N.LUCHNIK

Why I'm Like Dad

Mir Publishers

MOSCOW

Н. ЛУЧНИК

ПОЧЕМУ Я ПОХОЖ НА ПАПУ

ИЗДАТЕЛЬСТВО
ЦК ВЛКСМ
«МОЛОДАЯ ГВАРДИЯ»

N. Luchnik

Why I'm Like Dad

Translated from the Russian

by

Yuri Shirokov

Translation Edited

by

C. H. Creighton

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Prologue

The Professor v the Canon

Professor Carl von Naegeli of Munich University was famous as a stickler for precision and punctuality. And was proud of it. That may be why, as professor of botany, he had chosen hawkweeds (*Hieracium*) as the subject of his research, plants with crowns of yellow flowers resembling dandelions or sow-thistle. For work with them requires the utmost accuracy. The professor was exact in everything and always answered letters punctually. But one letter he had not answered for nearly two months, and that bothered him.

But what to say in reply? The letter had not come from a scientist, that was obvious from the subscription: 'I remain, Your Excellency's respectful and humble servant, Gregor Mendel, Canon of the Monastery and teacher at the *Realschule*.' But the date was 31 December 1866, and here it was already February 25th.

But it wasn't only the signature. Mendel had sent him an article, but no scientist could have written such a work. It was simply a kind of word-salad, a hodge-podge of botany and algebra.

'Render unto Caesar the things which are Caesar's; and unto God the things that are God's.' If you're a botanist you should stick to botany, and if you're a mathematician it's not your business to cross plants. But it is also not good to discourage a young author (Naegeli was unaware that Mendel was already over forty). He was very hard-working. The care and persistence of this canon could give a lesson to some of our 'young geniuses'. A rebuke and nothing more would be sure to discourage him from further experiments. And this Mendel with his diligence might prove a fairly good assistant. It was bad, though, that he imagined he had discovered the law of the formation of characters in crosses. One must dissuade him of that, of course.

A cunning smile crosses the Professor's face. He adjusts his spectacles, strokes his high, bald brow, and reaches for a pen.

'It seems to me that your experiments with *Pisum*, far from being finished, are only beginning,' he writes. 'The mistake made by all the more recent experimenters is that they have shown so much less perseverance than Koelreuter and Gaertner.'

That's it; since the experiments have only begun there can be no question of discoveries. But one must encourage the young researcher.

'I note with pleasure that you are not making this mistake, and that you are treading in the footsteps of your famous predecessors. You should, however, try to excel them, and in my view this will only be possible (and thus alone can any advance be made in the theory of hybridization) if experiments of an exhaustive character are made upon one single object in every conceivable direction.' That also is not a bad idea; after that word of approval he will continue his work with redoubled energy.

But Naegeli is not quite satisfied with his letter. He leans back in his big armchair and begins to finger his small beard. What about the equations? Mendel considers them the main thing, and the Professor has still not written anything about them. He doesn't like mathematics; and what use is it any way to a botanist? He remembers the distant days when he was a student and read maths. Half-forgotten terms come back to him—'rational formulae', 'empirical formulae'. And he recalls that formulae that express a general law are called rational, while empirical ones are mathematical expressions valid for certain special cases. Of course, that is what we have here. Mendel must be told that his formulae are only empirical. Naegeli again bends over his writing table to set down the idea that

has just come to him. And adds: 'Your design to experiment on plants of other kinds is excellent, and I am convinced that with these different forms you will get notably different results....'

Let him experiment with other objects. For that matter, why not advise him to busy himself with *Hieracium*? Mendel was apparently a methodical man, and something might come of it. And that would be a great help for Naegeli. The Professor folds the letter and seals the envelope with a square blue wafer with a big '6' in the middle. He felt much relieved. Now he could get back to his microscope.

Carl von Naegeli wrote fatal words. Johann Gregor Mendel, a teacher at the *Realschule* in Brünn (now Brno), had made a very great discovery. He had sought the support of a very eminent botanist, a specialist in hybridization, and the latter had understood nothing. No harm in that. After all Mendel himself believed he had discovered a general law of nature, that he had found not empirical formulae for the segregation of characters in hybrid generations, but rational ones.

The fatal circumstance was the fact that Naegeli advised him to work with *Hieracium*. Not only do these plants have very small flowers with which it is difficult to experiment, but they have a very rare property that makes them quite unsuitable for experiments in crossing. At the beginning of this century, some years after the deaths of both Mendel and Naegeli, Scandinavian botanists discovered that hawkweeds (like many other *Compositae*) can often set seeds without pollination. Fertilization is rare among them. Therefore the experiments with hawkweeds that Mendel persisted in for several years yielded quite different results than those with other plants, and in the end even forced him to doubt the validity of his discovery.

If Naegeli had realized that he had been told of a very great discovery, modern genetics would have been born in the 1860s. Instead, Mendel's work stood undisturbed on library shelves for three and a half decades. It was only in 1900 that his laws were rediscovered and his name rose to fame. Now his name is known to every schoolboy.

In August 1965 geneticists from all over the world gathered in Czechoslovakia to mark the centenary of the dis-

covery of the basic laws of heredity. The huge building of the New Theatre in Brno ('Nove divadlo' as the Czechs call it) was crowded with scientists, journalists, and the representatives of various organizations.

After the opening ceremony a short man with a completely grey beard went to the rostrum, B. Němec, the oldest Czech geneticist. He read a paper entitled 'Mendel's Discovery and His Time'. He was followed by other scientists with world famous names, who described the development of Mendelism in their countries and the successes of genetics in plant breeding, stock breeding, and medicine. Celebration of the 'birthday of genetics' was not confined to the New Theatre. The day became a national holiday for all Czechoslovakia. There were pictures of Mendel in the streets, and posters devoted to genetics. A foreign visitor did not have to look for the place of the meeting. It was sufficient to say 'Mendel' and any passer-by, whether schoolboy or old-age pensioner, could show him the way.

Then the celebrations moved to Prague where an international symposium on mutations was held. The Mendel Museum, the Academy of Sciences, the Government of the Czechoslovak Socialist Republic, all held receptions for the participants. Outstanding geneticists were granted honorary University doctorates and given commemorative medals.

I was lucky enough to take part in the celebrations and in the work of the symposium, and read a paper at one of the sessions. It was a fortnight of unforgettable impressions. But wherever I was, whether listening to a paper on modern views of the fine structure of the gene, or admiring the majestic waters of the Vltava from the Charles Bridge, or listening to Mozart's *Ave verum* at the memorial mass in the cathedral served in honour of the former Abbot and Prelate of the monastery, Gregor Mendel, or drinking beer at the 'U kaliha' (The Flagon), the same beer-hall where the good soldier Schweik used to spend his time, I kept thinking about one thing, the fate of science.

Of course, I heard nothing new in principle during the celebrations either about the history of Mendelism or about genetics, but the papers at the symposium and the whole atmosphere forced me to think over the paths taken by

genetics over those hundred years. There have been amazing things. That Mendel's discovery remained unrecognized and was then rediscovered simultaneously 34 years later by three scientists in three different countries is probably known to everyone. But do you know that the same fate befell the first work on the chemical nature of the gene, and the first work on the alteration of heredity by radiation and chemicals? Isn't it a marvel that geneticists, like physicists, have penetrated to the atomic and molecular level in recent years, and can now write the 'chemical formulae' of certain inherited diseases? But to how many is it clear that these breakthroughs have been made on a path (however meandering) taken by individual scientists as long ago as the end of the past century? And how could one not reflect on the fact that parallel with Mendelism there has also always been anti-Mendelism, which has sometimes had the upper hand?

It was then that I got the idea of writing a book about genetics and geneticists, about the fate of the science, about the people who created it, and their fates. Although my book is written for the general reader, it is not popular science. Apart from the achievements of science there are the living people who create them, people who experience the rapture of the pioneer, people who make mistakes and who suffer tragedy. Was it not tragic, what happened between Mendel and Naegeli? To me it is a theme worthy of a Shakespeare. If Naegeli had been able then, in 1866, to understand the article that had been sent to him the lives of both of them might have been changed. And Mendel would not have died in obscurity, involved in tiresome litigation over church taxes. And Naegeli would not now be remembered as the man who retarded the birth of a new science for 34 years.

So, although the fundamental scientific facts from both classical and modern genetics are assembled here, my book is not primarily about science but about scientists, about the fate of discoveries, about the development and transmission of ideas, about the circumstances in which we do science.

But I would like to warn the reader about two things right at the beginning. First, this is only a sketch. It is impossible, in a book like this, either to give a full account of genetics or even to talk about all the most impor-

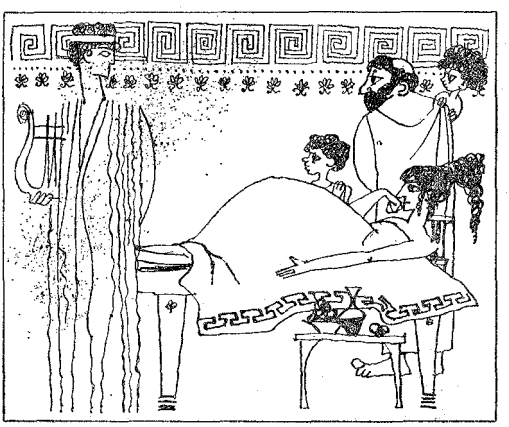
taut things. From the myriad of facts I have had to limit myself to selecting those that seem to me the most essential or the most interesting. Secondly it is not unlikely that I have been influenced by my personal tastes, by better knowledge of one field than another, and, of course, by personal acquaintance with fellow scientists.

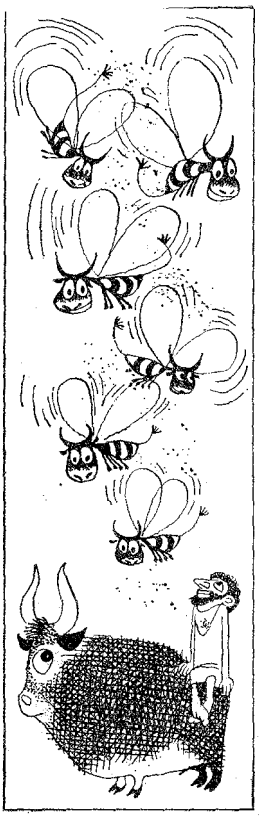
ıe Great Mystery

e tight-fisted master had been haggling with the shep-
·d for a long time. Finally they agreed that the latter
ıld keep all the speckled and spotted lambs from the
:k, while the black ones would remain with the owner. But the foxy master left all the black ones in the flock, culled the others, and drove them away a distance of two or three days' journey. But the shepherd turned out to be even more wily. He threw rods of green poplar, and hazel and chestnut into the watering troughs where the sheep drank. And to the astonishment of the tight-fisted master, the black sheep brought forth ringstraked, speckled, and spotted offspring. The shepherd grew rich.

The story is told in one of the oldest books known, the Book of Genesis in the Bible, where it tells how Jacob outwitted his miserly father-in-law. The tale is ancient but meaningful.

An ancient Greek would put a statue of Apollo beside his wife's bed when she was going to have a baby. He did so, of course, so that his son would resemble the handsome





god. Even today some people believ that a woman expecting a baby shoul not look at fire lest she give birtl to a redhead!

Many volumes could be writte about the legends and superstition connected with the birth of livin creatures and the inheritance or non inheritance of bodily and spiritua traits. No wonder. These question interest everyone. Isn't it a miracle that new living creatures come into the world that after a time begin to look like their parents? Is it not a great mystery, whether a baby will be a boy or a girl? And who it will take after? Naturally, so long as science could not answer questions about the birth of new creatures and about inheritance, fantasies filled the gap.

And what wild fantasies have been invented. Marcus Terentius Varro, the famous Roman scholar and writer (116-27 B.C.), wrote in his book on agriculture that honeybees were procreated partly by bees and partly by oxen. By oxen when they got rotten. That is why in his epigramme the Greek philosopher Archelaus called bees winged children of rotten oxen; he also wrote that wasps were procreated by horses, and bees by calves.

Ideas on fertilization were no less fantastic. Alcmaeon of Crotona (5th century B.C.) asserted that semen was part of the brain. Anaxagoras, Democritos, and Hippocrates, who supposed the seed to be formed in all parts of the body, disputed his belief. As we know from myths and legends, however, fertilization was not considered indispensable for the birth of living creatures.

But whatever the fairy tales said, it was necessary to work the land and raise cattle, and develop new varieties and breeds. And even when we turn to the most ancient times, we are amazed how far human practice had someti-

mes gone. Archaeologists have found a stone bas-relief on which a winged creature is carved with its wings spread out over a palm tree. Beside the tree are the Assyrian king and a priest in ritual garments performing artificial pollination of the female flowers of the date palm. The bas-relief is more than 2,500 years old. Yet scientists were still debating the existence of sex in plants in the last century. Most species of agricultural plants, however, were being cultivated in pre-historic times.

Thus, for long centuries, two groups of views on heredity and the phenomena linked with it existed side by side—on the one hand naive legends and superstitions, sometimes poetic, sometimes absurd, and on the other hand knowledge gleaned over millenia from chance discoveries and blind trial and error, a collection of rules that, though unsubstantiated, had been found to work in practice.

But things couldn't go on like that indefinitely. The development of human society had begun to face agriculture with new demands that could only be met in a scientific way. That was the situation that had developed in the nineteenth century. And Mendel's work, of course, was not uninfluenced by the practical needs of farmers and stock-breeders.

On the other hand, neither the chromosome theory of heredity nor molecular genetics could have appeared without Mendelism, just as Mendel could not have made his discovery if it had not been for several important earlier works that seemed to have no direct bearing on discovery of the laws of inheritance although they created the prerequisites for it.

Vesicles and Cells

Mikhail Lomonosov, member of the Russian Academy of Sciences, in 1750 wrote a *Letter on the Uses of Glass* (like many of his 'letters' it was in verse) in which he described the microscope and the 'mysteries that could be seen with it.'

He himself used the microscope to study both chemical substances and biological objects. In his day it was still a novelty. Less than a hundred years had passed since Hooke's invention of an improvement on the first optical glasses. Science and life still moved at a leisured pace and a century was not a long time. Lomonosov was right.

The microscope has revealed many 'mysteries', and still does; and one of these 'mysteries'—the cellular structure of living organisms—had to be discovered before the laws of inheritance could be elucidated.

As a matter of formal priority, Robert Hooke himself had first seen cells in 1667. He was the assistant of Robert Boyle, the famous English physicist and chemist and discoverer of the law (the Boyle-Mariotte law), for ignorance of which schoolboys all over the world are still failed. Hooke built a microscope and began to examine all sorts of things with it. One day an old wine cork came to hand and he put that under the microscope. Strange.... Though soft and smooth it turned out to consist of tiny cavities like honeycomb. Hooke called them 'cells'. He found the same kind of structure in other vegetable objects, in pieces of carrot and turnip. But no great discovery came of it. The young scientist limited himself to measuring the size of these cells, and wrote in astonishment that these pores were so tiny that the atoms Epicurus thought of would be too large to pass through them. And that was all.

But what else could he have written then? Before the great generalization was made nearly 200 years were to pass. Many scientists looked into microscopes, and observed a cellular or vesicular structure now and again. But not always. Their microscopes and microscope techniques were too imperfect. But by the end of the 1830s it was clear that a cellular structure was the law for all living creatures. It was not fortuitous that several scientists arrived at this idea independently of one another.

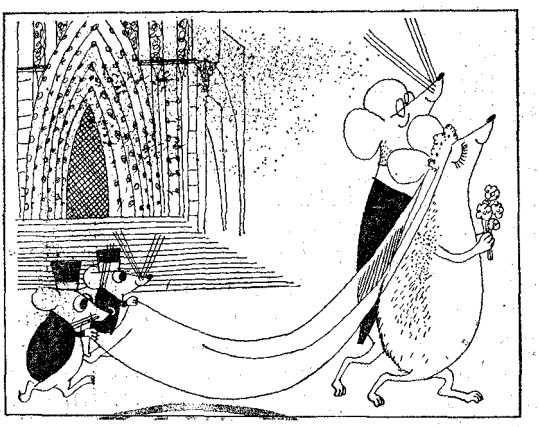
Credit for the cell theory is usually ascribed to two German professors, the botanist Matthias Jakob Schleiden (who worked for some years in Russia) and the zoologist Friedrich Theodor Schwann. But the same conclusion was drawn about the same time by the Czech Johannes Purkinje and a little earlier by the Russian Pavel Goryaninov, professor at the Medico-Surgical Academy in St. Petersburg, who wrote in 1837: 'Everything organic begins from a microscopic vesicle. From the union of new vesicles cellular tissue is formed—loose, with round vesicles, or compressed or fibrous, with long vesicles or cells. The principal vesicles of cell tissue, changing many times, produce all the types of organic tissue. A vegetable cell is marked by the mathematical regularity of the vesicles but is less va-

ried..., an animal cell, on the contrary, is less uniform but more varied.'

Of the cell itself little was known in those years. None of the founders of the cell theory knew even of the existence of chromosomes. Chromosomes, the laws of the division of cells and nuclei, and the processes occurring within cells during fertilization were all discovered and studied after Mendel had made his discovery, while the superfine structure of cells, and the inner structure of chromosomes and other cell organelles, have only been studied in our time.

All that Goryaninov and Purkinje, Schleiden and Schwann only knew about the structure of a cell was that it was a vesicle of viscid fluid (which they called protoplasm) surrounded by a membrane and containing a nucleus. The only fact established for certain was that all living matter consisted of cells. We shall have to concern ourselves with the finer details of cell structure, but it is too early to talk of them here. Let us still keep to the level at which science found itself in Mendel's day. It will then be easier to understand the greatness of his discovery and its fate.

Mendel's main work was his experiments in plant hybridization. It is hard to believe today that only a century ago the crossing of plants was in a way 'the last word in science'. We are living at an extraordinary time when science and technology are developing at a pace quite unprecedented in the history of mankind. To modern children a tele-



vision set is a common piece of household furniture, but only forty years ago, in my own childhood, in the early 1930s the unpretentious valve radio set seemed a miracle. Therefore, we cannot help being amazed when, turning to the history of science, we learn how long it took to clear up problems that seem so simple to us today.

That was the case, in particular, with the existence of sex in plants and the possibility of hybridization. Do plants have sex? Three hundred years ago science was still unable to give a clear answer to that question, although Assyrian priests carried out artificial pollination of date palms, and Pliny the Elder (A.D. 23-79) wrote about the role of wind in pollination; but that was not official science. Scientists long adhered to the most varied views, a situation that existed until the end of the seventeenth century.

Tübingen, a small town in Germany, is proud not only of its monuments of the Middle Ages that attract crowds of tourists but also of its Botanical Gardens, one of the oldest in Europe. Young Rudolf Jakob Camerarius, son of the Professor, spent all his spare time there examining exotic plants, watching the butterflies hover around them, and tracing how a bud turned into a flower, and a flower into an ovary, a fruit, and seed. Later he became director of the Gardens, and in 1694 published a small book entitled *Letter on the Sex of Plants* in which he collected together the findings of other scientists and summed up his own observations. He described in detail the structure of the flower, and of its male and female organs, and the phenomena of monoecism and dioecism. But most important of all, his book set out in detail the importance of pollen in the production of seed. Camerarius wrote quite plainly that seed could not be set without pollination.

Although his book was devoted to plants, Camerarius did not disregard the problem of sex in animals. Drawing a comparison between the vegetable and animal kingdoms he concluded that the formation of an embryo was impossible in both without the coming together of the female sex products and the male, though he did not clarify the exact role played by pollen or seminal fluid. Another 200 years had to pass before that happened.

Camerarius also did not answer another question whether a plant of one species can be fertilized by pollen from another species, but it is to his great credit that he posed the

question and racked his brains over what the result of such pollination would be if it were successful. It was not an easy question to answer, and not solely for purely scientific reasons. Indeed, if such pollination were possible the offspring would be unlike either of the parents. But at that time, however, it was generally believed that only those species existed on earth that had been created by God in the beginning.

The Academy Sponsors a Contest

Schoolboys receive A's for good essays, and scientists prizes. The theme of a school composition is given by the teacher, but no one sets a scientist the subject of an article. His work has a plan that he himself has drawn up, and when interesting results are obtained they are published in a paper.

That is how matters stand in the twentieth century. But it wasn't always that way. Or rather, schoolboys have always written on themes set by the teacher, and sometimes scientists have too. When a problem that seemed important had long remained unanswered some scientific academy or other set aside a certain sum for a prize from its modest funds and announced a competition.

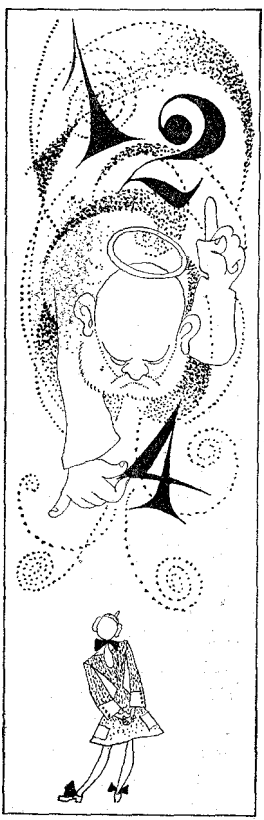
Several competitions were devoted to the problem of the possibility of hybridizing plants. As early as 1759 the Imperial Academy of Sciences in St. Petersburg announced one for the best treatise on sex in plants. The winner was the great Swedish botanist Carolus Linnaeus, compiler of the first scientific classification of species. He presented a treatise entitled *A Discourse on Sex in Plants.*

This work astounded many people. Linnaeus' views were quite well known and everybody remembered the following statement in his *Philosophy of Botany (Philosophia Botanica)*, published in 1751: 'There are as many different species as were originally created'. In his new work, however, the renowned Swede asserted that new species could be produced by an alien pollen; and he not only expressed the idea but confirmed it by his own experiments. He succeeded in crossing two species of goatsbeard (a plant of the family *Compositae*) and obtained a hybrid form.

This conclusion had not been easy for Linnaeus to draw. He was and remained a deeply religious man to the end of his life. Therefore, from the very beginning he had con-

sidered that all species were the result of divine creation and would never arise again. But he was also a naturalist, and was, besides, very painstaking and thoughtful. Gradually, under the influence of his own observations and experiments, Linnaeus began timidly to change his view.

The flowers of toadflax, for instance, gave him much trouble. This plant has yellow flowers of an irregular, asymmetrical shape, resembling those of the snapdragon, which is related to it. But occasionally these plants have perfectly regular petals arranged in rays around the centre of the flower. When Linnaeus first saw these flowers, he did not attach any significance to them, considering them sports. But when he learned that their progeny had the same symmetrical flowers, he was forced to state that species could arise anew. He racked his brains over this mysterious phenomenon for a long time, and in 1744 he even wrote a special article on toadflax.



Thus, it had to be admitted that new species could come into being now, and that different species could be crossed, producing offspring unlike their parents. But what about beliefs? Linnaeus did not renounce his. He began to think that species had not been all created at once and that the act of creation continued in his day. In his last years he expressed his ideas in a letter to a friend: 'It can be assumed that God created the figure '1' before '2' and '2' before '4', that he first created the simple and then the complex, that he first created a species in each genus and then mixed them to produce new species.'

Of course, Linnaeus was not an evolutionist. He admitted the possibility of hybridization only as a rare exception. But in his day there were people who talked of a blood relationship between all living things and made very serious experiments in plant

hybridization; but Linnaeus was a great scientist and his works were widely known, while their work passed unnoticed.

In 1778 a fascinating book appeared in St. Petersburg. Its title page read: *A Philosophical Discourse on the Transformation of Animals. Translated from the German by Ivan Morozov, teacher of German at the Smolensk Seminary.* The name of the author was not mentioned, but he wrote amazing things. He consistently refuted the views that species were invariable, and came to the conclusion that all animals were descended from a common ancestor. And he made no exception for man. Historians expended much effort to discover the name of the author and the origin of the book. It proved to be quite interesting.

In 1765, by decree of the Empress Catherine II, the first scientific society in Russia was established, the main purpose of which was to 'disseminate in the state knowledge useful for agriculture and industry'. It was called the Free Economic Society. Among other things, the society interested itself in bee-keeping; and it was decided to send two young people for training in this field to the then renowned apiculturist Adam Schirach, who lived in Saxony. The choice fell on two graduates of the Smolensk Seminary—Afanasy Kaverznev and Ivan Borodovsky. Both proved capable and inquisitive pupils. While abroad, they not only busied themselves with apiculture but on their own initiative studied many other sciences as well. Kaverznev proved to be particularly talented, and in 1775, before returning home, he published a book in German *On the Transformation of Animals.* It was this that was then translated into Russian, omitting the author's name.

This talented scientist had an unfortunate fate. Instead of carrying on his scientific pursuits he was forced to return to Smolensk where he became a petty official, and died in obscurity and poverty.

