symbol p^h for the mutation "hedlund" is proposed, instead of the conventional h. Besides, for this locus the third mutant allele p^s is known, which is responsible for the development of the steel-blue colour. The dominance relationships between the mutations analysed and be presented as follows: $P > p^s > p > p^h$. Keeping in mind the phenotypical effect of these mutations and supposing that cistrone subunits control the sequence of biochemical reactions, one can indicate their probable sequence in the cistrone: p^h p p^s.

However, when the breeding is carried out by the characters with low heritability, and wide variability of polygenic characters under the influence of environmental conditions is observed, then the selection by means of correlating characters can give good results.

In the basis of genetic cattle breeding there rests the conception of an evolutionary developed connection between the milk fatness and other adaptive characters, providing for the adaptation of the animals to the seasonal changes of environment.

A positive correlation is established between the fat content of the milk and the density of hair of the cows (in different stock groups $r = +0{\cdot}22 \pm 0{\cdot}07$— — $-0{\cdot}67 \pm 0{\cdot}11$). A positive correlation is also observed between the fat content of milk and the degree of spring-molt intensity of hair ($r = +0{\cdot}73 \pm \pm 0{\cdot}02$). In animals with high milk fatness the hair is longer in winter, there is more underhair and less guard hair. Besides, with the lowering of the air temperature (down to —15°, —20°), these cows reduce their heat irradiation through breathing almost without enhancing their heat-production; in the animals with low milk fatness just the contrary phenomena are observed.

Under high temperature conditions (+30° C) in animals with high milk fatness the body temperature was heightened only by 0·2° (a better sweating regulation); in animals with low milk fatness it was so only by 0·7°C.

Thus, the adaptive peculiarities of the hair cover structure and of the thermoregulation evidently can serve as important additional criteria in the estimation of animals in breeding for milk fatness.

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On the occasion of the hundredth anniversary of the publication of J. G. Mendel's basic treatise of genetics, the Czechoslovak Academy of Sciences has organized a series of scientific symposia on genetics. The commemorative part of the series, pertaining to mendelism and its development, took place in Brno where Mendel performed his experiments. This was followed by work sessions held in Prague (August 9—11, 1965) under the title

SYMPOSIUM ON THE MUTATIONAL PROCESS

This Symposium dealt with numerous topical problems of modern genetics and was divided into concurrent sessions.

Mechanism of Mutation and Inducing Factors

Proceedings of a Symposium held in Prague, August 9—11, 1965
Symposia ČSAV — pp. 524 — ill. and tables in text — in English — paper covers

Principles of Radiobiology and the Induction of Mutations by Means of Radiation — Chemomutagenesis — Chromosomal Abberations — Evolution of Protein Characteristics

The Physiology of Gene and Mutation Expression

Proceedings of a Symposium held in Prague, August 9—11, 1965
Symposia ČSAV — pp. 336 — ill. and table in text — in English — paper covers

Mechanism of Gene Mutation — Mechanism of Processes Leading to Recombination Phenomena —Mechanism of Gene Expression

Mutation in Population

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Symposia ČSAV — pp. 194 — ill. and tables in text in English — paper covers —

Mutation in Animal Population —Mutation in Plant Population —Mutation in Human Population

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Mutations of Somatic Cells — Hybridization of Somatic Cells — Transfer of Nucleic Acids to Somatic Cells — Selective Genetic Inactivation of Somatic Cells — Gene and Cell Differentiation — Antibody Formation as a Problem of Genetics of Somatic Cells — Genetic Consequences of Cell-Virus Interaction — Antigenic Variations of Somatic Cells and Cytogenetic of Cell Antigenicity — Synthesis and Speculation on Future Trends of Genetics of Somatic Cells

Distributors throughout the world, with exception of socialist countries: Academic Press Inc., 111 Fifth Avenue, New York 10003, N. Y., U.S.A.