The first serious works on hybridization also had a link with Russia. Their author was Joseph Gottlieb Koelreuter, who was born in Germany in 1733. Koelreuter travelled a great deal. He worked in his native town, in Kalw, St. Petersburg, Berlin, and Leipzig, and finally settled down in Karlsruhe where he was professor of natural science. He was elected a member of the St. Petersburg Academy of Sciences, and it was in Russia that he carried out his first successful experiments in crossing two species of tobacco.

As we know, data on the possibility of hybridization were already available, but before Koelreuter's experiments they were only chance observations or isolated crossings, and no general conclusions could be drawn from them. Koelreuter regarded them very critically and even doubted the reliability of Linnaeus' experiments in crossing goatsbeard. We must give credit to Koelreuter, for his experiments came close to the requirements demanded of modern experiments. He planned his experiments, carefully conducting them on a vast material, and investigated the progeny for several generations.

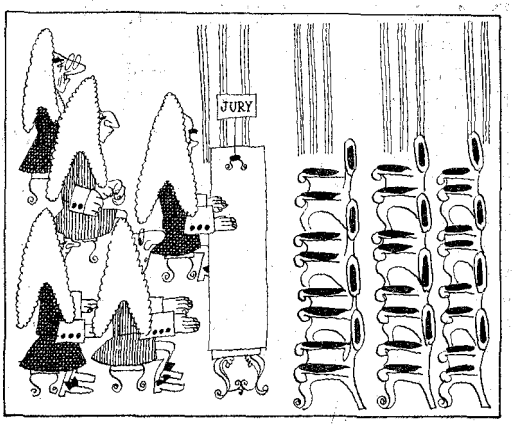
His first paper on the hybridization of tobacco appeared in 1761. It was followed by a number of other communications on experiments with other plants.

Koelreuter's name is not only known to us in connection with his successful experiments in hybridization. He also discovered the phenomenon of heterosis or hybrid vigour: hybrids of the first generation have increased productivity. Heterosis is utilized in our day to obtain record yields of maize and other crops. Koelreuter also made a big contribution to the study of sex in plants and the part played by insects in pollination.

Koelreuter's work was not appreciated by his contemporaries. Moreover, certain 'coryphaei' continued to deny the existence of sex in plants and challenged the results he obtained. They are all now forgotten, but it was not until this century that Koelreuter's contribution was fully appreciated.

The problem remained open. The example of the St. Petersburg Academy was followed sixty years later by the Prussian Academy of Sciences. At the suggestion of the botanist Link competition was announced in 1819 on the subject 'Does hybrid fertilization occur in the plant kingdom?' But it was a failure, not a single paper was submitted.

In 1822 the competition was repeated. Only one man entered it, A.F. Wiegmann, an apothecary and botanist from Braunschweig. In 1826 he submitted an essay on the evolvement of hybrids in the vegetable kingdom. Wiegmann carried out experiments with a whole series of plants, and although they were inadequate because of their small scale and because he did not himself do the pollination but employed insects, he obtained interesting results. His



work was not quite up to the requirements of the contest (or perhaps his results did not meet the wishes of its sponsors), so Wiegmann received only half the promised award.

In 1830 an analogous prize was sponsored by the Dutch Academy of Sciences in Haarlem. Its subject was formulated much more concretely: 'What does experience teach regarding the production of new species and varieties through the artificial fertilization of flowers of the one with the pollen of the other, and what economic and ornamental plants can be produced and multiplied in this way?' Again only one paper was submitted. Its author was Carl Friedrich von Gaertner, who presented a short communication from which it was quite unclear on what he based his conclusions. Some time later he submitted a detailed report supplemented with samples of 150 hybrids obtained by him. This was a serious work based on more than 9,000 experiments. In 1837 Gaertner was awarded the prize, but his work remained unpublished until 1849, one year before his death. It contained clear evidence of the possibility of hybridization and laid down certain rules of the transmission of characters from parents to progeny.

But that did not end the competitions. In 1861 a new prize was offered by the Paris Academy of Sciences on the study of vegetable hybrids from the viewpoint of their fecundity and preservation or loss of their characters. Interest in the problem had apparently grown because this time two papers were submitted. Their authors were

D. A. Gordon and C. Naudin. The prize quite deservedly was awarded to Naudin.

Before me lie the photographs of many outstanding scientists, people who have played a role of some sort in the development of genetics. Looking at them I try to understand their character, and to follow the train of their thinking. The photograph of Charles Naudin stands out among the rest. It is more like a portrait by a classical painter. He had the face of a prophet, with a huge grey beard, curly hair, very regular, classical features and quite remarkable eyes, wise and kind, the eyes of a Biblical prophet or patriarch. But this look was deceptive. Naudin was no patriarch of science; on the contrary, it is hard to imagine a more unhappy life. For long years Charles Naudin dragged out a miserable existence as an assistant in a Paris museum. It was not until he was 62 that he received the independent post of director of a plant acclimatization station. And then new misfortunes befell him. He lost all his children, became blind, and died in utter loneliness. Does his life not remind one of Job's in the Bible, who was afflicted by one misfortune after another. And like Job Naudin did not lose heart despite all his trials and tribulations.

His faith was different. Naudin believed in science and in the power of the human mind. And notwithstanding all his difficulties he continued to experiment and came closer than anyone else to discovery of Mendel's laws. He was able to draw conclusions about the 'purity of gametes', the uniformity of the first generation of hybrids, and the 'extreme medley' of the second. But his conditions did not permit large experiments, and those that he made were as unfortunate as himself; the plants were either killed by frost or destroyed by pests. In addition, he repeated the mistake of all Mendel's other predecessors of making interspecific rather than intra-specific crossings.

Academies and Science

Looking back from the heights of today's science at the works of a century or two centuries ago, it is easy to see their imperfections; and reading some of the naive arguments in their favour is apt to cause an involuntary smile, but that in no way detracts from their importance. The 'imperfect' works of Camerarius and Koelreuter were, of

course, much more important than most of the articles in modern scientific journals written according to the last word in science.

If we make an even closer scrutiny of the history of scientific concepts, the works of our scientific 'forefathers' do not seem as naive as they appear at first sight. The point is that the genuine course of science is sometimes difficult to trace through the volumes of monographs, the sets of journals, and the reports of academies. The official history of science does not always coincide with its true story.

Scientific academies and universities have existed for a long time, where learned men of extremely respectable mien sit on tall chairs or read lectures in well-modulated voices. The official history of science is written by these venerable people, whether they wear, according to period, powdered wigs or well-groomed beards, gowns or frock-coats or well-cut lounge suits. Their names are known to all their colleagues, and it is their works that historians mainly study.

Their profession is science. And of course it is they who make most of the great discoveries, and carry out most of the important research. But there are many exceptions to the rule. Very often, particularly in the past, the greatest discoveries were not always made by professionals (remember Gregor Mendel with whom we began our tale) or by scholars standing at 'the helm of science'. On the contrary, it has happened, and unfortunately not so seldom, that those 'at the helm' only held up the natural development of science by their activities. The prehistory of genetics, right up to the beginning of this century, is a graphic illustration of that.

The name of Mendel did not figure in official academic science. Now we cannot imagine the 1860's without him. But until 1900 his name did not exist for science; what did presented a fairly dismal picture.

In the first half of the last century official science still did not recognize the existence of sex in plants. Respectable German professors like Schelwehr and Henschel regarded Koelreuter's results as unsubstantiated on the grounds that the hybridization of plants was impossible in principle. And to the very end of the century there were only a few theories of natural philosophy from the worthy professors. These theories, cherished in the quiet of studies, were pu-

rely speculative and unbelievably confused. They were highly intricate constructions built up from 'idioplasm', 'micellae', 'gemmules', 'biophores', 'ids', 'idants', 'determinants', and other abstract categories. All of them were supported only by the authority of their creators and did not last long.

But far from the studies and university chairs science was developing according to its own inexorable laws. Before we turn to the birth of Mendelism, let us note certain milestones that preceded it.

Although isolated observations had been accumulated since time immemorial, a continuous line in the development of ideas and collection of facts can only be traced since the work of Koelreuter, about which we have already spoken in fair detail. It was he who finally proved the existence of sex and fertilization in plants and the possibility of their hybridization. He also developed the methods of crossing used in scientific work and in practical selection to this day.

Academic science was unwilling to accept Koelreuter's conclusions; but that did not mean that they remained unrecognized. Nurserymen and plant breeders were quick to notice his work and to take his methods into their arsenals and some practical horticulturists achieved spectacular results. Special mention in this connection is deserved by the English plant grower and selectionist of the late eighteenth and early nineteenth century Thomas Andrew Knight, for many years president of the British Horticultural Society. In addition to his important practical achievements, Knight, a meticulous observer and painstaking researcher, reached the conclusion that variety characteristics 'split' into separate small characters that cannot be further divided. It was precisely this discovery, made 150 years ago outside academic science, that constitutes the foundation of our modern views of the corpuscular character of heredity.

Academic science failed to take note of Knight's fundamental discovery, but it attracted the interest, for instance, of Augustin Sageret, a naturalist and agronomist, and member of the Agricultural Society of Paris. From 1825 to 1835, i.e. in the period when the academics were still debating whether or not plants had sex, he carried out brilliant experiments in crossing various vegetable crops,

particularly musk melons. In these experiments he established that certain ancestral characters disappeared in the first generation to recur in the second, i.e. he discovered the phenomena of dominance and splitting. Sageret was well acquainted with the work of Knight and Koelreuter, and defended the latter's findings against the attacks of the professors.

Naudin, who came closest to discovering the laws of heredity, followed the same line and was also thoroughly familiar with the work of his predecessors. Otherwise he certainly would not have achieved what he did.

And Mendel, of course, could not have pulled his discoveries out of thin air. Not being a member of academic circles, he too knew the works of all the above-mentioned workers in science and developed them further. And however we regard the work of all these scientists from our contemporary point of view, their names will always remain in the annals of science. Denied recognition in their lifetime, they are becoming increasingly famous today.

Johann Becomes Gregor

The lecture on physics was over, and the students began to rise noisily from their benches.

'You, Mendel, please stay behind,' Prof. Franz said to one of them, a stocky blonde young man with a big head, grey eyes, and curly hair.

'Rumours have reached me,' the Professor began when they were alone, 'that you have decided to give up your studies. Is that so, my boy?'

' Alas, it is. Science apparently is not for me. I passionately wanted to study, and everything was going well while my father was in good health. But since his chest was crushed by a tree-trunk, he has been ill all the time. He has made over his holding to Herr Sturm, my elder sister's husband, and Herr Sturm won't hear of supporting me until I finish the university. Only my younger sister has helped me. Theresia is a saint; God grant her health and a good husband! She renounced part of her dowry in my favour. Only thanks to her am I now able to get through the philosophy course.'

'But what if you tried to earn enough for your needs and studies?'

'Of course I have tried, Herr Professor. The money Theresia gave me scarcely lasted half a year. I have been earning my livelihood for several years now by private tuition. But I could wish for better health. When I was in the last year at the high school I was compelled to spend a year with my parents. But it is impossible for me to continue such strenuous exertions.'

Prof. Franz became thoughtful. This manly student was almost the best in his branch and had no equal for diligence. If only he could finish the university more could be expected from him than from those rich loafers who only thought about chasing girls or boozing in beer-halls.

'Do you know, Johann, what I think you should do? You should enter a monastery.'

'But what will that give me except free meals? Better for me to go back to the village and take up bee-keeping or gardening. I'll always earn my livelihood, and to observe the life of bees and plants is a fascinating and instructive pursuit.'

'You are wrong, my young friend. The monastery will not only spare you anxiety about a means of livelihood but it can also give you the opportunity to improve your knowledge. And not only in theology. Not just any monastery, of course. The Augustinian Monastery in Brünn, it seems to me, is a suitable place. The Abbot, Prelate Cyril Napp, is an old friend of mine. He is a man with a very good mind and very well educated. As for free thinking,' and here the Professor lowered his voice, 'old Napp can give a few pointers to some of our professors. Think my words over, and I shall help you if you wish. I think Napp still remembers me.'

That conversation settled Johann Mendel's fate. The peasant's son, born in 1822 in the village of Heinzendorf

(now Hinczice in Czechoslovakia), who had dreamt of becoming a teacher and scientist, was accepted as a novice by the Augustinian Monastery. In the autumn of 1843 he entered the monastery and assumed a new name, Gregor.

What Professor Franz had told him turned out to be true. The Abbot of the monastery, Prelate Cyril Napp, was a leading figure in the cultural life of Moravia in those years. Many progressive people were his friends and frequent guests at the monastery. Among the brothers Mendel met interesting people like the philosophers Mathhaeus Klacel and Tomáš Brátranek. The first-named subsequently went to America; the latter became a professor at the Jagello University in Cracow. Another monk was Paul Křižkovsky, the composer and reformer of Church music and teacher of the famous Czech composer Janacek.

Napp was a champion of enlightenment. Among the brothers there were also specialists in the natural sciences, mathematicians, physicists, mineralogists, and botanists. In addition to their religious duties, they worked as teachers, laid out a botanical garden, and built up a mineralogical collection and herbarium in the monastery. Newly consecrated Brother Gregorius studied theology and ancient Oriental languages in the monastery school, and in addition attended lectures on natural science at the Brünn Philosophical Institute. Mendel spent all his leisure working on the mineralogical and botanical collections, which were put at his complete disposal.

In 1847 Mendel was ordained priest and became a canon. One of his new duties was to confess the sick and dying in St. Anne's Hospital. But the sight of human suffering so depressed his sensitive soul that he had a nervous breakdown. Mendel was therefore relieved of his duties as a confessor, and invited instead to teach in a high school. Needless to say, he accepted the offer with enthusiasm. He gave lessons in mathematics, taught languages, and soon became a favourite teacher.

But he had no formal qualifications for a permanent teacher's post, and was considered only a supply teacher. To enable him to obtain a teacher's diploma he was permitted to take the external examinations in natural science and physics of Vienna University. Mendel submitted the essays required and was failed, apparently because in one of them he set forth in detail and in very favourable terms

the theory of the origin of the Earth according to Ka and Laplace, which patently contradicted the Biblical l gends and was at variance with his holy orders. In spi of this failure Mendel secured permission to be examine in person, but again did not pass, apparently owing to h lack of systematic education.

The monastery authorities were clearly favourably di posed toward Pater Gregor. He was allowed to carry c as a teacher, and in the autumn of 1851—with letters recommendation and a written request from the prelate i his pocket—he went to Vienna to complete his educatio There were then many first-class scientists in Vienna Un versity; suffice it to say that Mendel attended the lecture on physics of J. Doppler, whose name is known even t schoolboys today (the Doppler effect). After spending fou semesters at the University Mendel returned to his mona stery.

He was again appointed a teacher, this time in the *Rea schule* teaching physics and nature study. All this woul scarcely be worth describing if he had not begun, on hi return from Vienna, the experiments in crossing differen varieties of peas that brought him, belatedly, worl fame.

The work done by Mendel is truly amazing. When on reads his article 'Experiments in Plant Hybridization' now a hundred years later, one cannot help admiring his per sistence, diligence, clear thinking, and the spirit of inno vation manifested in several related fields.

Mendel returned from Vienna with a perfectly clear goa and, apparently, a completely worked-out plan of experi ments. Unlike his predecessors who had made interspecifi crossings, i.e. had dealt with differences in a large numbe of characters, Mendel decided to investigate separate, cle arly differentiated characters. In all his initial experiment he crossed plants that differed in only one character an were quite identical in all the others. Moreover, all hi predecessors had dissipated their efforts, experimenting o a large number of species. Mendel, however, decided t limit himself strictly but to obtain broad and uniform ma terial. It may be hard to believe, but he spent ten year on his planned series of experiments with peas.

It took Mendel a long time to select the experimental object. It is known, for instance, that he not only attemp-

led to experiment with plants. At home he raised white and grey mice and crossed them; but these experiments with animals he had to conceal as an 'immoral' pursuit, unsuitable for a clergyman. He did much work on bees, crossing different strains, but no information on the results he obtained has come down to us.

To select suitable material among plants, however, was far from easy. In his article Mendel wrote of the requirements an experimental object must meet. He settled on peas which proved suitable on all counts.

Laws of Nature

Mendel began with 34 varieties of peas ordered from various seed firms, but did not start his experiments immediately. For two years he checked these varieties for purity, and only when he was sure they produced quite uniform progeny did he embark on his experiments. And later, over all the years that he worked with peas, he continued to check the purity of the initial varieties. Many contemporary experimenters could learn from his exactitude in regard to the purity of his experimental material.

To this day Mendel's seed beds, or rather the spot where they used to be, are carefully preserved in the grounds of the monastery at Brno. It is a long plot, 35 metres by seven, along the monastery wall. All gardening work connected with the experiments, to say nothing of experiments themselves, was done by Mendel alone.

The experiments were difficult and painstaking. Peas had been selected, in particular, because chance cross-pollination was completely ruled out with them. A peculiarity of their flowers is that the stamens and pistil are completely enclosed by a 'keel' and the anthers burst while they are still in the bud. The stigma is therefore covered with its own pollen even before blossoming. But this form of flower also presented difficulties for the experimenter. Mendel kept a vigilant eye on his charges, watching for the moment when a bud was ready for fertilization. Then he opened it, removed the 'keel' and carefully broke off one stamen after another with a thin tweezers (scarcely breathing lest he brush the stigma). Then he powdered the stigma with foreign pollen. This procedure had to be repeated with every flower—and there were hundreds and thousands of them.

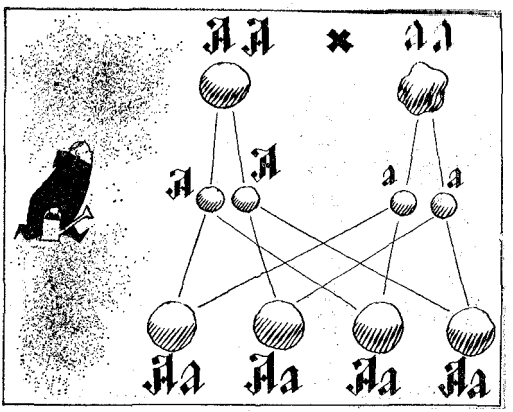
At last the first vegetation season was over. The harvest was gathered, studied, and counted. All the experiments gave a similar picture. For instance, Mendel had crossed varieties with round (or smooth) and wrinkled seeds; their progeny were all round. And the result was the same no matter whether maternal or paternal plant had had round seeds. That meant that the round type was completely dominant over the wrinkled.

But Mendel did not concern himself solely with the form of the seed. He investigated seven pairs of characters: the colour of the cotyledons (yellow or green), the colour of the seed-coat (white or coloured), the form of the pod (simply inflated or constricted), and so on. And in all the variants the same result was obtained: one character was dominant over the other, the yellow over green in the cotyledons, grey-brown seed-coat over white. This looked like a general pattern, but Mendel repeated his experiments many times over before he decided to tell anybody of his conclusions.

Spring came. Mendel sowed the hybrid seeds and did nothing more: let them pollinate themselves. But he did not sit by idly. He examined every flower. Occasionally he came across a sport in which the stigma stuck out of the keel. Pollen could be brought to them by the wind, so he culled them carefully. It was also necessary to protect his charges from pests. It was not simply a matter of preserving the harvest; more important was the danger that a beetle, nibbling at flowers, might carry pollen on its legs from one plant to another. All summer long Mendel was busy over his beds, but did not interfere with the pollination; all the plants were self-pollinated.

Finally, long-awaited August arrived—time to harvest the crop. Now the results could be summed up. It was amazing. Whereas all the plants in the first generation had been quite uniform, displaying only dominant characters, those of the second generation were found to be varied. Plants with dominant characters were in the majority, but those with opposite characters (known as recessive) also proved quite numerous. Their appearance could not be ascribed to chance, and most interesting, dominant and recessive characters occurred in a definite ratio.

Here is what resulted, for instance, from the experiments in which the initial varieties had differed in the

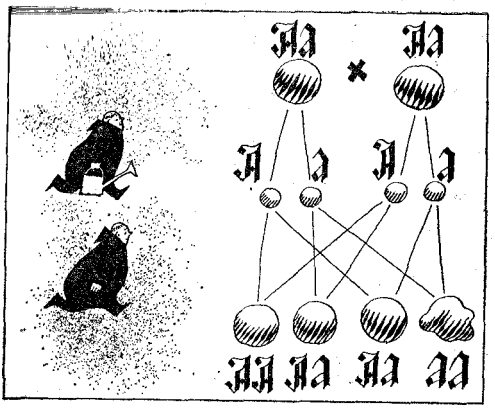


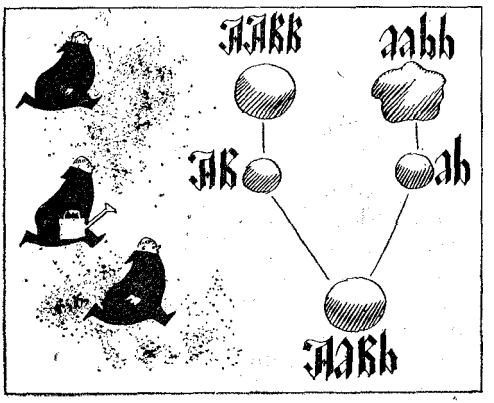
form of seed. It will be recalled that round seed was a dominant character, and wrinkled recessive, so that all seeds in the first generation had been round. In the second generation, however, 253 hybrids yielded 7,324 seeds; of these 5,474 were round and 1,850 wrinkled. The number of round seeds was 2.96 times larger, i.e. almost treble.

In the experiment in which the colour of cotyledons was studied, 6,022 were dominant yellow and 2,001 recessive green, a ratio of 3.01:1. A similar picture was obtained for all the seven pairs of characters. In the second generation segregation occurred, three dominant characters always being obtained for one recessive.

Thus another pattern had been found. The next year's experiments gave the same result. Mendel repeated his experiments and continued the original one. He wanted to know what would happen in the third generation after self-pollination. Again there was a new picture. Self-pollination of plants with recessive characters produced no segregation; all the progeny proved uniform. And no segregation subsequently occurred, though Mendel traced the characters to the seventh generation. As regards plants with dominant characters, they did not behave uniformly. Some, just like the plants with recessive characters, did not exhibit segregation; but the rest, as before, segregated in a ratio of 1 to 3. And here again a quite definite numerical ratio was observed: one third of the dominants did not split, while two thirds did.

Mendel concluded that it would be more accurate to





substitute the ratio 2 : 1 : 1 for the 3 : 1 observed. Half yielded hybrid seeds, a quarter dominant non-segregated, and a quarter recessive.

That was all. The phenomena of heredity had been reduced to a few simple rules. To explain them we shall need many words; in a drawing, however, these rules can be represented by a very simple diagram.

Such are the famous Mendelian laws, as the Dutch botanist de Vries called them later.

The first law (the law of homozygocity and reciprocity) states that the first hybrid generation remains fully homogeneous. The not quite justified term 'reciprocity' (mutua-

lity, equivalence), indicates that the result is the same whether the character is maternal or paternal.

The second law (that of segregation) applies to the second generation and concerns the segregation in the ratio already familiar to us—1 : 2 : 1.

There is a third Mendelian law (the law of independent assortment or recombination) which applies to cases in which the parents differ in more than one pair of characters. If we cross a variety having round yellow seeds with one whose seeds are wrinkled and green, all seeds in the first hybrid generation will, of course, be round and yellow since these characters are dominant. In the second hybrid generation, however, all the four possible assortments of characters will be observed after self-pollination. What is more, both pairs of characters will split quite independently of one another, producing a general segregation in the ratio 9 : 3 : 3 : 1. Consequently, in this example we will get

9 round and yellow;
3 round and green;
3 wrinkled and yellow;
1 wrinkled and green.

You may still not be clear why the ratio 9 : 3 : 3 : 1 corresponds to independent segregation. It will be more easily understood a little later.

If Mendel had gone no further than that, he would fully deserve the credit we now give him. For these were the first laws of heredity that science had established; and they were perhaps the first case of quantitative laws to be laid down in biology. But Mendel did more and went on to explain why characters were inherited in this particular way.

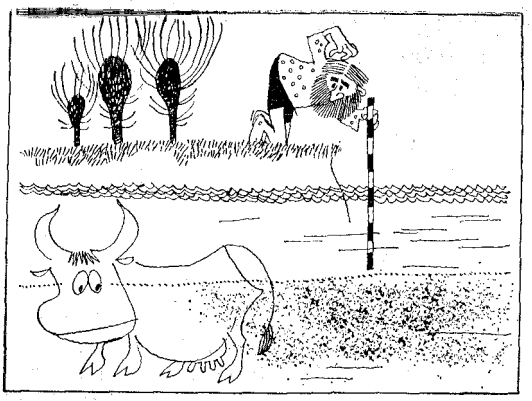
The Game of Dice

There are ideas that the lay mind rebels against with particular force. One of them is statistics. How often I have seen some wiseacre 'demolish' statistics with gusto.

'I hear a cow drowned in a pond knee-deep on average. She didn't know what an average was!'

' Look, I'll eat two dinners, while you go without. That way we'll each have one meal on average, ha, ha, ha!'

As jokes go, they are not below average. But I don't advise that type of humour, because it reveals a complete and ignorant lack of understanding statistics. The very



term 'on average' implies that a quantity is subject to variation. If a cow drowned in a pond only knee-deep at every point, it really would be paradoxical. As for 'averages', statistics exists because a mean is quite inadequate to characterize a variable. To use such a quantity you must know just how far it departs from the notorious average.

Statistical thinking contradicts common sense, but it cannot be helped. Statistics tell us, for instance, that there are no 'lucky' tickets in a lottery. That is absolutely true, a mathematical law. Nevertheless, nearly everyone who buys lottery tickets either avoids those with numbers that run in succession or relies on some other principle, though any combination of tickets has the same mathematical chances of winning. Yet although I know enough about statistics to have read lectures on the subject at the university, I must confess in strict confidence that I too hesitate about my choice when buying lottery tickets, though I know quite well that it makes no difference whatever.

One reason why Mendel's laws were not recognized for so long, and were opposed by many even after they had been recognized, is that they had a statistical character. There have been quite a few papers whose authors had obtained segregations in experiments, that differed from the 3 : 1 ratio, claimed that they had refuted Mendel's laws. What is more, they added that Mendel himself had never observed an exact 3 : 1 segregation.

All science has arisen from the summing up of man's experience, and been developed to meet his practical

requirements of one kind or another. The theory of probability is no exception. But unlike other sciences it is apparently 'ashamed' of its origin. For this branch of mathematics came into being from attempts to evolve a theory of games of chance and find a sure method of winning. Now the theory of probability is concerned with very serious subjects, but in the sixteenth and seventeenth centuries it was used to try and forecast the results of game of dice, tossing coins, and other forms of gambling.

We too shall have to concern ourselves with this unsavoury subject since examples from such games best illustrate the principles of the theory of probability, without which we cannot carry on our story.

Let us consider the simplest of gambling games—tossing pennies. Two gamblers toss coins and win accordingly as they fall heads up or tails. If the coins are not deformed and the two play fairly the chances are that the heads or tails will come up with equal frequency. As mathematicians put it, the probability of the occurrence is equal. Does that mean, however, that a coin tossed twice is certain to fall once heads and once tails, or vice versa? Of course not. Common sense tells us that the result may be anything; but one heads and one tails is most probable. The theory of probability states that such a result can be expected in 50 per cent of cases; in 25 per cent one could expect heads twice, in the remaining 25 per cent of cases tails twice. Thus, although the most probable result is one heads and one tails, it is not unlikely that heads or tails will occur twice in succession.

It follows therefore that for chance occurrences, like a coin falling heads or tails, we are unable to predict a definite result with accuracy. We can only forecast the probability of a particular result. The accuracy of our forecasts will depend largely on the number of attempts. With a single toss the forecast is quite uncertain, the probability of either result being equal. With two tosses it is also well nigh indeterminate. But if we have enough patience to toss the coin a thousand times it can be expected to come up heads almost 50 per cent of the time; and such a prediction is not apt to be mistaken.

It is particularly important to realize the following. Theoretically, tossing a coin one thousand times can give 1,001 different results, and their probability is far from

uniform. For instance, the chances of heads coming up in all the thousand tossings are practically nil (theoretically they are $1 : 2^{1000}$, which is infinitesimally small). The chance of heads and tails coming up 500 times each is the most probable, but it too is very slight, because it is only one chance in a great many, even if the most likely. Should we obtain such an accurate result in an experiment it would be something to marvel at. No matter, however, whether heads occur exactly 500 times or 512 times, the result will differ little from the 50 per cent that is expected.

So the occurrence of heads in 50 per cent of the time is the most probable result. Yet with one or two tosses we may well not get it at all. With a hundred tosses we should come closer to it, and with a thousand closer still. All that is exactly demonstrated by the theorems of the theory of probability; even with such a simple example as tossing a coin our conclusions are clear enough.

What has been said about the principal ideas of the theory of probability, the science underlying variation statistics, gives us the means to study variables; and biology has to deal with variables at every step. Take, for instance, the question whether a baby will be a boy or a girl. It is known that the probability of either is the same. But no one can tell whether a boy or a girl will be born in a given family. It is no problem, however, to predict how many boys and girls will be born in a big city in the course of a year. To say that 510 boys will be born on average per 1,000 births would not be far off the truth.

Now let us go back to Mendel's laws. We said that certain people who did not know or understand statistics tried to refute them, alleging that segregation almost never occurred exactly in a 3 : 1 ratio. But that is what follows from the laws of statistics, which state that with a large number of experiments the result will be close to that expected, but which also say that the chance of obtaining exactly the result expected is most improbable.

In this connection, I would like to recall an amusing incident. A certain scientist (whose name I shall omit, although it all happened long ago and in another country; you will see why later) studied the inheritance of characters in a unicellular alga. He made a great many experiments and reported them in a published article. Then an-

which scientists noted that his findings were unfairly close to the expected 3 : 1 ratio. The second geneticist took pencil and paper (he was well versed in mathematics) and calculated the probability of such 'good' figures. The result proved close to zero. Too large a discrepancy in the results expected would have been contrary to Mendel's laws, but too accurate findings should be interpreted as being artificially adjusted to the expected results. Just what was in this case—deliberate falsification or, what is more probable, naive avoidance of 'failures' (which, unfortunately, is not uncommon)—it is hard to say. That is not the point. I only want to show that too close a coincidence in statistics is even worse than a bad one.

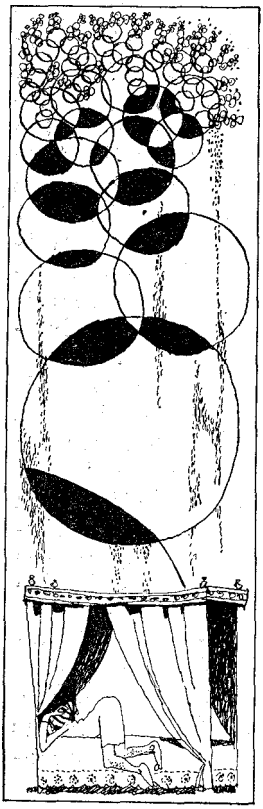
The most amazing thing about Mendel's work was his ability to give a quite correct explanation of his laws at the then level of science. Reflecting on his findings, he concluded that inheritance was discontinuous, and that it was individual characters that were inherited rather than a large assemblage of them; and he linked individual characters to individual hereditary 'factors' present in the germ cells. These concepts gave him the only possible clue to these findings.

In his article Mendel used terms and symbols different from those accepted in modern genetics. For instance, what Mendel himself called factors came to be called genes in the twentieth century. In going over Mendel's arguments we shall not use his terminology (as we should have to abandon it in the later chapters in any case) and when it differs from modern terms, we shall translate it into the language of contemporary science.

A Mad Hypothesis

So Mendel conjectured that there were material structures in the germ cells—we shall call them genes—that were responsible for the formation of characters, and on that basis attempted to explain the laws he had discovered. And here we come to his most remarkable achievement.

In order to explain the equality of male and female factors in heredity, Mendel reasoned, it must be assumed that each parent gives its offspring one gene of each sort. It has to be that way since the characters of both parents appear in the second hybrid generation again, but how does it happen? The simplest way is the union of two reproductive cells,



male and female. Then the embryonic cell will have all the characters of the parental genes. But then what? The parental cells had one gene of each kind, so their progeny must have two of each kind. But that's absurd. After a few generations the peas would consist of nothing but genes.

Mendel continued to ponder and became even more withdrawn and reticent. At night he was haunted by nightmares. A pea turned into a bubble packed with genes. Two peas merged into one, and the merger was repeated over and over again. The pea grew as big as an apple, and soon it filled the whole room. It would crush him. He must escape, but it was too late. The giant pea burst with a deafening report. Mendel woke and again turned to his painful thoughts.

But why on earth should the cells necessarily merge? Perhaps they could give the embryo only half their material. But then each parent would have to have a double assortment of genes from the very beginning. Why not? Mendel did some simple arithmetic, and found a perfectly logical explanation for all the results. It was only necessary to suppose that each parent had two genes of each kind and that the embryo received only one from them. Now he could get down to a detailed examination of his results.

Let us go back to his experiments with crossing pea varieties having round and wrinkled seeds and examine them from this new angle. Apparently the gene determining the form of the seed is not identical in these varieties. Let us denote the dominant gene (or dominant allele, as it is now called) with a capital letter and the recessive one (recessive allele), with a small letter. The allele of round seed will be designated A, and that of wrinkled seed a. Thus the cells of one parent contain AA and the cells of the other aa. As

a result of cross-fertilization the cell from which the embryo will later develop receives one *A* and one *a*; in other words, its genetic formula is *Aa*. But since the allele *A* (round seed) completely dominates its rival *a* (wrinkled seed), the progeny will inherit the character of only one of the parents, and that will hold for all the others, since the interaction of *AA* and *aa* cannot produce anything but *Aa*.

Genetics, just as any other science, has its own terminology that puts many people off. But we cannot do without terminologies, and besides genetics has not many specific terms. No more, at any rate, than school geometry. It would be difficult to study geometry without using such terms as 'hypotenuse', 'cosine', or 'bisector'. But everybody does geometry, whereas genetics is still only for specialists. I have a friend, a theoretical physicist, who found the following phrase in a book on genetics: 'The genotype is expressed in the phenotype only when the recessive allele is in a homozygotic state'. This abracadabra, as he thought it, so impressed him that he learned it by heart and began to use it as a strong expletive.

I have a guilty feeling toward the reader who may think he has been decoyed into reading a textbook masquerading as popular science. But this is not a textbook and I am doing my best to write simply. That is why I write 'dominant allele' (you already know what that is) instead of 'a kind of material hereditary factor that suppresses the manifestation of another variety of the same factor'. Don't you agree that that would be even worse?

But let us return to the phrase that so impressed my friend and look at two words that we are going to need now. You know already what 'allele' and 'recessive' mean. Now let us try and understand the meaning of the terms 'homozygotic' and 'heterozygotic'. Strange words are often made up of familiar bits, which makes it easier to understand and remember them. The prefixes 'homo' and 'hetero' are used very often and of course you know many words with them (homogeneous, homologous, and so on). 'Homo' means the same; 'hetero' different. As to the word 'zygotic', it will be new to you if you are not a biologist. Zygote is the name given to the primary cell (the fertilized egg) from which an embryo develops and is formed by the union of male and female germ cells. Now if I tell you that an organism (or cell) containing identical alleles is called homozy-

gotic, while one with different alleles is called heterozygotic, the words will seem quite natural to you. In the example the *AA* and *aa* parent plants alone were homozygotic, while their hybrid *Aa* offspring were heterozygotic. As for 'genotype' and 'phenotype', these are the assortment of hereditary particles or factors (genes) and the sum of external characters.

Now the brain-racking phrase is clear. It explains exactly why the gene for wrinkled form in the *Aa* plants is not manifested in their visible characteristics.

This is about all there is to the explanation of Mendel's first law as he himself understood it. We should only add that dominance is not always complete. When four o'clock (*Mirabilis jalapa*) which have red and white flowers are crossed their heterozygous progeny turn out pink. This does not contradict Mendel's first law, for it states that hybrids of the first generation will all be identical. That always happens but the hybrids are not always exactly like their parents.

Now let us turn to his second law which deals with the second generation of hybrids. Let us see what to expect when the heterozygous hybrids of the first generation are self-pollinated. With self-pollination there is no question of two parents, but the embryo is also produced by the union of male and female elements. All the cells of the plant are heterozygous (*Aa*); therefore, the embryo may receive either *A* or *a* from each side. Let us look at all four possible variants:

paternal *A* unites with maternal *a*, producing *Aa*;
paternal *A* unites with maternal *A*, producing *AA*;
paternal *a* unites with maternal *a* producing *aa*;
paternal *a* unites with maternal *A*, producing *aA*.

It is not difficult to see that the probability of all these combinations is the same. Consequently, one would expect that two out of every four descendants on average will be heterozygous, one homozygous dominant and one homozygous recessive, i.e. the Mendelian 1:2:1 segregation will be observed. And since the heterozygotes display only the dominant allele (I hope that now you easily understand these 'incantations'), they should outwardly ('phenotypically') look just like full dominants, i.e. the visible characteristics manifest a 3:1 segregation—one part of wrinkled

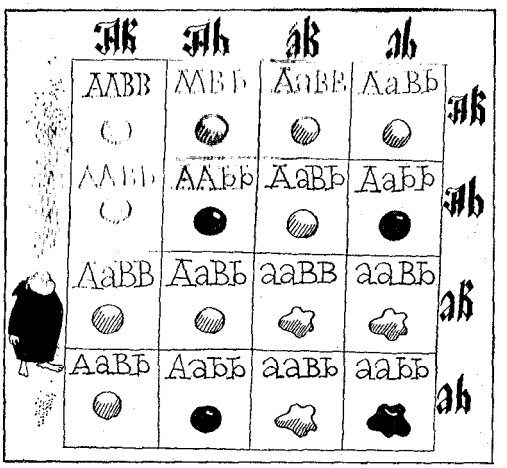
seeds to three parts of smooth seeds, which is precisely what was observed in all Mendel's experiments. When dominance is incomplete, however, 1:2:1 segregation will be manifested. There remains Mendel's third law, which applies when the parents differ from one another in more than one pair of characters. Let us take the example already discussed, that of crossing varieties with round yellow seeds and wrinkled green seeds. If the colour gene of the cotyledons is designated by the letter *B* and the dominant allele (yellow colour) is designated, as before, by the capital letter, and the recessive allele (green colour) by a lowercase *b*, the genetic formulae of the parents will accordingly be *AABB* and *aabb*. Since they are homozygous, the first hybrid generation will be completely homogeneous, although it will contain all the kinds of genes. You can now write the genetic formula of the hybrids yourself. It will be *AaBb*. Only the dominant alleles will be manifested, and outwardly the hybrids will look exactly like the first parent, which is precisely what was observed in all the experiments.

It is rather more difficult to understand what must happen in the second hybrid generation after self-pollination. Let us first see which alleles will be transmitted to the embryo. Four combinations are possible on each side: *AB*, *Ab*, *aB* and *ab*, and these can be met in 16 different variants. It is too much to do in one's head. It is simpler to draw up a table. Let us write all the four combinations along the top and down the side; the intersections will indicate all the possible variants. There are many of them, but since only the dominant allele will be manifested, the progeny in the second hybrid generation will be of only four types. Each group of 16 seeds should contain the following:

9 round yellow;
3 round green;
3 wrinkled yellow;
1 wrinkled green.

In other words, we can expect segregation in the 9 : 3 : 3 : 1 ratio in the second generation, as has already been said. It remains to add that this is precisely the result that was observed in the experiments, with certain variations, of course, according to the laws of statistics.

As you see, Mendel's laws are easily explained on the assumption that hereditary characters are transmitted by



individual material factors (genes) present in the germ cells. Of course, the existence of genes was only a hypothesis in 1865 and in 1900 when Mendel's laws were rediscovered. Today the hypothesis has been corroborated by facts, and very much is known about the genes themselves.

That is why I found it quite difficult to write about Mendel's laws. I was trying to express them in abstract form at a level corresponding to Mendel's time. Now they could be described in simpler and more convincing language. That is why we can call Mendel a genius, since he was able to carry out his epoch-making work at a time when little of what is available to every scientist today was yet known. Not only did he discover the principal laws of heredity but he was also in a position then to explain them. No praise is too high.

The Abbot of St. Thomas' Monastery

Mendel had hesitated a long time before publishing his discovery. Again and again he repeated his experiments, and each time obtained the same results. Finally he made up his mind. On 8 February and 8 March 1865 he read a paper 'Experiments in Plant Hybridization' to the Natural History Society of Brünn of which he was a founder. The minutes of the meeting have been preserved. From them it appears that the speaker was not asked a single question. To put it bluntly, nobody had understood him.

It is not surprising that they did not understand him. Mendel's work was too innovatory. He discussed the phenomena of heredity in terms quite different from the accepted ones. And in addition he had widely used mathematics in his biological research, which was quite unprecedented at that time. So his lecture, and later his article, were truly difficult for his contemporaries to understand.

There was also another circumstance of no small importance. Not only had Mendel no scientific prestige but he was not even a professional scientist. If the same work had come from the pen of, say, Professor Naegeli, it perhaps would not have been acclaimed immediately by many, but it would certainly have been given careful attention, for the author would have been an eminent scientist. Even if it had been difficult people would have tried to understand it. But when the work came from a churchman that no one knew, it might be one of two things: either an outstanding work or utter rubbish. Since the first was difficult to believe, everyone treated the work as not worth considering.

As we know from Mendel's letters, he had no illusions about the members of his society of provincial naturalists. He decided to seek the support of Professor Naegeli, famous for his works on hybridization. What came out of it is known to you from the beginning of our story. The advice of Naegeli, whose authority Mendel much esteemed, proved fatal for the further course of his experiments.

It is not fair, however, to put all the blame on Naegeli alone. In the autumn of 1867 Cyril Napp, the abbot of St. Thomas' Monastery, died, and in the spring of 1868 Gregor Mendel was elected in his place. The responsibilities falling on him left little time for experiments; and as his duties became ever greater, age began to sap his health.

It was Mendel's way to do everything he took up earnestly and thoroughly. So he went about his new duties with the same persistence and patience that he had shown in his experiments with peas.

Often, when people write about Mendel's life, they try to depict it as tragic; and at first glance it seems so. Besides it has a 'ring'. I can hardly keep myself from painting everything in that tradition; it would be easier to write, and more entertaining for you to read. But let us try to picture things the way they really were.

The fate of Mendel's discovery, of course, was real tragic: but the fate of a discovery and the fate of a ma are far from being the same thing. If Mendel had been professional scientist for whom study of the laws of hered ty had been his life's work, the fate of the discovery ar of the man would have been equally tragic. The traged of his discovery would have become his personal traged;

Mendel, however, did not, apparently, suffer any trag dy. He could well have obtained recognition of his discov ry, but he did absolutely nothing about it. He need n have limited himself to publishing a single article, and that brief, in a provincial journal. He could have sent articles to other journals with a wider circulation. But he didn't. What is more, if that had not succeeded, he could have published a book on his experiments and theory which would have been easy since by that time he was quite well off. And finally, the world did not hang on Professor Naegeli; Mendel could have solicited attention from other great representatives of official science, but he did nothing about it.

Why? Perhaps he was not confident of his correctness or did not attach much significance to his discovery? One cannot say that, for we know, from his article and from his letters to Naegeli, that Mendel was absolutely sure that he was right and was quite aware of the importance of his discovery. All the facts indicate that he was not bothered about recognition of his contribution.

That may strike you as strange, but it is not so surprising. Even today among professional scientists there are people who do very good work but are not concerned about anything more. Friends keep on at them almost every day: 'When are you finally going to write an article?' And they just laugh it off: 'Get along, don't

'et'. It happens that a scientist may be fascinated by the course of the work itself, and though conscious of having found something new, may be much less concerned about recognition or about what his colleagues say. For colleagues criticize more often than they praise and there is little satisfaction in that. And sometimes it is not as simple as that. Ahead is the next, more interesting and important work. 'When all the experiments are finished, then I'll write them all up together.' That is the way professional scientists behave, and Mendel was only an amateur.

Little information about Mendel has survived. From what has come down to us we know that his interests were very wide. He was no less interested in bee-keeping and meteorology than in crossing plants. And whereas he only published two papers on that subject, he published five on meteorology (both before and after the work that brought him fame). He did not consider plant hybridization the only thing in his life at all. What is more, Mendel was not, and did not consider himself, a professional scientist. He was drawn to many other things. He was very fond of teaching and kept it up almost all his life. As a teacher and then as a prelate, he was a leading figure in the town and was inevitably concerned with public affairs: the Society of Natural Science, the Moravian *landtag* of which he was a member, and many other things. And as we know, he devoted himself to all these with great enthusiasm.

As for his experiments Mendel apparently wanted to take another step, to prove that his laws had general significance. He did much work on hawkweeds, but it proved a failure. He had less opportunity to continue the work, and it remained unfinished.

And in addition to all that Mendel was a simple man to whom nothing human was foreign. Having become a monk he had deprived himself of having a family of his own, so he was very solicitous of his relatives and fellow villagers. He loved his mother tenderly and thought of her all his life. And he did not remain indebted to his sister Theresia who had given up part of her dowry for her brother's education. When he could stand on his own feet he took her three sons under his care and supported them until they completed their education. When his native village was damaged by fire he donated a large sum to build a fire station there.

Mendel enjoyed the love and respect of his fellow citizens. When he died on 6 January 1884, a long procession followed his coffin, and many fine words were spoken at his grave; but by the irony of fate none of the speakers said anything about the Mendel we know today, the great scientist who discovered the laws of heredity and laid the foundation of modern genetics.

Sixteen Years On

Time passed. Science developed and inevitably came closer and closer to the concepts of heredity set forth in Mendel's forgotten work.

In 1884 Professor Naegeli published a book on evolution. Some of his ideas bore too strong a resemblance to those of his former correspondent, who had died in the same year; but Mendel's name was not once mentioned in it. Naegeli had either forgotten about it or did not think it worth writing. But Naegeli's theory was highly abstruse and vague, and, therefore, it lacked the clarity of Mendel's work.

Meanwhile agriculture required wider and wider application of hybridization in stock breeding and farming. This naturally engaged the interest of scientists. In July 1899 the Royal Horticultural Society called a conference in London on hybridization. The conference was well attended and later it came to be regarded as the first international congress on genetics. Many leading geneticists were there. The most interesting report was made by the English biologist Bateson who spoke of the discontinuous character of inheritance, i.e. about what forms the theoretical basis of Mendelism; but Mendel's name was not once recalled at the conference.

The nineteenth century was over—1900 dawned the time when Mendel's laws were rediscovered and his contribution recognized. Only a year had passed since the London conference; if it had taken place a year later Mendel's name would have been on everybody's lips. It is worth noting that 16 years had now passed since his death and 35 years since his first attempt undertaken at the Brünn Society of Natural Science to communicate his discovery to the scientific world.

In the course of one and the same year three articles by three different scientists from three countries were publish-

od in one and the same journal. Their content was clos to what Mendel had said 35 years before. All three deal with the fundamental quantitative laws of heredity.

On 14 March 1900 the editors of the *Reports of the German Botanical Society* received a packet from Amsterdam It contained the manuscript of an article by a well-know Dutch botanist, Professor Hugo de Vries, entitled 'The Law of the Splitting of Hybrids'. Fully aware of the importanc of his discovery, de Vries simultaneously sent a brief communication to the Paris Academy of the Sciences. Bot articles soon appeared. In the French one not a word wa said about Mendel. In the German one there was a footnot in the usual fine print, in which the author wrote of Mendel's work: '...This important monograph (of Mendel's is so rarely quoted that I myself did not become acquainted with it until I had concluded most of my experiments, and had independently deduced the above propositions.' At that time de Vries was 52, and his name was widely known in the scientific circles.

But even before de Vries' article appeared, a little over a month after the packet had arrived from Holland, the editors received a new manuscript. Its title was completely different: 'Gregor Mendel's Rules Concerning the Behaviour of Racial Hybrids'. It was contributed by Carl Correns, the 36-year-old Professor of botany at Tübingen in Germany. He also had learned of Mendel's work after completing experiments, but described it in much greater detail. Correns in general did much to bring Mendel's discovery to public notice. It was he who first published Mendel's letters to Naegeli.

A little while later the editors received a third article 'On Artificial Crossing of *Pisum Savitum*'. Its author, the Austrian Erich Tschermak was the youngest of the three 'rediscoverers'. He was only 29, and still an assistant lecturer. And he too had read Mendel's work after completing his experiments.

Such a coincidence may seem unusual, yet it is quite legitimate. While Mendel had been much ahead of science of his time, by the turn of the century discovery of the laws of heredity were literally in the air. Credit for the rediscovery of Mendel's laws is usually only given to these three scientists—de Vries, Correns and Tschermak. But that is not quite fair. While they had been crossing plants,

others had been making similar experiments on animals. In England W. Bateson had been crossing poultry, and in France L. Cuénot, mice, and independently of the botanists they had arrived at the same conclusions. But experiments on animals take longer, so they published their work rather later.

Does it not seem suspicious that all three 'rediscoverers' wrote that they had become acquainted with Mendel's article only after completing their own work? But there is nothing suspicious about it. Each of them, in preparing his article for the press, went through the relevant literature, so could not miss Focke's monumental survey on hybridization (*Die Pflanzen-Mischlinge*) which mentioned Mendel's article.

This was the beginning. Scores of scientists set about verifying Mendel's laws on the most varied objects and invariably confirmed them. Within a few years thick volumes had appeared on Mendelism, and lectures began to be read to students on his work.

In rounding off our story about Mendel we must say a few more words about what he actually did. It may seem superfluous, but scientists are often praised for what they did not while their real contribution remains in the shade. That is the way it was with Mendel. If you were to ask what was the main thing he did you would most likely be told that he discovered the laws of heredity, and that is what many scientists think, too, but in point of fact, it is not so.

As for 'Mendel's laws' themselves it is now becoming clear that several scientists had discovered them earlier. After the work of Knight and Gaertner, Sageret and Naudin the corpuscular nature of heredity, dominance, the equality of the sexes in heredity, the uniformity of the first generation of hybrids, and the splitting of the second had become known, everything in fact, that constitutes the essence of 'Mendel's laws'.

Mendel was not the discoverer of the laws of heredity. But in depriving him of the credit, we would like to pay him an even greater honour. Mendel did two things much greater than a mere statement of the facts (which others had also done).

His first contribution was that he conducted his experiments on a much higher plane than his predecessors. Instead of studying inheritance of the general 'appearance',

he was the first to investigate separate hereditary characteristics. He began with plants that differed in only one character, then proceeded to experiments of gradually increasing complexity. That is why his experiments were absolutely convincing. It remains to add that no one before him was so exacting in the accuracy and purity of experiments.

His second and main contribution was the hypothesis of the material factors contained in double set in the germ cells and received by the embryo from both parents. That was a truly 'mad idea', comparable to those of Newton and Einstein. And therefore, without the least exaggeration we call Mendel a genius. Mendelism is the foundation of modern genetics. T. H. Morgan, of whom we shall speak later, was fated to build the ground floor. He wrote that in the ten years that Mendel worked with his plants in the monastery garden he achieved the greatest discovery in biology in the past 500 years.

Like in a Film

A certain elderly lady made a sensational announcement that cells were formed from structureless 'living matter'. Her conclusion was confirmed by numerous photographs. One showed a completely uniform mass of matter, another, tiny particles forming within it. These particles collected into larger granules, and then a semblance of a living cell could be discerned, and finally a real cell with all its typical details.

Absurd? But her contention was based on genuine photographs. The explanation, however, is very simple. If the photographs are examined not as they are given in the book but in the reverse order, the familiar picture of the disintegration of dying cells can easily be recognized. The venerable old lady had made a large number of photographs but, guided by wishful thinking, had sorted them out wrong.

It is a familiar effect. If a film is run backward you can see many wonders: smoke is sucked back into a locomotive's funnel; a bullet flies out of the target and back into the pistol barrel; gusts of wind carry petals to a common point, they converge into a flower, and the flower becomes a bud.

But if the film is run properly, you see no miracles. On the contrary, the bud slowly turns into a beautiful flower. That is also a miracle in its own way. A process that takes hours and days passes before our eyes in a few seconds. This wonder is produced by a very simple technique, slow-motion filming.

Where do living cells come from? What changes do they undergo during their life cycle? What could be simpler? Watch them through a microscope. The life cycle of a cell, it is true, lasts several hours or a few days. But the slow-motion films we have just mentioned can show us the life of a cell in a matter of minutes just as with the bursting of a bud.

Unfortunately, it is not as simple as it seems at first glance. Nowadays it is possible in fact to examine the finest microscopic details of cell structure, and even to film their life, but that is one of the latest achievements of science. A hundred years ago, however, when knowledge of the living cell was in its infancy, only fairly primitive microscopes were available to scientists.

If we look at a living cell through an ordinary microscope, we see nothing in it. The cell is optically void, just a vesicle without internal structure. Why is that?

We see the brightly coloured and varied world around us only because the various different bodies absorb light differently. Glass lets all visible rays pass, so that we do not see window glass when it is freshly washed. Sometimes windows are painted white (in public baths, for instance); then we see the glass quite clearly. Or rather we don't see the glass itself but we clearly see where it is, how big it is, and what shape it has. Coloured glass is clearly visible even when it is quite clean, because it does not let all rays of light pass through it.

We are unable to see the internal structure of a living cell because all of its parts are equally transparent. What are we to do? Clearly, we could colour it like we do glass, staining either the whole cell or the parts that interest us.

Until recently that was the only method known for examining the internal structure of cells, and the procedure for making preparations for the microscope was quite complicated.

The living cell resists being penetrated by foreign matter from outside so it just has to be killed, taking care to preserve its structure. For that purpose we use mixtures of various substances, sometimes very rare and costly like osmic acid which is several times dearer than gold. This process of killing a cell is known as fixation. It is followed by a long and painstaking process in which a fixed specimen of animal or vegetable tissue is soaked in one liquid after another for a quite definite period. Then the preparation is immersed in molten paraffin wax and left there until it is completely saturated.

After that comes the most responsible procedure of making sections. The block of wax with its embedded specimen is cut into thin, perfectly even slices a few thousandths of a millimetre thick. It is quite impossible to do that by hand, but there are special instruments, microtomes, for

making sections. To obtain a good section, however, it is not enough just to have a microtome. If the specimen is not properly embedded in wax, or the knife is dull, or the microtome is not in good working order, the wax will be crushed or broken, and the experiment will be spoiled.

At last, when a section is ready (most of the material, of course, goes to waste) it must then be stained. For that purpose we use various stains that act on one of two principles. Some really stain the appropriate parts of the cell, penetrating it and producing something that can be likened to coloured glass. Others are only absorbed by the surface (like a painted window). The staining is done on slides, on which the extremely fine sections are placed. First, the wax is removed in a special way, then a stain is applied, sometimes changing the solvent several times, and that is followed by differentiation and bleaching. Each procedure requires another liquid which may easily wash away the section it has taken such pains to prepare. Finally, the stained preparation is put into a layer of transparent resin between two slides. When the resin is dry, the specimen is ready for examination under the microscope. The entire process takes at least several days, and sometimes weeks.

Of course, an experienced worker makes good sections and none of the procedures wash them off the slide, but that requires long practice.

It would seem obvious that a cinema film cannot be made from separate sections of killed cells. But is it really so? For even in real cinema films there is no real motion. Separate stills (frames) following each other in rapid succession give us the sensation of a moving picture. Or take Bidstrup's wonderful cartoons which, arranged in a definite sequence, tell us a whole story.

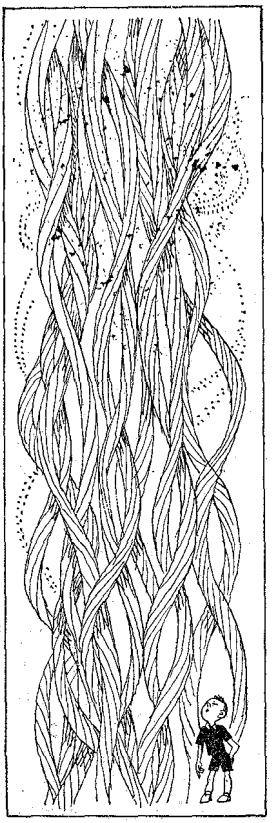
But what if a series of such pictures gets mixed up and muddled? With a little effort we soon get them into the correct sequence; and that is precisely what cytologists used to do. They killed cells, made sections, stained them, prepared microscope slides, and then searched for cells at different stages in their life cycle, and by comparing them with one another tried to establish the sequence in which one picture followed another. It is not so difficult to do, and I recalled the story about the old lady at the beginning of this chapter only as a rare curiosity.

A quite exceptional role in the phenomena of heredity is played by chromosomes, threadlike bodies found in the cell nucleus that stain readily with many dyes (to which they owe their name: Gr. *chroma* colour, and *soma* body). Who discovered them? Who was the first to point out their importance? It is difficult to give an answer.

They were christened chromosomes by Waldeyer, but had been known before him. Back in the middle of last century Hofmeister had established before others the true sequence of the different stages of the cell cycle but failed to draw the proper conclusions. The foundations of the modern theory of the living cell were laid in the last quarter of the century by the work of Strasburger and Chistyakov, Flemming and Navashin, Hertwig, Peremezhko, Waldeyer, Bütschli, and others. They were genuine scientists and did not quarrel like Tweedledum and Tweedledee as to who was first. Each clarified some detail in the general process. And little by little a clear mosaic was formed from these bits. It should be said once more that all this took place after Mendel had written his historic article.

We do not, however, need to trace the course of the individual investigations, because we live a century later. Sit comfortably in an armchair and watch a film about the life of cells. And not one made like a cartoon film. There are now phase-contrast microscopes with which we can see the inner structure of cells without recourse to staining. It means that we do not need to kill them and can observe them *in vivo*. Moreover, by using slow motion a film can be made; and such films are now available.

Let us switch off the light and watch a living cell on the screen. We see a sac filled with viscid fluid—protoplasm—containing granules of varying size. They differ in nature and purpose. Two types are particularly important: mitochondria and microsomes. Mitochondria are bodies of oblong shape and laminar structure. They are the power houses of the cells. In them 'fuel is burned'; nutrient substances are oxidized and the energy obtained stored in a form convenient for further use: molecules of adenosintriphosphoric acid are built up (molecular chemical storage batteries that give off their energy exactly when and where it is needed by the cell). Microsomes are smaller granules. They are veritab-



le microscopic chemical works building molecules of protein, the basic substance essential for life.

But it is not to protoplasmic granules that we shall now turn our attention. Near the centre of the cell we can see a fairly large, round formation—the cell nucleus. It is surrounded by a membrane and like the cell itself is filled with a viscid fluid, karyoplasm. Inside the nucleus there is a smaller, round body, the nucleolus. But where are the chromosomes that we are mainly interested in? They are nowhere to be seen, but they will soon appear on the screen. Now the cell is in the stage which has been misnamed the resting stage. In fact, the metabolic processes within the cell are the most intense at this time and the chromosomes are such thin threads that an electron microscope is needed to see them.

When a cell is about to divide, the long, thin chromosomes coil up and become thicker and shorter. Then they can be seen through an ordinary microscope. Now they appear on the screen. The nucleus is filled with threads with blurred outlines. The threads are rather long and so chaotically tangled that it is hard to tell where one begins and another ends. They move slowly, becoming thicker, shorter, and more distinct.

While we were watching the chromosomes we missed two essential changes in the cell. The nuclear membrane and nucleolus disappeared. Now the chromosomes are directly in the protoplasm. They have become quite short and are arranged all in the same plane, in the middle of the cell. A cytologist would call it the equatorial plane. However, we can now see not only the equator but also the poles. From two points on opposite sides of the cell threads grow and form a spindle-shaped structure. These threads are connected to definite points on each chromosome.

Now let us be on the watch. We are about to witness the most important events, but since they proceed very much faster on the screen than in real life, they will pass in a matter of seconds. Look, the chromosomes that appeared to be dense rods have split lengthwise and doubled in number. The sister chromosomes lie parallel to one another and are joined at one point only, the one to which the threads of the spindle are attached. Now the spindle itself comes into play. Its threads contract and draw the sister chromosomes to the two opposite poles. Two groups of chromosomes are formed on the opposite sides of the cell. A cell partition arises between them, on the site of the former equator.

After that it seems as if the film were running backwards. The nuclear membrane and nucleolus are formed again, the chromosomes lose their spiral shape and gradually disappear. Before us are two cells exactly identical with the original cell. Then the screen is dimmed, and the lights are turned up.

The Halving Process

Before we see the second part of our film, let us examine a few microphotographs of various cells in the process of division.

First let us compare photographs of cells of identical type, say cells of peas, on which Mendel discovered the laws of heredity. Though they've been taken from different individuals and different parts of the plant each cell contains 14 chromosomes. If we examine them carefully, we shall see that each one contains seven different kinds of chromosomes, two of each kind. The picture is the same in all the pea cells; in each of them we can distinguish seven types of chromosomes characterized by definite length, thickness, position of constrictions, and other structural details.

Now let us compare the chromosome numbers of different species. They vary within very wide limits. Human cells have 46 chromosomes, maize cells ten, the cells of *Haplopapus gracilis* only two. Every species has a quite definite number of chromosomes, which is always even, and can be divided into pairs.

For that reason cytogeneticists say that the cells of each species have a certain number of chromosome pairs. But

there is an important exception in that rule—sex cells Now let us switch off the light again to see the second par of the film which shows the division of sex cells and th process of fertilization.

On the screen we see exactly the same cell as in the firs part, but its division will result in the formation of se cells—eggs or sperms. The processes unfolding before u resemble those we have already seen, but the initial stag of division proceed much more slowly, although the filn was shot and is being run at the same speed. The chromoso mes have already become thick and short, but they hav not yet lined up in the equatorial plane.

Instead, they gather together in pairs. Each chromosom seeks out its opposite number. They draw together alon one another and nearly merge. We see them as a singl whole. But after a time they begin to draw apart but tha does not go smoothly. The chromosomes become strangel tangled, and form loops as they break contact. The point i that while they are in contact almost all chromosome exchange segments. The new chromosome has a 'head' fro one of the old chromosomes and 'tail' from another.

Among the audience watching our imaginary film (tho ugh such films do exist, you may be sure of that) there ar probably physicists. Cell division, particularly the divi sion of sex cells, is an unexplored field of fascinating rese arch for physicist interested in biology. There are forces o a very specific interaction between chromosomes and thei parts. What is their nature? We still do not know.

The process preceding cell division takes a long time. It is followed by two divisions one after the other witho a break, so that the chromosomes do not have time to se parate. As a result, there is only one division of chromoso mes for the two cell divisions. Thus, each of the four newly formed cells has half the number of chromosomes in th ordinary (somatic) cells of the organism. A somatic cell ha two of each chromosome (known as a diploid set), while a mature germ cell has only one (haploid) set. This fact i of exceptional importance. If it were not for this amazin halving of the chromosome number in mature germ cells, life, at least its higher forms, would not exist on our planet. It will soon become clear why.

Before we desert the world of cells for a while, let us just have a look at what takes place during fertilization.

Two centuries ago Joseph Koelreuter conclusively showed that pollen was needed to form the embryo of plants. Some 20 years later the Italian naturalist Lazaro Spallanzani showed that the same was true for animals. He found that the presence of the threadlike sperm cells (spermatozoa) was indispensable for the formation of an embryo. But their specific role in fertilization remained unknown. It was usually thought that the spermatozoon simply activated the egg, causing it to divide. The truth was discovered at the end of the last century.

What happens is the following. A spermatozoon penetrates the egg cell, losing its membrane, neck piece, and tail in doing so, but retains its nucleus. As a result, a binuclear cell is produced; one nucleus belongs to the egg cell itself and the other is the sperm's. It will be recalled that each of them contains only half the normal double set of chromosomes. Then the nuclei fuse. The result is not difficult to imagine; a normal nucleus with a normal diploid set of chromosomes is formed. The newly-formed cell (known as a zygote, as we have already learned) divides many times, and forms an embryo that gradually develops into an organism.

Those are the basic facts of cytogenesis, a science without which the existence of modern genetics is unthinkable.

Hypothesis Becomes Theory

If you are an attentive reader (and I am sure you are) a seminal thought will probably have come to you, that what I have just said about chromosomes resembles the behaviour of Mendel's hypothetical 'factors' now known as genes. Indeed, the cell has a double complement of both. And just as in Mendel's theory the embryo received one gene of each sort from each of its parents, so the zygote receives one chromosome of each sort from the maternal and paternal cells. This similarity is so close that it can hardly be accidental.

And this is what comes to mind; but when the chief processes affecting chromosomes during normal cell division, during the division of sex cells and in fertilization were cleared up, nothing was still known of Mendel's work. It had been published but no one at that time had read it.

Then a most intriguing thing happened. Intelligent people, who knew nothing of Mendel's hypothesis, reflected

on the strange behaviour of chromosomes. They saw th there was an intricate and highly accurate mechanism the living cell for redistributing the substance of chromos mes. Every cell had an equal number of chromosomes. Pr geny also had the same number of chromosomes, one ha inherited from the male parent and the other half from tl female. It could not simply be a gamble of nature; the st kes are too high. The mechanism apparently performe some highly important function. And so, without knowin anything about Mendel's work, they inferred toward tl end of the century that chromosomes played a very impo tant part in the transmission of hereditary characters.

Other evidence in favour of this hypothesis was al available. The equality of sexes in heredity had been knov in pre-scientific times. A child may equally take aft both its mother and its father. But ova are generally amo the largest cells. Indeed, a hen's egg is a single ovu On the other hand, the spermatozoon is one of the smalle cells. The female germ cell (ovum of humans, for examp is 80,000 times bigger than the male cell (spermatozoo In birds the difference is even more impressive. In the he for instance, the female germ cell is roughly a million m lion times bigger than the male cell—a truly fantastic d ference. And what about the ostrich?! Such a differen in cell size was hard to reconcile with the idea of equali of the sexes in heredity.

But when we were more familiar with the inner stru ture of cells, it became clear that the size of the nucle

varied much less than that of the cell. Chromosomes, however, proved to be identical in size in cells of a given species. Was that not further evidence that it was merely the chromosomes that constituted, or at least contained, the 'hereditary substance'?

Under the impact of these facts, and of certain others, many scientists, though equally ignorant of Mendel's hypothesis, spoke more and more confidently of chromosomes playing a vital role in heredity. Therefore, as soon as Mendel's laws were recovered from the limbo, attention was drawn to the similarity in the behaviour of the Mendel's hypothetical 'factors' and chromosomes, which were already suspected of being involved.

By 1902 an article had already appeared in the American journal *Science* on Mendel's principles of heredity and the maturation of the germ cells. Its author was E. B. Wilson, whose monumental book *The Cell in Development and Inheritance* had had a second edition in 1900. Wilson dotted the i's: genes were locked in the chromosomes of the cell nucleus. Since the chromosomes behaved as the carriers of genes would be expected to in accordance with Mendel's hypothesis, it was thereby brilliantly corroborated. Mendel's 'mad hypothesis' had become a theory and so the chromosome theory of heredity was born.

This theory furnished the material basis for the development of genetics, and that had great importance for the further development of the theory itself. Now any new law had to satisfy what was known about chromosomes. The speculative theories of heredity that circulated at the end of last century were finished for good and all.

At first everything went swimmingly. Mendel's laws and the chromosome theory of heredity were invariably confirmed in experiments on various characters and organisms. But not all scientists were enthusiastic. Some raised objections that were difficult to meet. Perhaps the genes were indeed located in the chromosomes but why were there so few chromosomes? Organisms whose cells contained more than a hundred chromosomes were rare exceptions; ordinarily cells had about twenty or thirty. How was the host of characters to be explained then?

Facts began to appear that contradicted the theory, sometimes they were discovered by the most ardent supporters of Mendelism. Bateson, one of the first champions of

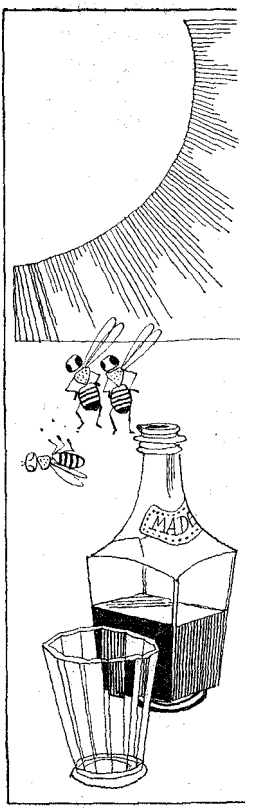
Mendelism, who had confirmed the validity of Mendel laws for the animal kingdom, also experimented with plants. He chose the classical object, peas. And strange as it may seem, with these very same peas he observed a sharp departure from Mendel's third law. Bateson had crossed sweet peas with purple flower and long pollen, and did not obtain independent segregation in the second hybrid generation; none of the plants had both these characters together. When he had taken one parent with both these characters at the very beginning, they did not separate. In the second hybrid generation he observed simple segregation in a ratio of 1 to 3—one plant with purple flower and long pollen for three normal ones. It was a brain-teaser. It was enough to make one doubt Mendel's principles and the existence of genes. And some people began to be very dubious.

One of the sceptics was Thomas Hunt Morgan, professor of zoology at Columbia University. He was already past forty, the age at which Mendel had made his discovery, but unlike Mendel he was an established scientist. True, he had nothing to do with genetics. His speciality was experimental embryology, and his monograph on the development of the frog's egg had brought him a considerable reputation. Morgan was so annoyed by talk about the reality of genes he heard from the young enthusiasts around him that he decided to take a hand in the solution of this problem. For him, an experienced and skilful experimenter, that would hardly be difficult.

The Vinegar Fly

It happened in England. A distinguished foreigner was entertaining guests. And as he was an American, he treated his guests to a few bottles of Madeira from his native state of Virginia. When wine was poured from one of the bottles, three drowned flies were found in the glass. The host had heard at one time that drowned flies come to life when warmed by sunrays and he proposed to make an experiment. The flies were put in the sun on the same strainer with which they had been recovered from the glass. In less than three hours two of them began to come to life gradually; they rose to their feet, cleaned their eyes with their front legs, shook their wings and cleaned them with their hind legs, then flew about in the air, evidently unconcerned about their mysterious arrival in good old England.

This was told way back in the eighteenth century by Benjamin Franklin, the famous American scientist and statesman. The flies he mentioned had not got into the wine by accident. They actually help ferment grape juice into wine by introducing wine yeast into it. They also promote the conversion of wine into vinegar. They used to be commonly called vinegar flies, but now they are better known as fruit or banana flies. Their scientific Latin name is Drosophila.



I do not know if anyone experimented with Drosophila before Franklin, but even when its scientific career is traced from the moment when it was first taken from a wine glass by an inquisitive scientist and put in the sun to warm it is quite long. For many decades, however, few experimenters used it as a winged 'guinea-pig'. But since Professor Morgan decided to use Drosophila to check views that contradicted his own, the fruit fly has become a favourite laboratory animal.

Morgan's group that began to study the genetics of Drosophila was small. There was his assistant, Calvin B. Bridges, who, of course helped him from the outset. They were very soon joine by two others—H. G. Muller and A. H. Sturtevant. Fo long years they continued to work together in the smal laboratory of Columbia University.

Drosophila proved a lucky choice. Deviants from th third law were found to have very many pairs of charac ters. The experiments proceeded quickly and yielded muc material. And instead of disproving the third law the brought to light evidence pointing to a new regularity Morgan first decided to experiment with Drosophila in 1909 and already by the beginning of 1911 the picture was clear all the characters of Drosophila fell into four groups which came to be called linkage groups. When flies witl

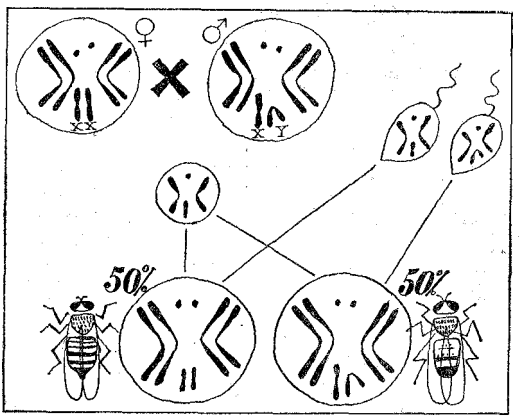
characters from different groups were crossed everything went as supposed, in complete agreement with Mendel's third law; but when the characters belonged to the same group, they behaved in an extraordinary way, just like 'purple flower' and 'long pollen' in Bateson's experiments with peas. In the experiments with Drosophila, however, what had been the exception became the rule, even a law. It was called law of linkage.

Now what about chromosomes? They could no longer be disregarded. Drosophila was found to have four linkage groups, three large, and one small. (Here we are concerned only with the one quite definite species, *Drosophila melanogaster*, the one most often used in experiments. Other species have more linkage groups and accordingly different number of chromosomes.) Under the microscope each Drosophila cell is seen to contain four pairs of chromosomes. Three pairs are huge and the fourth very small. Even at a very high magnification the chromosomes of the fourth pair appear as dots.

So linkage groups correspond to chromosome pairs. And that is how it should be. If certain genes are on one and the same chromosome they should be inherited together: independent segregation is not to be expected. In that way, instead of being disproved, the chromosome theory of heredity was brilliantly confirmed, and a large step forward was taken.

Many 'surprises' were found in experiments with Drosophila. Amazing results were produced, for instance, by crossing normal red-eyed flies with white-eyed ones. When normal females were crossed with white-eyed males, everything went 'according to Mendel': in the first hybrid generation all the offspring were identical and looked like the female parent, which indicated that the 'red eyes' was a dominant character with respect to 'white eyes'. But when the descendants were crossed with one another, something strange happened. True, there was 3 : 1 segregation, three red-eyed individuals for one with white eyes, but none of the females had white eyes, while half the males had red eyes, and the other half white ones.

Even more surprising results were obtained from crossing white-eyed females with red-eyed males. Then there were no heterogeneous offspring even in the first generation, and moreover, segregation also occurred at an unusual ratio



1 : 1. Half were red-eyed and half white-eyed, the red-
d flies being all females and the white-eyed all males.
t was evident that inheritance of the genes determining
-colour was somehow connected with sex. And for that
son they are called sex-linked characters. How to ex-
in their existence? To answer that question we must
rn to examining the chromosomes of Drosophila.
Each normal cell of Drosophila (excluding the sex cells,
course, in which the chromosome number is halved) con-
is four pairs of chromosomes, three pairs large and
small. But while that is so, the chromosomes in males
females are slightly different. In females all four are
pairs but in males only three are true pairs, while the
th (which, however, is called the first) consists of non-
tical chromosomes. One of them is rod-like, exactly
same as both chromosomes of the female, but the other
a quite striking hook-like shape. Chromosome pairs
given numbers, but the chromosomes of this first pair
e, in addition, their own names. The rod-like chromoso-
are called X chromosomes, while hook-shaped ones
known as Y chromosomes. It is evident that these chro-
somes are connected with the determination of sex. If
chromosome set has two X chromosomes a female is
n; but if it has one X chromosome and one Y chromosome
n a male is born.
After that it was easy to explain why half the progeny
most species are male and the other half female. In Dro-

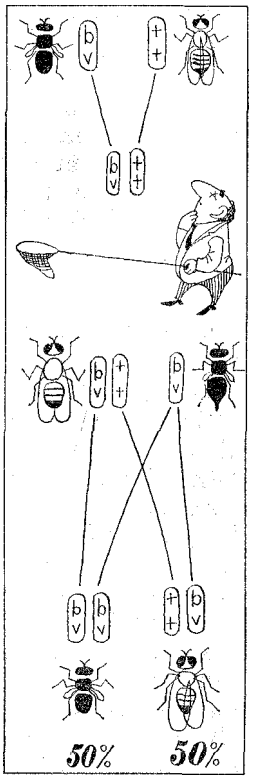
sophila all the ova are identical, but the sperms resulting from halving of the chromosome number are different: half contain an X chromosome, and half, a Y chromosome. And depending on which kind fertilizes the ovum a male or a female is born.

It should be noted, however, that sex is not determined in all of species in the same way as in Drosophila. In birds, for example, it is the other way round; the female has different sex chromosomes, producing two types of egg, whereas the males have identical sex chromosomes. In some cases one sex has two X chromosomes, and in others only one X chromosome and no Y chromosome. There may even be more complex cases. You are probably wondering, 'What about man?' We know. In humans the mechanism of sex determination is the same as in Drosophila. The sex of a child is inherited from the father. Therefore, fathers, who want a son but get a daughter, and blame their wives for it, show an abysmal ignorance of genetics.

Now we can return to our red-eyed and white-eyed fruit flies. They have many genes controlling eye-colour and these are located on different chromosomes. In the present case we are only concerned with one of these genes. From what we have learned from the experiments it is quite clear that the gene responsible for eye-colour is located on the X chromosome, and not on the Y chromosome. A glance at the drawing will show why. Study of sex-linked inheritance has unravelled the riddle of the permanent correlation of sexes and has given new confirmation of the chromosome theory of heredity.

Some people may infer from what we have said that linkage phenomena disprove Mendel's laws, and attempts have really been made to do so. Their only reason was misunderstanding of the laws of scientific development. No physicist would say that Einstein's work refutes Newton's laws. Einstein has discovered more general laws, but Newton's laws remained and will remain, no matter how physics develops. Since Einstein we have learned that Newton's laws are only valid with regard to a quite large mass and not very great speed. In exactly the same way Mendel's laws will always remain valid for a definite range of phenomena. Ascertaining the conditions that limit the sphere of operation of known laws means only to deepen our knowledge. Mendelian segregation is valid for genes located on different

chromosomes. We learned that after cases of departure from independent segregation were discovered. The law of linkage established by Morgan is concerned with genes located on the same chromosome, and study of cases when such genes violate this law has given us a deeper insight into the mysteries of inheritance. And that is what we are now going to talk about.



The Map of Heredity

Let us make a few more experiments with Drosophila. Since we have no live flies to hand, we shall experiment on paper.

Let us take flies differing from the normal, wild type in two characters: the black (ebony) body colour and very reduced (vestigial) wings, and cross them with the normal type. When I tell you that both these characters are recessive and that the relevant genes are located on the second chromosome, you will easily guess the result: all the progeny should look normal, but in latent form (in the heterozygous state) they will have both recessive characters. And you will be quite right.

Now let us pass to the second hybrid generation. When hybrids are crossed with each other, then—since the genes are linked—the experiment should produce 3 : 1 segregation, or three normal flies for every one with both recessive characters. And that is just what happens in reality. But the experiment can also be conducted in rather different way. The hybrids can be crossed not with each other but with one of the parents that had recessive characters. This is known as back-cross or analytical crossing. It is convenient since it brings out all the recessive characters. This crossing is depicted in the drawing, which shows clearly that there should be 1 : 1 segregation, that is the proportion of different types of germ cells produced by the hybrids.

That is the way segregation should proceed, and if w cross hybrid males with black short-winged (vestigial-ty pe) females that is what we shall get. But if we mak reciprocal crosses taking hybrid females and black shor winged males, we shall get a new phenomenon. Instea of 50 per cent of flies of each sort, we shall obtain appr ximately the following: normal flies, 41 per cent (instea of 50); black (ebony) flies with vestigial wings, 41 pe cent (instead of 50); ebony flies with normal wings, per cent; normally coloured flies with vestigial wings, per cent.

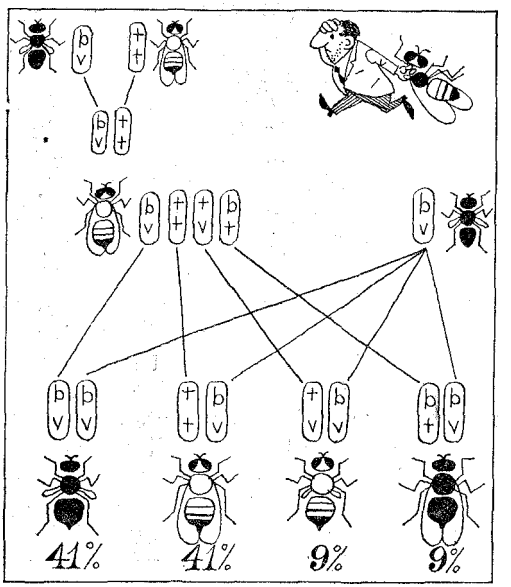
Thus, in addition to what we would expect we get a ce tain number of exceptional, or 'stray', individuals. In ou experiment they are fairly numerous: 18 per cent.

Such results are not obtained solely in experiments wit ebony vestigial-winged flies. When we take hybrid female 'strays' are always observed, sometimes more, sometime less. If we take, for example, such characters as yello body and white eyes the 'strays' will be 1.5 per cent. Som times the percentage is insignificant, at other times it s ars to 50 per cent. It would seem that linkage is not com plete, and is sometimes strong and sometimes weak.

Do these results refute the chromosome theory? If tw genes are located on the same chromosome can they b recombined and, if so, how? It turns out that they ca Even before this strange phenomenon was discovered ol servations had been made suggesting the possibility of suc recombination.

The Dutch botanist de Vries and the Russian Koltsc had told their students about it even before Morgan an his associates began to come upon 'strays' in their exper ments.

Let us recall what happens to chromosomes during th division of mature sex cells. Two homologous chromosom (one from the mother, and the other from the father) appr ach each other, enter into close contact and interchan segments. There is, therefore, nothing surprising in th fact that chromosomes carrying the genes of the ebon body and vestigial wings interchange segments with norm chromosomes together with their linked genes. Geneticis have called this phenomenon crossing-over, and this Englis term has been adopted in most languages, including Ru sian.



Once more, the discovery of a new phenomenon provided fresh confirmation of the chromosome theory and deepened our knowledge of the transmission of hereditary characters.

Crossing-over is very common. But in certain species there are exceptions to the rule. We are already familiar with one of them, the Drosophila male. Crossing-over does not usually take place in them in normal conditions, but it *can be induced artificially, for instance, by irradiation.*

Crossing-over of the different genes occurs with varying frequency: with some it is frequent, with others rare. But every pair of genes is subject to crossing-over at an exactly defined frequency. For instance, in the example above of ebony body and vestigial wings the number of 'strays' was 18 per cent. The figure varies slightly from experiment to experiment, as would be expected from the law of statistics but if the numbers involved are big enough we get a more or less constant figure. Consequently, crossing-over takes place here in only 18 per cent of the chromosomes.

It was not long before crossing-over became an efficient tool in the hands of geneticists. When Morgan's group were pondering over the pattern of crossing-over, they had a bright idea. Apparently it occurred accidentally. The

variation of the value observed and certain other facts favou red that explanation; and it seemed that the greater th distance between genes, the more often crossing-over sepa rated them, and *vice versa*. If that were true, experiment in crossing-over could help determine the relative distanc between genes. This was a fantastic idea but very tempting at any rate it deserved to be tested.

Experiments confirmed the hypothesis. The figures ag reed very well. When, for instance, genes A and B gave 2 per cent crossing-over, and genes B and C 3 per cent crossing-over between genes A and C was observed in per cent of chromosomes. And after a large number of ex periments had been made the genes could be built up int a chain within each linkage group (i.e. within each chrc mosome). The idea suggested itself of likening chromosc mes to a thread on which genes were strung like beads Comparison of the chromosome to a string of beads ha long been current in popular literature, and although it structure has now been studied in much greater detail the comparison remains good as a first approximation because genes are really arranged linearly along the chrc mosome.

This work marked the beginning of drawing up 'geneti maps' that schematically indicated the mutual arrangemen of genes and the relative distance between them. Progres was particularly rapid with Drosophila, which was idea for the purpose. Already by 1915 works had appeared wit detailed maps of the individual chromosomes of this fly Analogous studies were made on other species less conve nient for experiment, but important commercially lik maize, peas, poultry, cattle. Material for genetic maps c human beings was also collected, though slowly.

Nevertheless the gene still remained an abstract notio and it is all the more amazing that then, when no one ha ever seen a gene or knew what it was like chemically, gene ticists learned to locate their position with precision.

Show Me a Gene

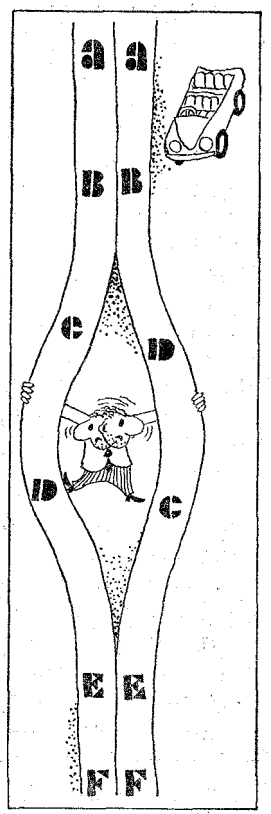
'To see a gene'—what could be more fascinating for geneticist? At first it seemed a dream; but thanks to lucky chance it became possible for them to see, if not th genes themselves, then at least the place (locus) where the were located, with their own eyes.

Late in the last century the Italian cytologist Balbiani studied the larvae of fruit flies under the microscope. In their salivary glands he saw a quite unusual picture. They consisted of huge cells many times larger than normal, and the cells contained something very much like nuclei, but also very large and of quite unusual structure. Under the microscope, these structures resembled a piece of thick rope with transverse stripes. Balbiani was surprised, described the picture observed, and left it at that. And for a long time no one took any interest in these strange formations.

It was not until 1933 that they again attracted attention. The nature of the structures described by the observant Balbiani was finally clarified. This was done simultaneously by Heitz and Bauer in Germany and Painter in the United States quite independently of one another. A new technique in preparing slides helped them.

If the cells of salivary glands had been embedded in wax as in the old method and cut with a microtome, it would have been impossible to discover the nature of these mysterious structures. These investigators used a different method. They took the salivary glands from a Drosophila larva (it should be noted that a picture like that reported by Balbiani is also seen with other flies and mosquitoes) and stained them with carmine dissolved in acetic acid. The whole gland was placed on a slide, covered with another slide and pressed. The different workers used slightly different methods. The American applied pressure with the thumb of his right hand; the Germans, with a pencil; but the results were the same. The nuclear membranes burst and the puzzling structures uncoiled. An amazing picture opened out before them. Long strands or ribbons issued from the loose, faintly coloured centre, each consisting of brightly coloured transverse stripes of varying width alternating with colourless portions.

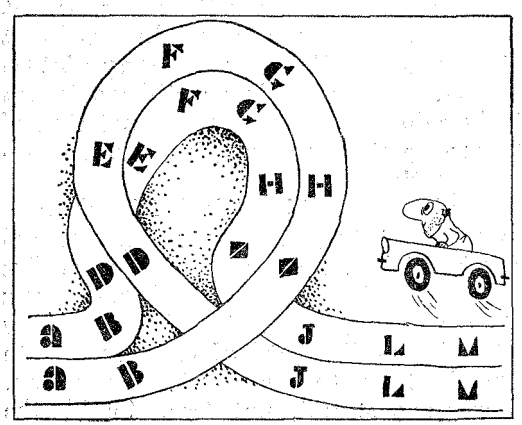
What were these strands? They did not look like chromosomes. Suffice it to say that they were about a hundred times longer and much thicker. Moreover, they were five in number, whereas Drosophila has eight chromosomes: six large ones and two very small ones. On closer scrutiny a quite tiny sixth strand was discerned of the same width as the others but so short as to merge with the centre. But still there was only one strand, not two. Could the



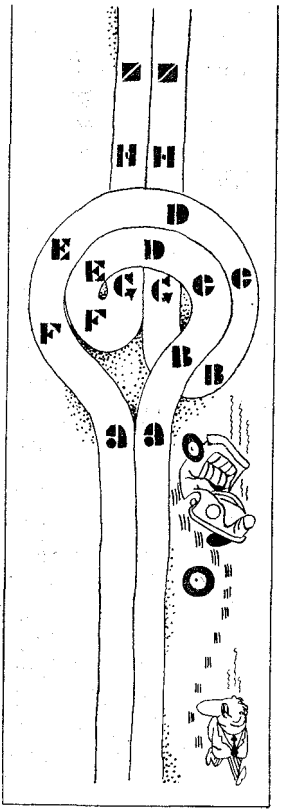
strands correspond to chromosome pairs? But Drosophila had four pairs of chromosomes.

Where this mysterious figure of six come from? Wait. Surely that is the number of chromosome 'arms' in the haploid set. Each chromosome has a definite point to which the spindle threads are attached during division. If the point is in the middle of a chromosome, it divides it into two arms; if it is at the end, the chromosome has only one arm. In Drosophila the X chromosome (which is the first) has only one arm, the second and third chromosomes have two, and the fourth is a dot.

The origin of the strange structures began to become clear. Various cases of incomplete cell division were recollected. It may happen that the chromosomes and nuclei divide, but the cells do not, resulting in binuclear or multinuclear cells. At other times the chromosomes divide, but the nuclei do not, producing cells with twice the number of chromosomes. Why could it not be supposed that



the chromosomes divide but remain in place together? That would exactly explain the origin of giant chromosomes in the salivary glands of Diptera. Homologous chromosomes—paternal and maternal—came into contact, just as they did during the maturation division of sex cells, and divided repeatedly, all at a stage when they were completely uncoiled—hence their enormous length.



But what were the transverse stripes? That was also explained easily. Scientists had previously happened to observe uncoiled chromosomes in certain particularly suitable objects. And it had been found that they were very delicate filaments (called chromonemas) on which there were granules of a substance that took a nuclear stain (called chromomeres). The transverse stripes on the giant chromosomes were nothing more than a large number of chromomeres lying side by side.

All that seemed to argue in favour of the hypothesis, and the origin of giant chromosomes could not be explained otherwise. But scientists are an inquisitive lot: they always seek new evidence. And it was not long in coming.

Chromosome mutations had already been discovered a fairly long time ago. The term was used for inheritable changes in the linear arrangement of genes in chromosomes. A common type of chromosome mutation is what is known as inversion. If we denote the order of the genes on a chromosome with the letters of the alphabet, the order ABCDEFGHIJKLM will correspond to the normal arrangement, but with inversion it may appear as ABCJIHGFEDKLM. The middle section from D to J is reversed 180° compared with the order assumed as normal.

What will we get if we cross normal flies with those

having inversion? Ordinarily we consider the transverss discs (or stripes) to be a series of identical chromomeree joined closely together; with this type of crossing different chromomeres would come face to face. If the hypothesis were true new phenomenon should be expected, but it means we must cross flies with chromosome mutations with normal ones.

No sooner said than done. And although only a few days were needed to obtain the larvae the Morgan's group were eagerly looking forward to the moment when they could disembowel the white worms and press the cover slide down with the thumb of the right hand. Finally they looked at them into the microscope and—lo and behold!—they saw pictures never seen before. In cases of slight inversions, a longitudinal split was visible at a definite place on the chromosome, exactly where inversion should occur according to genetical forecasts. At the places where different chromomeres lay face to face they failed to fuse, or rather, fusion had occurred separately among the 'maternal' chromomeres and among the 'paternal' ones, but unite they could not. Excellent.

But when flies with large inversions were crossed with normal flies, splits were not visible, full fusion of the chromomeres had taken place in all cases. How could that happen? But here, too, the chromosomes looked abnormal. Some had large loops. That's how it was. The chromosomes had coiled up in such an odd way that every point on one chromosome was facing an exactly corresponding point on another. To describe how it all came about is very complicated, but it is very easy to show in the drawing.

It follows that every 'ribbon' in the nuclei of salivary glands consists of closely united 'paternal' and 'maternal' chromosomes connected at strictly homologous points. And again, as had more than once occurred before, not only did the new findings corroborated earlier conjectures but they enabled a big advance to be made.

The transverse discs on the giant chromosomes are not identical. Some are wide, others narrow, and others still double, and in places parts of the chromosomes are thickened. Therefore, it is possible to establish on the preparations we have just been speaking about just where each inversion begins and ends. An experienced cytogeneticist can determine it within a disc.

So cytological maps of Drosophila's giant chromosomes were compiled. All the transverse discs were depicted, divided into sections, and numbered. In that way, every point (locus) has been given a conventional name consisting of letters and figures. By using these charts we can easily locate the points where inversion has taken place. The most exciting stage of the research then began—comparison of genetical maps (based on crossing-over experiments) with cytological maps (based on microscopy of chromosomes). The genetic experiments indicated exactly which particular genes were 'inverted' in the chromosomes of a corresponding linkage of Drosophila. The cytogenetic experiments said which discs were arranged in reverse order. By comparing them we could tell in which portions of the chromosome visible under a microscope a particular gene was located. In certain cases it was even possible to indicate the specific disc in which the gene was localized.

Yet the nature of the gene was still unknown. It was still an open question whether it was a single transverse disc or the adjoining uncoloured section, or whether several genes were located in each disc. But it was perfectly clear that a particular gene was linked with a particular point on a chromosome, and that was a tremendous achievement.

What I have described is the foundation of the chromosome theory of heredity, its ABC. What we have learned in rough outline is the essence of what was done in a very brief period by Morgan's group at Columbia University.

We could round off our story here. But there is one gnawing question. Why does Drosophila (or other Diptera) need giant chromosomes? Not, to be sure, to help geneticists unravel the mystery of the laws of heredity.

The purpose of giant chromosomes proved simple enough. The genes contained in the cells are constantly at work, producing substances controlling the cell's entire activity. In different cells and under different conditions, the various genes work now more, now less, intensively, and at times knock off altogether. But what if the cells have to cope with a big load? Normal cells that have only two genes of each kind can sometimes fail to cope with their task.

Nature found a way out of this predicament by increasing the number of cells that work together, so producing

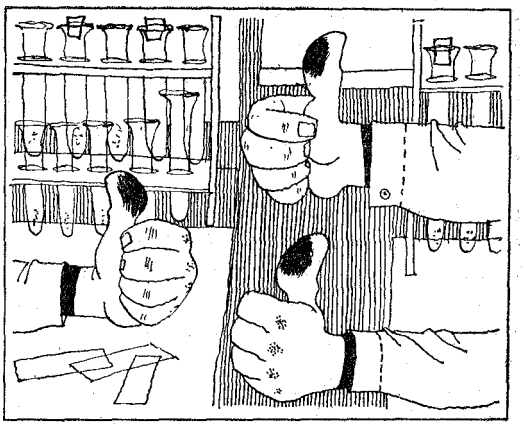
multinuclear cells, cells with an increased chromosome number. The evolution of Diptera (flies and mosquitoes) proceeded in a rather different way, with the formation of polytene (multifilamentous) chromosomes. It should be noted that in these insects giant chromosomes are found not only in the salivary glands but also in other organs where, however, the degree of polyteny is less and the chromosomes are not nearly so gigantic.

Just why the chromosomes are particularly large in the salivary glands of larvae of the final stage is not difficult to guess. For the chief work being done by larvae at that time is to spin a cocoon for the future pupa. The cocoon is produced within a very short time, and the substance for making it is secreted by the salivary glands. In preparations of salivary glands the eye is caught by the individual sections where the chromosomes are greatly thickened. These may be the sites of the genes controlling secretion of the substances from which cocoons are made.

But why suppose so? Science believes nothing but facts. Several years ago facts favouring this conjecture were obtained. It was not Drosophila, however, that yielded the first facts but a fungus gnat of the genus *Sciara*. By examining their larvae at different stages of development, biologists succeeded in tracing the time of the appearance, development, and disappearance of individual swellings on the giant chromosomes. It was found that some began to develop just when the larva started to spin the cocoon. Later they disappeared. Fairly convincing, isn't it?

Now much work of this kind is being done on Drosophila and other two-winged flies, particularly on the larvae of non-biting midges of the Chironomidae family. These blood-red larvae are the bloodworms known to every angler or owner of an aquarium. The giant chromosomes of their salivary glands are even larger than those of Drosophila.

The chromosome theory of heredity (or Morganism, as it is sometimes called) was developed on Drosophila, material quite uninteresting from a commercial viewpoint. Modern technology has rendered it unnecessary even for converting must into wine. But the laws of heredity Drosophila helped to discover are valid not only for it. Indeed, if it had been otherwise, hardly anyone would have taken an interest in them. The laws are valid for all living organisms—for wheat, and cattle, and man. Of course, what



is valid for one kind of organism is not necessarily valid for all. But as far as the chromosome theory is concerned, its basic principles have been verified on a tremendous number of species. And it is now as clear as day that the same laws govern the heredity of flies and elephants.

How Does It Happen?

We have seen how chromosomes behave during cell division and fertilization, and become acquainted with the interesting conclusions drawn from the study of them. But we still know next to nothing about how they are studied. We know that a complicated method of wax sections used to be employed. But now it is seldom used. We also know that living cells can be observed and microfilms made. That requires the very latest equipment, which of course is not always available for routine laboratory work. What then are the most common modern methods of studying chromosomes?

To learn that we can drop in at any laboratory where chromosomes are studied. Techniques have become much simpler than they were in the time of Chistyakov and Strasburger, and it wouldn't take more than a day to learn all about them. Let us drop in at my laboratory where, as I write, studies are under way on the chromosomes of peas, about which we have already talked so much.

On a table stands a battery of small test-tubes in a special holder. They contain pea roots that are being studied.

A week ago they were cut off the plants, soaked for two hours in a mixture of alcohol, acetic acid, and chloroform, and then put into alcohol to preserve them. Anyone at all can show you how the preparation is made, an experienced senior scientist who is working on his doctorate or the schoolgirl who recently came to us for practice.

The hospitable host, desirous of initiating you into the secrets of his art, takes out a root, places it on a watch-crystal, and wets it with ten drops of stain dissolved in dilute acetic acid, and a drop of hydrochloric acid. If the material is fresh it will be fixed and stained at the same time. The drop of hydrochloric acid is most important because it dissolves the substance holding the cells together.

Then he heats the glass gently, and after a certain time cuts off the very tip of the root, puts it on a slide, covers it with a thin cover slide and... presses it with the thumb of his right hand. The stained cells spread out uniformly in the drop of liquid between the slides, and the preparation is ready. Simple, isn't it? But it took a long time to develop it.

Now, looking into the microscope, you see pale cells with brightly coloured nuclei. On closer scrutiny you will note that they are not identical. Most have a regular round shape and are stained quite uniformly. Only, in the centre, there is a paler point, known as the nucleolus. But some cells are quite different. They look like a tangle of threads of varying thickness, some without a nucleolus or even a nucleus, but having a few brightly coloured rods in its place. Those are chromosomes.

Peas are, of course, an easy object for observation. But we are not really interested in peas as such. What interests us are the general laws of nature. Yet it may so happen that our favourite material misbehaves. Opponents of the chromosome theory liked to scream that Drosophila had no commercial value, that geneticists were making mountains out of mole-hills, etc. That, of course, had nothing in common with scientific argument.

If we are to speak of the most important subject at all, that, of course, is man. We cannot experiment on human beings but we can experiment on human cells. Not so long ago it was an unrealistic dream, but in recent years it has become a fairly simple matter. And in the next room, incidentally, scientists are experimenting on them.

That phrase 'experimenting on human cells' has an ıinous ring, hasn't it? But it is a very humane occupation. piece of tissue excised during an operation was put a special nutrient medium, and for several years now cells have been living and multiplying outside the huın body. Small slides coated with a layer of pink liquid at the bottom of vials of penicillin. Human cells are ɔwing on them. Whenever necessary, a slide can be taken t, fixed in a mixture of alcohol and acetic acid, and ıined. Then the cells can be examined under a microspe.

What you have just seen, however, scientists have been le to do for a fairly long time although by a rather diffeıt method. Here, beside them, are the most interesting ings. The same pink liquid is seen in the flat-bottomed ıic flasks. Take the flask and examine the bottom, preably against a dark background. You will see a large mber of whitish dots and spots with your naked eye. ey are colonies of human cells. A fortnight ago the retort s 'seeded' with about a hundred separate cells. Now each them has multiplied to the size of a colony visible witut a microscope. That is very important. Not only do want to learn what happens to the chromosomes in a l but we also want to know how that affects the fate of e cell, whether it will retain its ability to proliferate d whether it will produce normal daughter cells. It is ly recently that we learned how to obtain colonies from lividual cells.

There are many other things we could show you, but at you have seen is enough to make it clear that genetits work with a variety of material, and it is generally nplicated. But to carry out serious experiments is not a simple business. It requires patience and imagination. And it is even more difficult to make a discovery, even a minor one. But to learn the main facts of genetics is simple enough, and if it were decided to institute practical lessons in genetics and cytology at school, it would be perfectly feasible to do so.

It is too early yet to leave our laboratories. We have not seen the famous Drosophila that helped Morgan's group to evolve the chromosome theory of heredity. Unfortunately I have no fruit flies here just now, so we shall have to go to another laboratory in a neighbouring building.

It is said that any European who has ever been to Hawaii dreams all his life of returning there. I have never been there and cannot judge whether it is really a paradise on earth. But I have years of experience with Drosophila and I can testify that any geneticist who has ever worked with the fruit fly has very fond memories of it. And when the course of research forces him to turn to other material he never gives up hope of returning to Drosophila.

The Story of a Suicide

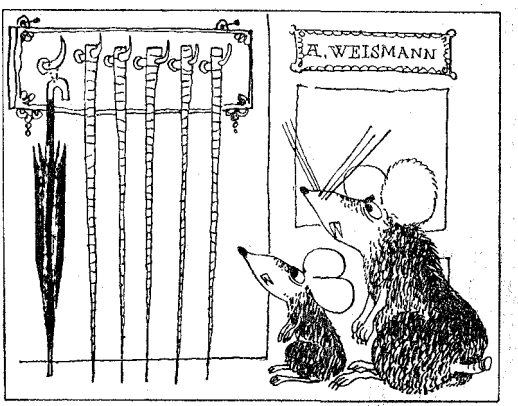
Tailless monsters scurry about in the cage. Speaking of mice, what can be more monstrous, in fact, than absence of a tail? But all these mice are without tails, except the tiny, still pink sucklings.

For several years now Privy Councillor August Weismann, professor of zoology at Freiburg University, had been coming here with truly German punctuality and cutting off the tails in all newly-born mice. Once a new litter was born, he could be expected to arrive soon.

Indeed, a bearded head with gold-rimmed spectacles is bending over the cage and, as usual, the professor is accompanied by Martha whom the mice see every day, because she feeds them and cleans the cages.

The professor opens the cage, takes out each baby mouse and carefully measures its tail, and Martha writes down the figures he dictates in a notebook.

'Now, Fraulein Schultze,' Weismann says, 'the experiment is over. Please remove the mice from the laboratory today.'



Whatever August Weismann may deserve to be reproached for, it is not for a lack of patience. He cut the tails off in 22 generations of mice to make sure that this did not affect the length of the tails of their descendants. As can easily be guessed, for 22 generations the tails remained just as they had been before the experiment began.

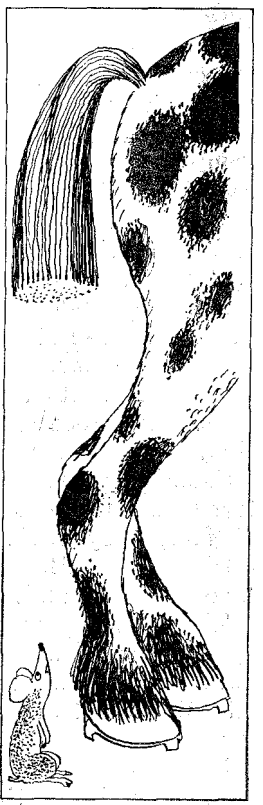
For centuries nobody bothered whether or not acquired characters were transmitted to progeny. It seemed clear to everyone that they were. There was a host of legends and beliefs associated with this idea, but in science the question was not considered for a long time. Both Lamarck and Darwin, great naturalists, believed that the basic material of evolution was provided by variations occurring during the lifetime of an individual organism and passed on through heredity.

Toward the end of the last century August Weismann evolved an intricate and abstruse theory of germ plasm. It contained little factual evidence and many contradictions, but certain elements of it were correct, and have been adopted by modern science. The theory itself does not interest us now; for us another point is important. It followed from Weismann's ideas that acquired characters could not be inherited, and that ran counter to existing views. It was necessary to demonstrate that they were not inheritable, so Weismann, who was generally more prone to theorizing than to experimenting, decided to make the *experimentum crucis*, and so cut off the tails of twenty-two generations of mice.

It is hardly necessary to say that few people were persuaded by his experiment, though some were greatly impressed by them. Boss, for instance, patiently repeated them on rats, obtaining the same results.

Most scientists, however, asked what was the influence of conditions. This is mutilation, physical damage, and would not be inherited. But if tail length were related to conditions of life, it might be different; the character might be inherited by the progeny. It is well known, for instance, that the coat of animals raised in the cold becomes thicker, and the tail, ears, and legs shorter. If several generations of animals were kept at a lowered temperature, then the 'short tail' character would, of course, become hereditary. As for mutilation, Weismann might just as well not have performed his experiments. Stock-breeders

have been carrying them out for ages. Shepherds have been cutting off the tails of merino sheep for years, and horse-breeders docking the tails of horses, and dog-fancies the tails and ears of many breeds of dogs, but their descendants remain just the same as their distant ancestors.



New experiments were begun, this time to refute Weismann. Sumner began raising mice under extreme temperature conditions, keeping some at 6°C, and others in 30-degree heat. The difference in the length of the tails of adult 'hot' and 'cold' mice was as much as 30 per cent, but their offspring were nevertheless quite identical. Przibram, experimenting on rats, used even wider temperature variations, but obtained the same results.

That seemed strange as it contradicted the generally accepted views, including those of the scientists who had performed the experiments. Weismann's followers were jubilant. Adherents of the older views, however, believed that something was wrong with the experiments. So more and more were carried out on different objects, with different characters, in different conditions. The problem soon became a burning issue, and the biologists of the world were split into two camps over it, the champions of the theory of inheritance of acquired characters and its opponents.

Today the assertion that acquired characters are not inherited no longer causes much doubt, since we now know the chemical nature of the gene, and the most delicate mechanisms of the inheritance of characters. But at the turn of the century most scientists had foggy, and often fantastic, views of heredity, so that the possibility of the transmission of acquired characters by no means seemed absurd.

Many reasoned roughly as follows. Temperature, affec-

ting the course of physiological processes, tends to chan the length of the tail (of course, it is not necessarily a qu stion of tails or of temperature), and that in turn according alters the 'heredity' of the organism (what heredity wa however, still remained obscure). Thereafter the proge would also be born with similarly altered tails. Scientis called this imaginary process somatic induction.

Even in those days, this process seemed unlikely to so and they viewed the matter rather differently, reasoni as follows. Temperature tends to change the length of t tail owing to changes occurring in the cells, but the temp rature affects not only the tail but also the germ cells, which the same changes take place. It would be expecte therefore, that the offspring too would have alter tails. This process, also imaginary, was called parallel indu tion.

Thus proponents of the inheritance of acquired chara ters had sufficient theoretical prerequisites. As a matt of fact, they revived Lamarck's views of the causes inherited modifications and therefore called themselv 'neo-Lamarckians'.

They were opposed by supporters of the views formulat by Weismann, who called themselves 'neo-Darwinists'. Y both these viewpoints were purely speculative. In such situation the truth could be elicited only by an accurate mounted experiment. So they continued experimenting. this connection the name of the Austrian zoologist Pa Kammerer is particularly famous. He was a convinc neo-Lamarckian, and his experiments became widely know far beyond the limits of the academic circles.

Kammerer made experiments with spotted salamander The bodies of these animals are covered with black ar yellow spots that vary in number and form in the wil Kammerer raised them on black and yellow background Those raised on a black background gradually showed pr ponderance of dark spots, and in time the animals becan almost completely black, save for two rows of small pa spots running along the back. Those raised on a yello background grew increasingly yellow.

This result was not unexpected; any zoologist kno that many animals are capable of adapting their colourir to that of their environment, and this is particularly ch racteristic of amphibians and reptiles. (Think of the ch

meleon, which changes colour literally before your eyes; its name has become proverbial.)

But then Kammerer began obtaining offspring from his varicoloured charges. Now they were kept in identical conditions, but the young of black animals proved darker than those of yellow ones. What arguments could be raised against such results? But his opponents did raise objections. The German Herbst was particularly active and opposed him both in word and in deed. He too began experimenting with salamanders. Unlike Kammerer, he raised not adult salamanders but larvae on different soils. Their modification proceeded even faster than in Kammerer's experiments, but when the matured salamanders continued to be kept on coloured soil their differences in colour, far from becoming greater, actually diminished.

Did that mean that Kammerer had made a mistake? Or perhaps something worse? His name was almost discredited. Then K. Frisch came to his defence. He painstakingly repeated, although on a small scale, the experiments of both Kammerer and Herbst. The results of both were confirmed, which meant that only adult animals should be experimented with. Frisch was seconded by Schleip and Przibram. It seemed that it was settled.

But Herbst was not one to accept defeat. He published new much more detailed work that again completely refuted Kammerer's results—not his theories, of course (for no one is guaranteed against that), but his facts, his experimental findings. Nothing could be worse. Kammerer was put to shame. But his supporters again came to his rescue. They had found that the two men had worked on different varieties of spotted salamander, and the use of different experimental material can explain any discrepancy. Again everything cooled down, but who was right and who was wrong in the story of salamanders remained uncertain.

Kammerer, however, was a man of fighting spirit. He began completely new experiments, this time on obstetrical toads. These animals are remarkable for their peculiar mode of reproduction. Unlike all their kin, obstetrical toads spawn on land rather than in the water. The male winds strings of spawn about its body, and the eggs enveloped in slime develop over a certain period. When it is time for them to hatch, the male seeks water where the tadpoles come out and develop further.

But what if the animals are kept in water all the time? Kammerer raised the air temperature, and the toads crawled into the water even before spawning time. The males attempted to behave as before but failed: the slime was washed off and the eggs sank to the bottom. After several spawnings, the males desisted from their vain attempts; their hereditary instinct changed. Moreover, some of their outward characters also changed: the front legs grew much stronger, and the toes developed the callosities characteristic of frogs and toads reproducing in water. Interesting as this finding was, however, it had no connection with heredity. Kammerer then crossed his charges with normal obstetrical toads, and obtained nothing less than Mendelian segregation in their progeny. And if, in cross-breeding, characters segregate in the progeny according to Mendel's laws, that is the most conclusive evidence that these characters are inherited. This seemed to be Kammerer's full triumph.

His experiments, however, had the most tragic consequences for him. The issue of the British journal *Nature* of 7 August, 1925 published an article by G. K. Noble. He was a bitter enemy of Kammerer and went further than Herbst. He visited the Vienna biological institute where Kammerer's specimens were kept and examined them under the microscope. Soon he announced that what were believed to be newly-formed warts on the toads had been produced by the injection of Indian ink. Fraud! What Kammerer's numerous foes had previously only hinted at was proclaimed by Noble in public and backed by factual evidence.

Thus Noble dealt the first blow to Kammerer in a rabid campaign instigated against him by persons whose motives had nothing to do with science. Driven to despair Paul Kammerer committed suicide in September 1926, leaving a letter in which he denied his involvement in the fraud.

Did Salieri really poison Mozart? Did Martynov really kill Lermontov? After such doubts had leaked out, historians began an inquest that continues to this day. Here is how matters stand with the dramatic question whether or not Kammerer was really a fraud.

The incident became public property. It was written up in the press. Kammerer's story was used for a film called *Salamander*. The controversy still continues. Some regard Kammerer as a faker, others, as a knight without

fear and without reproach, asserting that the fraud was the work of one of his supporters. Why couldn't it have been done, say, by a laboratory assistant, some rather dim Gretchen fond of her brilliant chief and eager to help him obtain the desired result? Still others think that the fraud was the work of Kammerer's enemies, and that they might have done it to ruin his cause and his life. It is hard to say whether the truth will ever come out.

All that, however, concerns the fate of Kammerer himself. As to his theories, their value is clear enough. Whether or not he was an honest scientist, his contentions were wrong. Many a volume has been written about the experiments made to check the assertion that acquired characters are inheritable, with the invariable conclusion that characters acquired by parents cannot be transmitted to offspring.

An Engineer Challenges a Scientist

'He died in obscurity and misery. It was not until many years later that posterity could appreciate the greatness of his discovery.' Phrases like that, alas, are too often met in the biographies of great personalities, especially great scientists of the past.

But there are no rules without exceptions. When Charles Darwin's work *The Origin of Species* appeared it immediately caught the public eye. One edition followed another. Soon it had been translated into other languages. Not only scientists read it. When our great grandmothers were still schoolgirls and wore plaits and pinafores they would hide Darwin's *Origin of Species* together with Chernyshevsky's seditious novel *What Is to Be Done?* from the watchful eye of their tutors.

No one was indifferent. But not everyone admired the work of the great naturalist. He was disputed, denied, and accused. Anti-Darwinism came into being immediately after the birth of Darwinism, and the truth had to be defended against heavy odds.

When one reads articles by anti-Darwinists now, the naivity and untenability of their arguments strike the eye. And Darwin, who had been evolving his theory for years, who had weighed all pros and cons long before, easily found indisputable arguments to defeat his opponents.

But in 1867 a question was put to Darwin that he was

unable to answer for the rest of his life. And it could not be answered by his followers for many years after his death. The man who posed this question was not a biologist, not even a scientist, but an engineer. Fleeming Jenkin, like many educated men of the period, had read *The Origin of Species*. First he began to think, then did some simple arithmetic, and produced what is known as 'Jenkin's paradox'. Darwin was unable to answer it, frankly admitted it to be the weightiest argument against his theory, and revised certain of his views under its influence, unfortunately in the wrong direction. But let us not run ahead of our story.

How often scientists are praised for what has never added to their prestige or even for what they have never done, while their true merits remain unnoticed. Mendel is praised for his discovery of the laws of the inheritance of characters in hybridization, but they had been known in general outline even before his time. The fact that Mendel was the first to propound the principles of corpuscular heredity is recalled much less often. Something like that happened to Darwin. Although Darwinism is widely known, and it is not the subject of our book, we must make clear the real import of Darwin's contribution before we can tell about 'Jenkin's paradox' and how it was finally solved.

In popular science Darwin is extolled as the author of the idea of evolution, which is not true. Even in school and university curricula the theory of evolution is often called Darwinism, but there were quite a few evolutionists before him. We have already mentioned Kaverznev, but the idea of evolution had been put forward by many others. And one scientist had created a well-composed and detailed theory of evolution half-a-century before Darwin. It was published in 1809, the year of Darwin's birth, in two volumes entitled *Philosophie zoologique*. The author was the great French scientist Jean Baptiste Lamarck.

Like Darwin later, Lamarck spoke of evolution—the origin of new forms through a series of changes in old ones—and of development from simpler to more highly organized types. But there was a fundamental difference in their views on the driving forces of this evolution. Charles Darwin's great contribution was his discovery of the true driving force of the evolution of species.

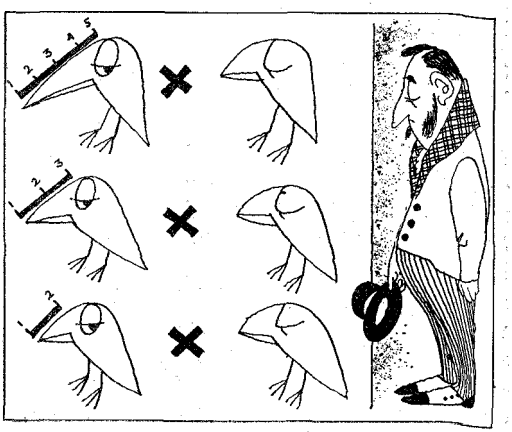
Lamarck held that organisms changed under direct influence of the environment, that the cause of evolution was

the 'exercise' or 'non-exercise' of organs, and 'an inner tendency toward progress'. As is known, Lamarck erred on this score.

Darwin was the first scientist to demonstrate the existence of a common principle—natural selection—in living nature. In biology this was the discovery of a first universal law as significant as Newton's laws in physics. Darwin had no predecessors in this field, and the significance of this principle is wider than the theory of the evolution of species. It is for that that we should pay tribute to the genius of Darwin.

In the theory of evolution two aspects need to be distinguished: the theory of material for evolution and the theory of its factors, its driving force. Indeed, it is quite clear that for natural selection to operate there must be something to select from. There must be hereditable variations. Darwin's work contained a brilliant exposition of this question and the development of science brings more and more evidence that this theory is correct, that the driving force of evolution is natural selection.

As regards the material for evolution, this was developed much less strongly by Darwin, which is not really surprising. For we are talking of inheritable variations, and genetics did not exist in Darwin's time. But he was a scientist of genius, and the first to give a generally correct answer to the problem of the elementary material of the evolutionary process. He believed this material to be provided by the chance occurrence of inheritable variations.



Now we can come back to 'Jenkin's paradox'. Jenkin reasoned as follows: let us suppose that some individual has changed in a certain way, say in the most useful one. What will happen to its offspring? In the first generation they will consist of half-breeds, in the second generation they will consist of quarterbreeds of them will be related to the parent stock, and after several generations the useful variation will be totally dissolved among the descendants. So what importance can it have for evolution?

The absorbing influence of free crossing—such is the gist of 'Jenkin's paradox'. It was not very difficult to raise this objection; it is not fortuitous that it was also voiced by the prominent Russian biologist Nikolai Danilevsky, one of Darwin's most serious opponents. It was more difficult to answer it.

Darwin himself admitted its seriousness. Gradually he began to attach less and less importance to accidental, isolated variations, and to adduce a greater role to mass deviations. But what are mass deviations? They are known to occur only through the directed influence of the environment. In that way, toward the end of his life, Darwin drew rather closer to Lamarck, but not, of course, as regards the driving forces of evolution—there he firmly stood his ground—but on the question of the elementary material for evolution.

In Darwin's time there was no clarity on the problem of the inheritance of acquired characters, and corpuscular genetics did not exist. It is quite natural, therefore, that he could attribute importance to the direct influence of the environment on the formation of hereditary modifications and be unable to find evidence against the absorbing influence of free crossing.

Only genetics could resolve these two problems but much time had to pass before it became allied with the theory of evolution. It may seem strange today that most Darwinists were hostile to the birth of the new science. Because they were not geneticists they were unable to appreciate, let alone apply, its findings for the advancement of Darwinism. As to the geneticists, they were initially too busy with their own problems, and simply had no time for deeper study of the problems of evolution. The isolated, insufficiently detailed works that did appear only served to discredit the idea of a union of genetics with the evolutionary

theory. The evolutionists of the older generation therefore began to regard these first efforts as an attempt to substitute Mendelism for Darwinism. The evolutionists developing Darwinism began to be called neo-Darwinists and to be counterposed to Darwin for the simple reason that they were ridding his theory of its Lamarckian attachments. This mistake was not avoided, in particular, by the prominent Russian Darwinist, Klimenty Timiryazev.

New But Long Forgotten

In 1900 Mendel's laws were rediscovered. The old concepts of 'mixed blood' were thrown overboard. Even in the last century crossing was regarded as mixing; 'mixed blood' was often referred to in the literal sense of the dissolution of one blood in another. Now it became clear that inheritance was based on the indivisible and unmixable Mendelian factors or genes. These new concepts could not help changing views on the problems of evolution as well, but various scientists looked at them in different ways.

Much confusion was introduced into evolutionary theory by August Weismann. You will recall how he cut off the tails of white mice for twenty-two generations. His affirmation of the non-inheritance of acquired characters was correct, but he also developed a theory of germ plasm, that denied the possibility of any change whatever in it. There remained only one route for hereditary variations, the mixing of parental 'determinants'. Obviously nothing new could be produced in that way. According to Weismann, the organism was nothing but a container for eternal and unchangeable germ plasm.

Yet Weismann was an evolutionist and a leading Darwinist. He evolved a theory of the germ route. His hypothesis of 'germ plasm' with its 'ids', 'idants', 'determinants', and so on, proved far-fetched and speculative and was shown to be wrong. In recent years it has become common when writing about Weismann to stress and exaggerate his mistakes and delusions, and to pass over the important elements of his theory.

The theory of eternal and unchangeable germ plasm has been refuted, but the concept of the germ route remains. Indeed, the transmission of characters from one generation of living organisms to another is effected through a number of germ cells. This is a firmly established fact. Weismann

was the first to appreciate its importance for evolutionary theory. For evolution only those changes are important that have taken place in the germ cells. Weismann also introduced the concept of 'germ selection', of selection taking place at the level of the sex cells.

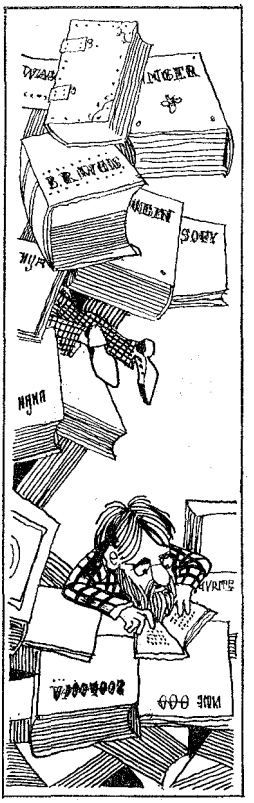
Whatever his mistakes, Weismann was the first to rid Darwinism of Lamarckian concepts. It was then that the term neo-Darwinism was coined, which meant Darwinism freed from concepts of the directed influence of the environment on hereditary variations. If a scientist believes in 'an inner tendency toward progress', that a baby giraffe has a long neck because its parents had to stretch their necks to reach the leaves of trees, he is not a Darwinist whatever he may say about selection. Moreover, if there were such a directed influence of the environment on hereditary variations, selection would be almost unnecessary or, at any rate, would cease to be the driving force of evolution.

Darwinism considers natural selection the basis of evolution. It is precisely through selection that the directed influence of conditions of life is exerted on hereditary variations. Hereditary variations of themselves are accidental, but under the influence of the environment the characters best adapted to the conditions of life are selected. Neo-Darwinism is in effect a re-instatement of Darwin's initial views on the origin of species that he held until Jenkin puzzled him with his paradox.

Weismann developed his theories before the rediscovery of Mendel's laws. Subsequent discussions of evolutionary theory were not always linked with the development of Mendelism. The chief problem at the end of the century was to choose between neo-Darwinism and neo-Lamarckism, or rather to decide whether or not characters acquired by the organism during its lifetime could be inherited.

During this great controversy not everyone made laboratory experiments like Kammerer. Many scientists carried out observations in nature, trying to find the answer to this exciting problem there. Some sought the truth in the dust of libraries and archives, and brought to light most fascinating writings. It was found, for instance, that the idea of the noninheritance of acquired characters was not at all new. In 1834 a treatise entitled *The Universal Law of Nature* had been published, in which it was said: 'Pe-

ople with an amputated leg are just as intact individuals from the viewpoint of reproduction as animals with their tails and ears cut off, because children of the former are no more one-legged than the offspring of the latter are born with shortened ears.... If one saws off the horns of cows and bulls their calves will still have horns. But if you cross a cow that has no horns because of its inner predisposition (such specimens are encountered in certain localities) with a similarly hornless bull their offspring will also have no horns.'



Those lines were written by the Russian Academician Karl Baer, a man whose name is unjustly seldom recalled. He made such a great contribution to biology (and not only to biology) that he deserves a few words. Baer was an Estonian by birth and was educated in his native land. He wanted to become a doctor, and after graduating from Derpt (now Tartu) University, he continued his education abroad where he was attracted to biology and became a naturalist. At first he worked in Königsberg, and in 1834 (the year of publication of his *Universal Law of Nature*) he was elected to the Russian Academy of Sciences and returned home for good. He died at a very old age, and almost to his dying day, although half-blind, he continued to dictate his works.

Baer's greatest contribution was to embryology. He was, in effect, the founder of this science. Although Harvey had already studied the development of the hen's egg before him, it was Baer who first clarified all the delicate mechanisms of the development of the embryo. He was a predecessor of Muller and Haeckel in the discovery of the biogenetic law according to which the individual development of the organism repeats in general outline the evolution of a species, and was a pioneer evolutionist.

His activities, however, were not limited to pure biology. He did much to organize the fisheries of the Volga and the Caspian. He discovered what is known as 'Baer's law', according to which the right bank of a river in the northern hemisphere, as a rule, is higher than the left, attributing this to forces generated by the Earth's revolution. He wrote a book on the role of Peter the Great in the study of geography and even investigated the history of the wanderings of the wily Odysseus. By comparing the descriptions in *Odyssey* with real geography he demonstrated conclusively that Odysseus travelled on Pontus Euxinus, the ancient name of the Black Sea. Baer was the first to conclude that acquired characters were not inheritable.

Yet whoever asserted it, only experiment could give the final judgement. Scores of scientists in different countries experimented for years to ascertain whether the characters acquired by parents could be transmitted to their offspring. The experiments yielded one of two alternative results. Either they immediately gave negative results or repeated the Kammerer story: at first they seemed to confirm the inheritance of acquired characters, but then a mistake was revealed and the result disproved. Of the many hundreds of experiments performed none furnished conclusive evidence.

Geneticists Get to Work

Somewhere, in a field, on a river bank, or in a forest glade, you have probably seen tall plants, up to a metre high, with large yellow flowers that open at night. This is the evening primrose*, a plant closely related to the common great willow-herb. In gardens you can find another, cultivated variety of the evening primrose known under the name of *Godetia*. To botanists and many gardeners the evening primrose is better known by its Latin name *Oenothera*. I must admit that I have only recently learned that the *Oenothera* that played such an important part in genetics and the common Russian weed asses' ears are the same plant.

But I was even more surprised to learn that the wild flower growing in the Russian fields is an emigrant. Its home is North America. From its overseas habitat it found

* Known in Russia as asses' ears.

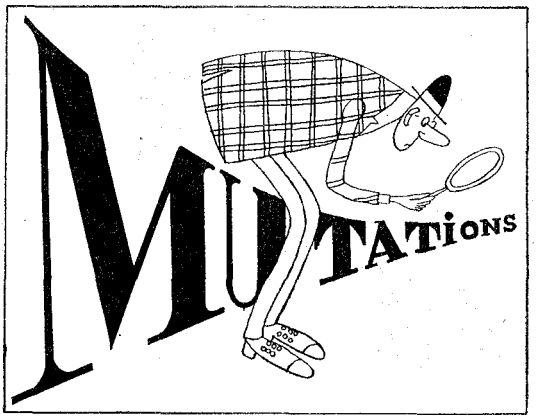
its way to Europe, spread with amazing rapidity, and reached Russia where it became a common wild flower. Since the time of Linnaeus, the scientific names of plants and animals consist of two words—the name of the genus and the name of the species. The evening primrose growing in European fields is called *Oenothera biennis.* It is closely related to *Oenothera lamarckiana*, named after the great French biologist, which has given geneticists much trouble.

Every experimental biologist has his favourite object. For Mendel it was peas, for Morgan, the fruit fly Drosophila. And Professor Hugo de Vries, one of the three rediscoverers of Mendel's laws, favoured the evening primrose. He began to take an interest in it in 1880. At first he observed it in the wild, then set aside a few beds for it in his garden where he bred and cross-bred his favourites. Observing *Oenothera*, he discovered a curious phenomenon. Very rarely, but seemingly quite regularly, new forms appeared among exactly identical plants. Some were so different from the parent stock that a botanist meeting them in the wild would have taken them for new species. Incidentally, these new forms proved hereditary. De Vries called them 'mutations', and they furnished the basis for rediscovery of Mendel's laws.

It is interesting that not all species of the *Oenothera* (de Vries experimented with many of them) produced mutations. *Oenothera lamarckiana* mutated especially frequently. De Vries was astonished and delighted: was he not witnessing the birth of new species? He began to formulate his mutation theory which he worked on and defended for many years.

But why was the phenomenon so regularly observed in *Oenothera lamarckiana* absent in other plants? Probably because, de Vries reasoned, the process of species formation was not taking place in our day in other groups of plants, while *Oenothera lamarckiana* was just in the mutation period.

So far so good. At last the route was found by which new hereditary changes appeared. But everything went too smoothly for de Vries. New species appeared overnight for him. They originated within the old species and came forth ready-made just as Athena sprang fully armoured from the head of Zeus the Thunderer in the classical legend. But if new species arise immediately, where does natural



selectrion come in? They can form without recourse to it, and at best selection can only eliminate species less adapted to their environment.

De Vries developed a new theory. In the history of every species, he thought, there were premutation periods, when it was preparing for the coming changes, followed by a mutation period during which new species came into being at once, in a leap. Were these periods linked with the external environment? Apparently not at all. Evolution, it seemed, was conditioned by some internal cause.

Why were so few species involved in the mutation process? De Vries began to think that it did not always proceed at the same rate. Mutations had once been more frequent than now, and concluded that the evolutionary process was gradually coming to an end.

Oenothera played a dirty trick on Professor de Vries. It became clear, many years later, that the inheritance of characters in certain varieties of this genus (including *Oenothera lamarckiana*) proceeded abnormally. Their chromosomes are greatly altered and form large complexes during division that unite with one another in chains or rings. In that way, the complexes are transmitted from generation to generation without breaking apart. Certain wild types are very heterozygotic, but because of this peculiarity they do not undergo segregation, and they behave like pure species. It is only rarely, as a result of crossing-over, that the complexes are re-arranged, producing what de Vries called mutations.

Geneticists now also talk about mutations as of hereditary changes in individual genes. The altered characters that Morgan and his associates observed in Drosophila (changed eye or body colour, venation of wings, position of bristles) are what we mean by mutation. We shall soon see that they really serve as the elementary material for evolution. De Vries was right on that score. In the same years as de Vries the Russian botanist Sergei Korzhinsky arrived in his theory of heterogenesis at a realization of the importance of abrupt hereditary changes, or leaps, for evolution.

But de Vries' mutations were not, in one way, new changes. Just because of the cytogenetic characteristics of *Oenothera* they could remain in a latent state for a long time. On the other hand, they were not elementary variations (like true mutations), but were a whole complex of changes, and though truly individual varieties, they were not new ones. The unusual character of mutations in *Oenothera* led de Vries to an erroneous view of the evolutionary process as a whole.

De Vries was challenged. One of his opponents was a fellow countryman Professor J. P. Lotsy, who had studied the interspecific hybrids of certain decorative plants, snapdragons and carnations. These were not hybrids like those studied by the cautious and meticulous Mendel who crossed varieties differing only in one or two pairs of characters. The crossing of species differing in a large number of characters gives such a variety of offspring that it becomes quite impossible to sort them out. Such crossings had been made by Gaertner, Naudin, and other predecessors of Mendel.

Mendel, in turning to intraspecific crossings, had taken a step in the right direction. Lotsy, however, took a step backward. He was so impressed by the variety of forms in the progeny of interspecific hybrids that he began to regard crossing as the only cause of evolution. After all he could see these 'new species' in the progeny of snapdragon with his own eyes.

Lotsy knew that acquired characters, so-called modifications, were not inheritable and therefore could not serve as material for evolution. What else could? De Vries' mutations? Lotsy categorically refused to acknowledge them as new hereditary changes. As an exponent of the view that crossing was important for species formation, Lotsy

considered de Vries' mutations also to be the result of crossing.

And if they were, then the only mechanism of evolution was crossing. But since, as he presumed, species were hereditarily homogeneous crossing could only lead to recombination of what already existed and had always existed. He evolved a theory of 'the permanence of species in evolution'. If the species was permanent, then evolution as a result of the selection of small hereditary changes was impossible. That meant that Darwin was wrong, which is what Lotsy concluded.

Of all the types of hereditary changes Lotsy recognized only the destruction of genes. It followed that the history of the development of species was nothing more than a re-combination of the existing 'gene pool' accompanied with a gradual regression due to the elimination of genes.

But where did the existing variety of organic forms come from? To explain that, Lotsy renounced the idea that all living organisms originated from one and the same ancestral form and maintained on the contrary that a large variety of forms appeared originally independent of one another. He tried to draw an analogy between living and dead matter, likening genes to chemical elements, and the process of species formation to various combinations. Thus having set out from Darwinism, he arrived at extreme anti-Darwinism.

The famous Danish geneticist W. Johannsen made a very detailed and specialized study of the role of selection in the development of forms. His experiments are a model of precision and persuasiveness. Like Mendel he was very meticulous in selecting the material for examination and also decided on self-pollination. He experimented with kidney beans of the *Princess* variety.

The work Johannsen did was tedious. He planted beans harvested them, and then measured the size of the seeds He did it very accurately, collecting the seeds from each plant and measuring them separately. Then he plotted curves showing how they were distributed in size within the total harvest and within the offspring of individual plants. The seeds widely varied in size and not only from plant to plant. Those gathered from one plant were also large and small.

Then Johannsen began to select his seeds, and did i

in a double fashion. On the one hand he did it as everybody had done before him. He selected the largest and smallest beans from the total harvest, planted them, repeated the same procedure with their offspring, and so on. And just like everybody else he obtained quite appreciable results. In one case the average size of the beans increased and in the other it fell. But Johannsen did not stop at that.

In addition, he carried out selection in a pure line, i.e. among descendants of one and the same plant. That is why self-pollination was so important for his experiments—all the descendants were genetically homogeneous. Although the size of the beans varied fairly widely within the limits of a pure line selection had no influence on it. No matter how long it was carried on, the average size of the beans remained unchanged. The degree of variability also remained the same.

Selection in pure lines was useless—that was the conclusion Johannsen came to from his exact experiments. It was an extremely important conclusion. On the one hand, it made it perfectly clear that modifications—variations within pure lines during the individual development of specimens—could not provide material for evolution. On the other hand, his experiments demonstrated that selection was effective only in hereditarily heterogeneous communities of living organisms.

When Johannsen began his experiments, mutations were almost unknown. That is perhaps why he did not take the next step then and there and failed to draw conclusions on the importance of new hereditary changes for evolution. At first he was even prone to underestimate the significance of genetics in the development of the theory of evolution, but after a time he became one of the geneticists who did most active and fruitful work on the problems of evolution and genetics.

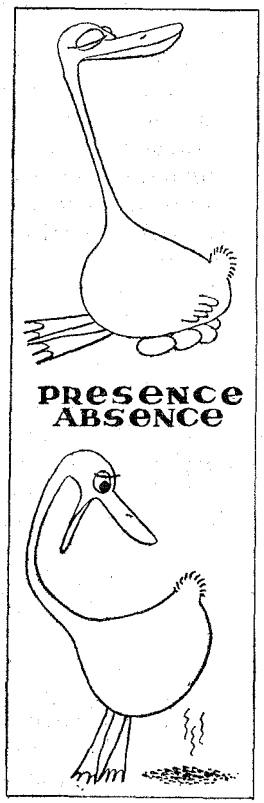
While we are speaking of Johannsen we must recall that it was he who coined the word 'gene'. He is the 'godfather' of genes and genetics.

De Vries' mutation theory, and Lotsy's theory of the permanence of species in evolution, and Johannsen's experiments with pure lines belong to the early years of this century when Mendel's laws were already rediscovered, and the chromosome theory of heredity was just being evolved, and

the remarkable work of Morgan's school on Drosophila, which raised genetics to a still higher plane, was yet to be carried out. The Achilles heel of early theories of evolution and genetics was the absence of clear ideas of the possibility of new hereditary characters emerging. De Vries saw them where they did not exist. Lotsy denied they were possible at all.

However, soon after Morgan's laboratory at Columbia University began experimenting with Drosophila, it became clear that new hereditary changes did appear. The indefatigable investigators obtained hundreds of mutations new hereditary changes. Here it was, the basic material for the evolutionary process.

It was not, however, as simple then as it appears now That mutations do occur it would have been absurd to dispute, but how to regard them and what role to attribute to them in evolution was quite another question



In England, for instance, there was an eminent zoologist and geneticis named William Bateson. We have already mentioned his name on several occasions. He did much to purge Darwinism of Lamarckian ideas, and to develop Mendelism. In short, Bateson was a famous geneticist. Having pondered a great deal over the nature of mutations he had a clever (although not quite original) idea. All hereditary changes can be reduced to the absence or presence of a particular character That may be explained as due to the presence or absence of the gene responsible for the formation of this character in the cells of the organism. So Bateson began to explain all cases of hereditary variation by the absence or presence of a particular gene. His theory was called accordingly 'the presence-absence theory' It had a kernel of the truth. Today we know for certain that hereditary characters are sometimes connected wit

the absence of genes, but Bateson asserted that it was always like that.

He upheld his theory vigorously and, as he had then already become famous and a great authority, many believed him. Bateson's theory was not original. Lotsy, who became an opponent of Darwinism, had already asserted that new hereditary characters were due to the elimination of genes. It was quite logical that Bateson, too, arrived at similar conclusions. Shortly before his death in 1926 he began to say that science had no evidence of evolution. He held that new species arose on Earth but maintained that this was only a matter of belief. We can witness changes of various kinds, he said, but not the origin of species.

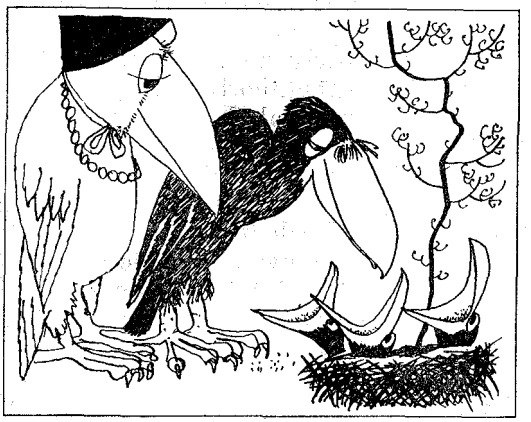
Had Darwinism reached an impasse? Not at all. There were Darwinists who were going about their business and looking with disapproval on attempts to apply the findings of the young study of genetics to the theory of evolution. Geneticists were also busy with their work, evolving the chromosome theory of heredity. The few attempts at flirtation between genetics and Darwinism that we have told you about were unsuccessful. Their 'engagement' had still a long time to wait.

The Fate of a White Crow

Hunting for a needle in a haystack is proverbially a hopeless task. But there are problems that are even more hopeless. Just try to find a drop of ink in the Atlantic Ocean, or even in a pail of water. Pour a drop of ink into the pail and try to take it back.

Hardly anyone would even try to find it in a glass of water because it would not be there. It will become diluted. As for needles in haystacks, they are difficult to find, of course, but at least they stay there until found. It is a matter of luck. You probably will not find it if you start looking for it, but if you should happen to sleep in that haystack, it is quite likely that the needle will prick you in the right side.

We are coming back to 'Jenkin's paradox'. Until it was solved Darwinism could not advance. Only genetics could provide the answer. That is where the 'engagement' should have started. Solution to this paradox rather than a hypothesis of 'absence-presence' could have been the basis for a 'love-match' between Darwinism and genetics.



There were people who began exactly there, but they were neither geneticists nor Darwinists. Just as the author of 'Jenkin's paradox' was not a biologist, so the man who solved it was also not one.

A white crow appeared among thousands of black ones. What is it—a drop in the ocean or a needle in a haystack? Of course, not a drop in the ocean. A white crow is a crow and will remain so until it dies. Whether or not it is difficult to spot among the thousands of black crows is neither here nor there. At least it will not dissolve. But what will happen after it dies? Not to the white crow itself, of course, but to its offspring whiteness is an inherited character, and a recessive one. A solitary white crow will mate with a black male and produce black fledglings. But they will only be black outwardly, because each of them, in addition to the dominant gene of black colour, will carry a latent mutation of white colour. What will happen to these genes in subsequent generations?

This is a question we must examine. And once more we are confronted with the dilemma—a drop of ink or a needle? In Darwin's and Jenkin's time heredity was looked upon as the 'mixing of blood', and a hereditary predisposition to whiteness would really be regarded as a drop in the ocean. And if that were so, it was a wonder that different species of animals and plants exist on Earth at all, and why, after all, we ourselves exist.

Mendel proved, however, that hereditary factors were

not drops of liquid, but behaved like indivisible particles. Now we call them genes. A gene for white colour can therefore be likened to a needle in a haystack rather than a drop in the ocean. So what? Frankly speaking, nothing at all. Even taking the concept of the corpuscular nature of heredity it is still hard to tell what importance individual accidental changes may have for evolution. The answer cannot be taken out of thin air. Exact calculation is needed for it.

The problem of the fate of hereditary changes in natural populations—communities of living organisms—evoked an interest among biologists soon after the rediscovery of Mendel's laws, in the early years of this century.

In 1904 the famous British mathematician, Karl Pearson, published in the *Transactions of the Philosophical Society* an article with an abstruse title referring to a generalized theory of alternative variability, in particular in relation to Mendel's laws. Its content was even more abstruse (for biologists, of course) because it was mainly mathematical. Few biologists took notice of it, and if they had, they would not have made head or tail of it. Yet it was worth understanding.

Four years later, another British mathematician, G. H. Hardy, printed a brief article 'Mendelian Proportions in a Mixed Population' in the American journal *Science*. It was written in simpler language and immediately attracted the attention of certain geneticists. This short article finally solved 'Jenkin's paradox' and solved it perfectly accurately for it was mathematical. What did Hardy do?

He discovered and proved the law of equilibrium in random crossing that is known as Hardy's law (or Hardy-Weinberg law of equilibrium) throughout the world. This law defines the conditions in which the proportion between homozygous and heterozygous types remains constant in conditions of random crossing. In terms of the progeny of a white and a black crow, it means that the genes for albinism will be retained indefinitely in a community of black crows, and that the numbers of carriers of latent white colour will remain constant.

Apart from that Hardy reiterated Pearson's conclusions. In the latter's work they were formulated so abstractly that things were difficult to grasp. Hardy expressed them in a more intelligible form. This second law, now called

Pearson's law, has a direct bearing on Hardy's law. It is the law of stabilized crossing. According to Pearson's law, in conditions of free crossing equilibrium is reached in a population immediately after the first crossing irrespective of the initial proportion between homozygous and heterozygous individuals.

The results reported by Pearson and Hardy appear a bit paradoxical, but they cannot be questioned. They are a direct mathematical extension of Mendel's laws. If the latter are valid, these laws too are valid. And the validity of Mendel's laws has been demonstrated.

Hardy did nothing more for biology. He examined a randomly mating 'ideal' population of infinite size in which mutations do not occur and which was not affected by natural selection. If he had taken them into account, then the process of evolution would have been explained from the standpoint of the laws of genetics. But Hardy could not do that, not only because he was not a biologist but also because genetics was still in its infancy. Indeed, the problem of the origin of mutations and their nature was still far from clear.

It had not become clearer by the mid-twenties. That mutations occur in all living organisms was no longer doubted by anyone. The experiments with Drosophila were enough to demonstrate it. Pure cultures of this fly had already yielded about four hundred mutations, each of which had been studied in detail, and the hereditary character of the change demonstrated. In most cases it had also been found with which chromosome and with which section of the chromosome a given mutation was linked.

Experiments had not solely been carried out on Drosophila. Mutations had been observed in all adequately studied species, whether experimental material particularly suited for observation or domestic animals and cultivated plants. Mutations were not only discovered, but new ones occurred. Yet the nature of the process remained a mystery. At that time it was commonly held among many biologists, including geneticists, that the appearance of mutations was the result of domestication or the influence of laboratory conditions. What was observed in the laboratory did not necessarily occur in the wild. It was an opinion very difficult to disprove, for in order to subject organisms to genetic

nalysis they had to be examined in he laboratory conditions about which keptics were so upset.

Assuming that we can show that nutations do exist in nature, how an we find evidence that they are nutations in the true sense of the vord, and not merely the result of recombination of pre-existing genes, s alleged by Lotsy?

But even if we prove that a natual hereditary change is not the prouct of recombination, that it is really ssociated with a change in a definite ocus of a definite chromosome, then we ıay be opposed by upholding of Baeson's 'absence-presence' theory. How re we to prove that it is a change f the gene rather than its destruc.on?

It was a difficult situation, of ourse. After the works of Pearson nd Hardy it became clear that furth- r development of the theory of volution required the conclusions nd findings of contemporary genetics) be examined from the standpoint f Darwinism. It would be wrong to ıy that no one developed Hardy's leas. Separate partial problems were solved, and methds of selecting domestic animals were worked out. But ıe broad generalizations so badly needed to advance Darinism were still to come.

The Great Synthesis

'How to relate evolution and genetics? How to introduce ur modern genetic views and concepts into the circle of leas embraced by this cardinal biological problem? Can we pproach the problems of variability, struggle for existen-e, and selection—in a word, Darwinism—not from the qui-e amorphous, diffuse, and vague opinions on heredity that revailed in the time of Darwin and his immediate succesors but from the firmly established laws of genetics?'

This was how one scientist formulated the riddle con fronting both geneticists and evolutionists. In fact, th problem was already clear to many by then, and it woul hardly have been worth citing in full if it had simply bee a matter of posing the problem. But the scientists wh wrote those words not only posed the problem but solve it, and did so in an extremely clear and convincing way

The article we have quoted from was printed in 192€ Its author was Sergei Chetverikov, one of the most interest ing Russian scientists of the century. He came from a ta lented family. His father was a pioneer of the breedin fine-fleece sheep in Russia. His brother, Nikolai, who i still living, is a prominent mathematician. His nephew Konstantin, is a well-known cameraman. The Chetverikov are close relatives of the Alexeyev family, the most famou of whom was K. S. Alexeyev, better known under the pseu donym of Konstantin Stanislavsky. And through the Ale xeyevs the Chetverikovs are related to the Koltsovs (w shall speak at length about Nikolai Koltsov in a later chap ter), and to the Alekhins (in particular with the brillian chess master Alexander Alekhine).

Sergei Chetverikov was a man of many parts. He bega his career in science as a zoologist. He was a great autho rity on butterflies and retained his love for them through out his life. When Russian scientists learned, after the en of the Civil War, about the success achieved by Morga and his associates in their experiments with Drosophila Chetverikov was one of the first to begin experimenting witl this remarkable material. And by 1921 he had organize a circle to study what had already been done on Drosophil and to discuss their own work. He was then working a the Institute of Experimental Biology in Moscow and th Zvenigorod biological station. In addition, he was givin an original course on experimental systematics at Moscov University, acquainting students, among other things, witl the foundations of genetics and biometrics. It is no exagge ration to say that all Soviet Drosophila geneticists wer in some way or another pupils of Chetverikov.

When Chetverikov wrote the remarkable article 'On Cer tain Features of the Evolutionary Process from the Poin of View of Modern Genetics' that made his name famous he was already an experienced researcher. His article appea red in two issues of the Russian *Journal of Experimenta*

Biology in 1926 when he was 46. A year later he reporte its basic tenets to the 5th International Genetic Congres in Berlin. Chetverikov's report was one of the two sensa tions of that congress (of the second we shall speak a littl later). His paper was given a long ovation. Indeed, geneti cists heard what they had been dreaming of for years. Th British scientist Holden rushed to the rostrum, hugged th speaker awkwardly and kissed him on both cheeks. He wa followed by H. J. Muller, one of the Morgan group and Ro nald Fisher, the founder of modern biometrics.

In his article Chetverikov had dealt with three prin cipal problems: the appearance of mutations in natural con ditions; the fate of mutations in conditions of random cross ing; and the significance of selection in those conditions

The problem of mutations was still a difficult one. N one had studied them in natural conditions, or was abl to induce them artificially. Having analysed the availabl data, Chetverikov drew the firm conclusion that mutation occurred naturally in the wild, and that these were true mu tations rather than Bateson's 'absence' phenomena. Artifi cial alteration of genes was possible, he asserted, and wa a task for the immediate future.

By the time Chetverikov delivered his paper in Berli both these contentions had been confirmed. His co-worker and disciples had embarked on broad genetic investigatio of natural Drosophila populations, which had yielded it first results by the time of the Congress. As for the artificia induction of mutations, at that same Congress Muller repor ted that he had produced a large number of mutations i Drosophila by means of X-rays.

Hardy examined the conditions of genetic balance in a natural population without mutations and natural selec tion. Chetverikov developed his theory considerably b taking account of both these factors—the appearance o mutations and natural selection. What conclusions did h reach? In his article all the arguments were based on exac mathematical calculations. For us it will be enough to ex plain them by examples.

Let us return to our white crows. Imagine that the popula tion of crows inhabiting a whole continent consists of a million of randomly mating individuals and that one of them has a latent gene of albinism (heterozygous condition) From generation to generation such a crow will mate with

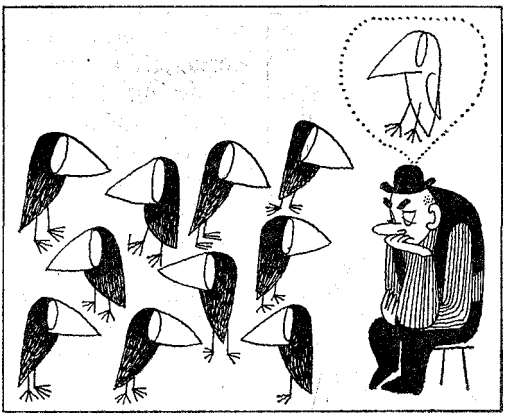
a black crow, and produce offspring carrying the rare character in the latent form. According to Hardy's law this concentration is one in a million, and will be maintained indefinitely.

But now another white mutation has appeared among the crows, also in the heterozygous condition so that it is latent. If the new mutation meets the carrier of the same gene, a quarter of their offspring will be real albinos. What is the probability of this event? It is easy to calculate that it is equal to one in a million, which means that it is practically impossible.

Now let us imagine that the same situation prevails not in a population of a million but in a population of ten crows that for some reason have become separated from the other members of their species. Here the probability of a union of two carriers of the recessive gene is only one in ten, which is fairly high. The birth of an albino in such a population is a quite probable event, and within a few generations a white crow is sure to appear in so small a community. But in a large population, too—if we have in mind a real population and not Hardy's ideal one—mutations can and must play an essential role.

The appearance of a new mutation of one gene is extremely rare. Let us assume that a definite gene mutates in one generation only in one individual in a million (in fact, they occur much more frequently than that, but let us deliberately take these understated figures to see what will come of them). Since mutations are not 'diluted' but continue to exist, the concentration of a given mutation will increase continually in the course of time. Moreover, as every species has thousands of different genes, one in a million multiplied a thousand times becomes one in a thousand.

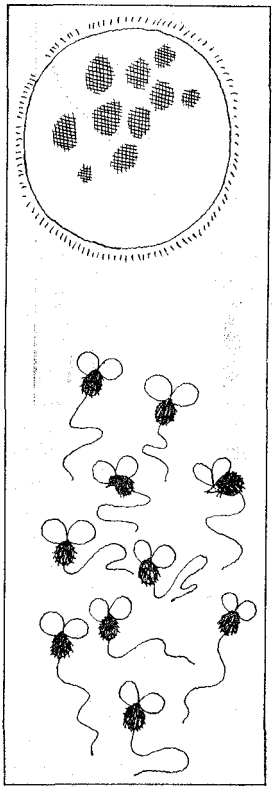
A species does not exist for a year or two, its lifetime is measured in geological periods. Hence it follows that all the species existing in the wild must literally teem with the most varied mutations, predominantly in a latent state. The longer a species has existed and the greater its numbers on our planet, the greater the number of mutations it will contain. It follows that there is plenty of material for evolution even if we assume that mutations occur much less frequently than they actually do. But what factors can change the genetic composition of a natural population? Several are known.



The first of them is the mutation process, not mut tions as such but the mutation process. The stabilizir force of random crossing is tremendous. According to P arson's law, the equilibrium is achieved immediately aft the first crossing. But in every generation new mutatio arise, crossing takes place that creates a new equilibriun and is followed by new mutations. In that way, through continuous process of mutation the state of equilibrium continually being altered.

A second factor is isolation. The smaller the size of population the more likely are hidden changes to becon manifest. The best known and demonstrative example provided by the populations of islands. In every archip lago, and on almost every individual island, there a species not to be met anywhere else on our planet. That ha already been noticed by Darwin during his voyage on tl *Beagle*, and the observation played a great role in the fo mation of his views. But isolation is not necessarily ter torial. It has long been known, for instance, that the comm herring inhabiting one and the same area form several c lonies that spawn in different places and at different time Therefore, in practice, they do not cross. Surveys have sho the characters of the colonies to be rather different. Isol tion may also be associated with different feeding habi or genetic traits interfering with cross-breeding.

A third factor bears the beautiful name of a 'life wav (or population wave). Isolation leads to reduction of tl



size of a population by dividing it into several parts. But the size of a population can also change without its being divided, which will have equal importance for evolution. Population waves are an extremely common phenomenon, particularly among all seasonal animals. How many of the flies that pester us in the autumn survive the winter? Rougly one in a million. That is the variation in the size of a fly population. The change in the seasons affects all species of animals and plants to some extent or other, and not only of flies.

Population waves are not just seasonal. Mouse populations, for instance, are known to vary within very wide limits; what are known as 'mouse years' occur when mice appear in fantastic numbers. What causes it? Scientists have noted that 'mouse years' occur at regular intervals and coincide with a marked increase in the number of sunspots. Interesting, isn't it?

What can sunspots have in common with the number of mice? Nothing at all, as it has been found. The solar cycle lasts about eleven years, the mouse cycle about ten. When this seeming connection was noticed, the 'peak' figures happened to coincide. But when data were collected over a longer period it turned out that there was no connection between them.

But sometimes the causes of such long population waves are clear enough. American scientists have noted that the lynx population of Canada varies widely. In some years it may be roughly ten times that of other years. What happens? It proved easy to explain. The Hudson Bay Company had been keeping exact records of the skins supplied by fur traders for over a century. When scientists obtained access to these records they found that 'lynx years' coincided exactly with 'hare' or 'rabbit' years. Everything became clear.

Snow-shoe rabbits are not sunspots but very real meat, food without which lynxes cannot survive and multiply.

But what is the cause of 'hare years'? That is a different problem. It is not excluded, of course, that 'hare years' depend on 'lynx years'. If lynxes are few, hares are plentiful; if lynxes multiply in large numbers, the hare population drops, and when hares are few, lynxes begin to die out. It looks a bit like a vicious circle. To use modern cybernetic terminology, we have a feed-back connection here.

Turning back to 'mouse years' we can say that an abundance of mice coincides not so much with the number of sunspots as with the numbers of predatory birds (and it is for that reason that we should protect rather than destroy feathered predators, our chief allies in fighting rodents).

And, finally, there is a fourth factor, selection. Its force is very great. Suffice it to recall just how many seeds are produced by every plant, how many eggs are deposited by insects, and how much roe is spawned by fish. But how many of their myriad offspring survive to reproductive age? A tiny fraction. But we do not need to say much about selection here because this factor is the clearest and the best known. It is also the most important.

What else? Nothing for the time being. Only four evolutionary factors are so far known to scientists: the mutation process, isolation, population waves, and selection. Their significance is far from identical. All are effective in changing the genetic composition of natural populations of living organisms. That is what they have in common; but the mutation process provides, in addition, elementary material for hereditary variations. Without these variations the evolutionary factors would be powerless.

All four factors alter the genetic composition of populations, but the mutation process, isolation, and life waves are nondirected factors changing the composition of a population in a quite random way. In contrast, selection works in a strictly definite direction, namely, the one that corresponds best to the environmental conditions.

All that is a summary of what was in Sergei Chetverikov's article published in 1926.

A New Lease of Life

Chetverikov's work gave biologists what they had been looking for for years—the basis for translating Darwinism

into the language of genetics. But that was not all it did. Previously the theory of evolution had been purely descriptive. Now it also became an experimental science.

Darwinism is the rare case of a scientific theory immediately accorded wide recognition. Shortly after the publication of the *Origin of Species* there was an upsurge of activity in all the fields that could contribute to the development of the new theory. But decades passed and the trends that started in Darwin's time were beginning to ebb. Darwinism was alive and had developed, but its rate of advance was becoming slower and slower.

After Chetverikov's work the dam literally burst. Scores of scientists everywhere strove to utilize the broad opportunities opened up. Darwinism was given a new lease of life. Unfortunately, I have to skip over this interesting subject. Forty years have passed since his article was published, forty years of intensive uninterrupted work. The development of Darwinism during those years would fill a huge volume, but it has yet to be written (of course, I leave out of account the treatises and monographs intended for specialists—there are many of them). I have still to tell you about radiation genetics, the chemical basis of heredity, and the genetic code.

But first allow me to say something about Chetverikov's paper in Berlin. It was a sensation only for the foreign scientists. Soviet scientists were informed about the work, while his pupils had known about it even before the paper was written, let alone published, for its main points had been widely discussed among Chetverikov's friends and sympathizers.

When the outlines of such fascinating views of the links between genetics and evolution began to transpire, it became a problem of verifying them. So Chetverikov's coworkers set about investigating the genetic composition of natural populations. This work was pioneered by a young man Boris Astaurov, now a member of the USSR Academy of Sciences and head of a major school of Soviet geneticists. In collaboration with other researchers he examined a large Drosophila population in Zvenigorod. About the same time colleagues of Chetverikov who were working abroad carried out a similar survey in Berlin. Other young scientists, subsequently famous geneticists, went to the North Caucasus to investigate these laws in other conditions. Their findings proved most interesting.

All the investigations fully confirmed what expectations had conjectured. Natural populations that outwardly appeared very uniform were found to be inwardly very heterogeneous, containing a multitude of mutations in a latent, heterozygous state. In addition, a number of new, interesting, and rather unexpected phenomena were discovered.

For instance, Astaurov discovered lines in one species of Drosophila completely without males. They propagated by mating with the males of other lines and invariably produced offspring consisting exclusively of females. It was not until recently that the nature of this interesting phenomenon was cleared up. It was found that the absence of males was due to an infection transmitted from generation to generation through the protoplasm of egg-cells. But the nature of the infection—whether it is a virus or rickettsia—is still obscure.

Discoveries were made not only in the field but also in laboratories, during microscopy. Sofia Frolova, for example, studied the chromosomes of many species of Drosophila from various localities. One of the most commonest species *Drosophila obscura* occurs in Europe and America. The chromosomes of the European and American types differed greatly; in spite of their outward similarity they turned out to be quite different species. So the American type was given a new scientific name *Drosophila pseudoobscura.*

Now we have come to the saddest part of the story. In 1929 Sergei Chetverikov left Moscow and abandoned the research in population genetics so brilliantly begun. For several years he was professor of genetics at Gorky. Toward the end of his life he became totally blind. But he was not forgotten. Many geneticists travelled specially to Gorky to visit him, and not only his old friends, but students who had learned somehow that the famous Chetverikov was still alive. And to one of them, in the last year of his life (he died on 5 July 1959) Chetverikov dictated a supplement to his article of 1926.

Chetverikov's departure from Moscow inevitably disrupted the joint work in the genetics of natural populations. Some of his students also changed their jobs or took up the study of other problems, but the research initiated by his group was successfully continued and developed.

In the thirties Nikolai Dubinin became the acknowledged

leader of Soviet population genetics. The big team of researchers working under him was not simply engaged in purely genetic analysis. Dubinin turned to account the exceptional advantages offered by the giant chromosomes of Drosophila salivary glands. The research carried out in his laboratory showed that the heterogeneity of natural populations was related not only to individual genes but also to the structure of the chromosomes. Almost every natural population was found to contain a definite percentage of individuals with modified chromosomes, and these altered chromosomes prevented crossing with normal flies, part of the offspring proving non-viable. This is one of the ways new species are formed.

Dubinin's work on population genetics was exceptionally comprehensive. Expeditions of geneticists travelled far and wide over the Soviet Union. The same populations were examined repeatedly over a number of years, which made it possible to draw far-reaching conclusions. Soviet population geneticists forged far ahead of their colleagues in other countries.

When this brilliant work, however, was at its peak, it was suppressed. We all remember that period when a group of people established a monopoly in Soviet biology, and began to prove the correctness of their views not by exact experiments and fine analysis, but by crude administrative measures. Their monopolizing caused untold harm to Soviet genetics, and not only to genetics. This was how research in population genetics came to be stopped; and to this day they have not been resumed on an adequate scale.

For several years Dubinin was deprived of opportunities to carry on with genetics, and when he resumed them there were many other urgent problems like radiation genetics, and space genetics. He was at the head of the largest group of Soviet geneticists and had to attend to everything.

Shortly before he was awarded the Lenin Prize I visited Academician Dubinin in his laboratory. A post-graduate student was reporting on his work. It was about population genetics. So that field is being revived.

Experimental study of evolution based on genetics is not limited, of course, to examining natural Drosophila populations. Natural communities of other species of animal and plant are also widely studied, and various methods of modelling are employed. Artificial laboratory popula-

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tions are cultivated in test-tubes or in special containers. In that way any initial population can be evolved and investigated in far greater detail. The method is indispensable, for instance, for clarifying the relative viability of various species and mutations. In recent years genetic populations have been modelled by means of electronic computers. These are only a few of the many different approaches. I shall describe only one of them in detail, one that undoubtedly has a great future, that is the further unification of the biological sciences on an even broader scale.

So far we have been talking about studying associations of living creatures on the joint standpoint of Darwinism and genetics. But a species does not exist of and by itself, but co-exists with other species of plants and animals. Nor is that all. None of these species lives in a vacuum. They all breathe and assimilate, and it is by no means unimportant what the climate is like in a locality, the atmosphere, soil, underlying rocks, and so on. Population genetics, biocoenology (the theory of communities of living organisms), Vernadsky's theory of the biosphere, biogeochemistry, and soil science together make a most intricate complex taking into account all the links of the organism with the living and inanimate component of an association. The foundations of this super-science were laid in his time by Vladimir Sukachev, member of the USSR Academy of Sciences. The problem is extremely complicated. Are we measuring up to it? We definitely are. Today we have at our disposal computers capable of doing things that are beyond man's unaided powers. Moreover, it is possible to investigate simpler artificial associations that lend themselves fairly easily to analysis. But all this is a completely different subject.

It is impossible even to list the main trends in modern population genetics. People are working on it in every corner of the globe, and it is all an extension of that rejuvenation of Darwinism inaugurated by Chetverikov's work.

In 1959 the civilized world celebrated the centenary of Darwin's *The Origin of Species*. The Academy of Sciences of the German Democratic Republic awarded memorial medals to scientists who had contributed most to the development of Darwinism. One of the small band so honoured was Sergei Chetverikov. But he did not live to receive the award; the presentation took place a few days after his death.

The aim of science is not simply to satisfy man's curiosity. Any scientific discovery sooner or later yields practical results. The practical importance of the union of genetics and the theory of evolution is apparent. Natural selection creates natural species and varieties; the selectionist evolves new breeds and varieties. The development of breeds of domestic animals gave Darwin rich material for substantiating his theory of the origin of species by means of natural selection. Today the alliance of his theory with genetics has opened new paths for selectionists.

Selectionists used to experiment at random. After the work described in this chapter two new ways of obtaining new varieties and breeds were opened up. I do not mean the importance of Mendelism for practical hybridization, for it was put to use much earlier. The two new methods were utilization of the riches bestowed by nature and artificially induced mutations.

Of singular importance for selection are the works of Nikolai Vavilov. In the early twenties he formulated the 'law of homologous lines'. This law, discovered before Chetverikov's work, is in effect closely connected with it. It is concerned with the peculiarities of hereditary variations. Its essence is that closely related species yield 'parallel lines' of hereditarily modified forms. Guided by this law one can confidently search for what it is possible to find and avoid futile efforts. For instance, if a species of wheat

as a gene of resistance to a certain disease this gene is almost sure to be found in other closely related species. But one would try in vain to obtain a blue-eyed mutation in Drosophila in spite of its numerous 'eye-colour' genes, for no species producing a blue eye pigment is known in natural populations.

An example of selection based on Vavilov's law is the development of sweet lupine. White lupine is a valuable fodder crop yielding record harvests, but it contains lupinine, a bitter, quite toxic substance, and because of that it cannot be used straight, and has to be mixed with some other crop, even for silage. Geneticists, however, knew that all leguminous crops had sweet varieties. One could be sure that there would be at least one plant in a large field with the desired property. In fact it was more a matter of chemistry than of genetics. When a method had been devised for quick determination of lupinine the required mutations were found.

The Earth is inhabited by around three million species of living organisms. Very few of them are cultivated; most of the cultivated plants and domestic animals have come down to us from prehistoric man. He took what caught his eye. The problem facing the selectionist today is to make full use of our natural wealth. Vavilov did something unprecedented. He travelled all over the world in search of relatives of our cultivated plants. He discovered the centres from where cultivated plants originated and collected an immense treasure of material for further selection work.

The work of developing this wealth, alas, ended just as it was beginning. In 1942 Vavilov died. His work is now being resumed by his followers. Several years ago when *Heredity*, the international journal of genetics, was founded in Great Britain, its modest red cover was framed with the names of the scientists who had made the greatest contribution to genetics, about a dozen names in all. Among them, along with that of Darwin, was Vavilov's.

The second road to evolving new varieties and breeds is artificial enhancement of hereditary variations, the inducing of mutations which will be the subject of our next chapter.

Genes Under Fire

A Fortress Surrenders

A very hard task was imposed on Ivan Tsarevich in Zhukovsky's fairy-tale. If it had not been for Grey Wolf, Baba Yaga the witch, and the Talking Pike, he would not have been able to marry Elena the Beautiful. The most difficult labour was to kill Kashchei (who was immortal). Let us recall the instructions that Baba Yaga gave Ivan:

> '... Far away in the ocean on the great island Buyan,
> 'There grows an old oak;
> 'Beneath that oak a coffer bound in iron is buried;
> 'Within the coffer lies a furry hare;
> 'And in the hare a grey duck sits;
> 'Within the duck there is an egg,
> 'And in the egg the death of Kashchei...
> 'Take the straight road to Kashchei the Immortal;
> 'In a trice he will breathe his last
> 'As soon as you break the egg over him.'

The task facing geneticists, of producing hereditary changes in genes, is very much like that. Nature has hidden the genes away no less safely than Tsar Kashchei hid his death. There is a full set of genes in every cell of the organism, but in order to induce changes that can be transmitted to descendants, the genes in the egg (or correspondingly in the male sex cells) must be changes. The sex cells are hidden deep within the body to protect them from exposure to the action of external factors. The sex cells contain nuclei, the nuclei chromosomes, the chromosomes the genes we must get at.

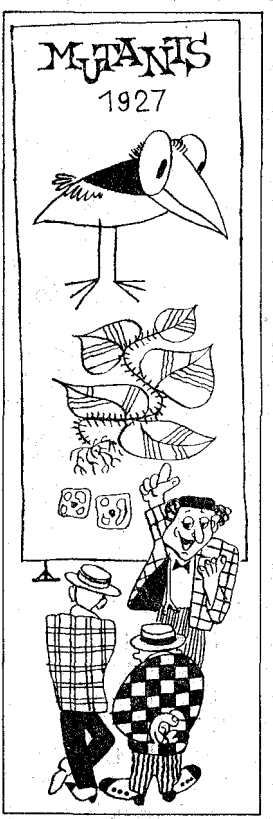
So it is not fortuitous that the numerous attempts at producing mutations artificially proved unsuccessful for a long time. Many influences do not reach the genes of the sex cells or only reach them in a greatly modified form.

It was not until 1927 that geneticists heard of successful experiments in artificial induction of mutations. They were reported to the 5th International Genetics Congress by the famous American geneticist, H. Muller, who was later awar-

ded the Nobel Prize. He had been able to produce a large number of mutations in Drosophila by means of X-rays. The dream of geneticists came true at last.

Discoveries are often made simultaneously. About the time Muller's work was published his fellow-countryman L. J. Stadler produced artificial mutations in barley and maize which he reported in 1928. He had experimented independently of Muller, also using X-rays.

Two years before Muller's experiments, however, mutations had been induced artificially by two Leningrad scientists—Georgy Nadson and his young associate Grigory Filippov, working at the Institute of Rontgenology and Radiology. They had obtained mutations through the action of radioactive substances, experimenting with yeast. Their first article on their experiments was published in the transactions of the Institute in 1925. They then published their findings in a French journal.



Thus, in the first experiments, mutations were produced in animals, in plants, and in micro-organisms. In all three instances the mutations were caused by irradiation. From that time a new science—radiation genetics—began to develop by leaps and bounds.

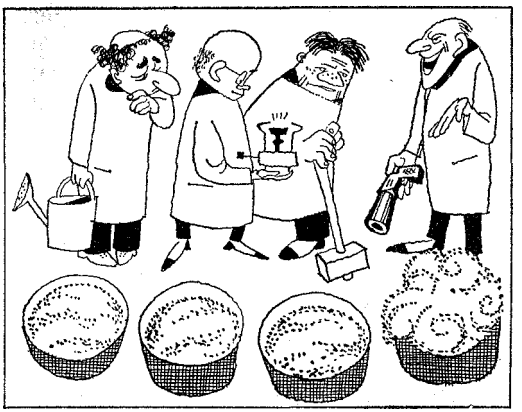
The origin of radiation genetics is usually associated with the names of Muller and Stadler, and primarily with that of Muller, though it is not quite just. The work of Nadson and Filippov was not a matter of chance observations to which the authors themselves, as has often happened, attach no significance; on the contrary, they carried out their experiments quite deliberately. They were working at an Institute of Roentgenology and fully appreciated the probable significance of their discovery. In their first publication they wrote, even in the title of their historic article, of the possible practical uses of radiation

mutants. Their first work was followed by a series of other in which they systematically induced mutations in ev new types of yeast. What was the matter then?

In May 1965 a symposium was held at the State Resear Institute of Roentgenology and Radiology on the occasi of the 40th anniversary of the discovery at the Institu of the mutagenic effect of radiation. In front of me as write is the invitation card bearing a picture of Filippov intelligent and pleasant face, a typically Russian fac with neatly combed hair and a sad smile. His fingers ho a cigarette, for he was an inveterate smoker. Below tl picture is a brief inscription: Filippov Grigory Semenovic 1898-1933. He died of tuberculosis at the age of 35. (Nadson outlived him only a short while.

That, of course, is one of the reasons why their wor in spite of their indisputable priority, played no apprec able role in the development of radiation genetics. But was not the only reason. The fact that the work of Nadsc and Filippov was published in Russian (which was muc less widely read then than now by scientists in other cou tries) in a publication with a small circulation also had a important bearing. And there was still another circumstan of no small importance. Muller and Stadler published the experiments more or less simultaneously in the same jou nal, yet Muller is the more frequently recalled. Why is tha so?

A major role was played here by the material of tl experiments. Muller experimented with Drosophila, the the favourite genetic subject. Its characteristics had bee studied in the minutest detail. Numerous pure lines (Drosophila had been bred in all laboratories. Scientis had learned to determine with the greatest of ease the mo delicate changes in its characters. It is no wonder, ther fore, that the chromosome theory of heredity was evolve primarily from experiments on Drosophila, and that th birth of radiation genetics was also linked mainly with i So it was that the majority of the classical works on radia tion genetics were very closely associated with Muller first experiments rather than with those of Stadler, to sa nothing of Nadson and Filippov. As to yeast—the objec on which the Leningrad scientists experimented—its ge netics is complicated and difficult to fathom and even toda there is much about it that is still unclear.



Nadson was a great authority on yeast, and experiments on producing mutations in yeasts are still based on his methods. Forty years ago, however, hardly anyone was competent to continue the experiments with yeasts as successfully as they had been started by Nadson and his gifted disciple Filippov.

As we have seen, attempts had been made to produce hereditary changes (or to prove that they are impossible) continuously ever since Weismann's experiments at the close of the century. Temperature, humidity, mechanical factors, and many other things were used for the purpose, but all attempts, however, proved unsuccessful. And when, in the mid-twenties, three laboratories finally managed to produce artificial mutations, all did so by using irradiation.

To understand why it was radiation that proved a mutagenic factor, we shall have to turn from biology to physics.

Many types of radiation are known to physicists but not many of them are capable of causing hereditary changes. Visible light, thermal radiation, and radiowaves do not produce mutations. The radiation emitted by the radioactive substances used by Nadson and Filippov and the X-rays used by the American scientists are classed together with certain other types in a single group of ionizing radiation. The feature they have in common is their capacity to ionize any substance they pass through (hence their name).

And one can see with one's own eyes, if not the ionizing radiation itself, at least the effect it produces.

Any modern physics laboratory working on problems of nuclear physics or cosmic rays has an instrument known after its inventor as a Wilson cloud chamber. Its principle is simple enough. It is a chamber filled with supersaturated water vapour, the volume of which can be changed, quickly causing the vapour to condense. An ionized particle passing through the chamber leaves a thin misty trail of minute droplets of water along its path.

Ionization can be discovered even more easily by means of an electroscope, a vessel containing two strips or leaves of thin foil suspended from a metal rod. When the rod is touched with an electrically charged object the leaves diverge. When a radioactive source is placed near the rod, the leaves quickly come together, because ionization is nothing else than electrical charging of the atoms of a substance. The trail in a Wilson cloud chamber is produced by droplets of water collecting on charged particles of vapour. The leaves of an electroscope fall because ionized air conducts current.

How do atoms become charged? You know, of course, that an atom consists of a positively charged nucleus with negatively charged electrons orbiting it. The number of electrons corresponds to the nucleus charge, so that, on the whole, an atom is electrically neutral. For it to become charged, its charges must be separated, that is an electron must be torn off. Then two ions will be formed, an atom lacking one electron, and therefore positively charged, and a negatively charged electron.

As you can easily imagine, much energy is needed for tearing an electron off an atom, so that not every type of radiation can produce ionization. When rays of visible light, and even of the more 'powerful' active ultra-violet light, are absorbed by particles of matter, they temporarily put them in a 'state of excitation'; an electron moves a little away from the nucleus and then returns to its normal orbit.

Ionizing radiation is of the same nature as visible light, ultra-violet and infra-red light, and radiowaves. All of them are electromagnetic emissions. But ionizing radiation differs from the others in having a much higher energy. The distinction is most important, because it is that which

makes this radiation capable of ionizing matter. An ionized state is very unstable. An ionized atom tends to enter into some chemical reaction as soon as possible. Therefore, ionizing radiation is capable of causing chemical changes in a substance. In addition, because of its high energy, this radiation can penetrate any obstacle, and for that reason it is used in medicine and technology for 'seeing through' things. No material fully impervious to these rays is known. At best a substance only weakens their flux. The air is almost fully transparent to them, glass and wood a little less so, and lead most of all. But no layer of lead is thick enough (at least theoretically) to absorb ionizing radiation completely; therefore, estimates of protection against radiation imply its reduction to a safe level rather than its complete blocking.

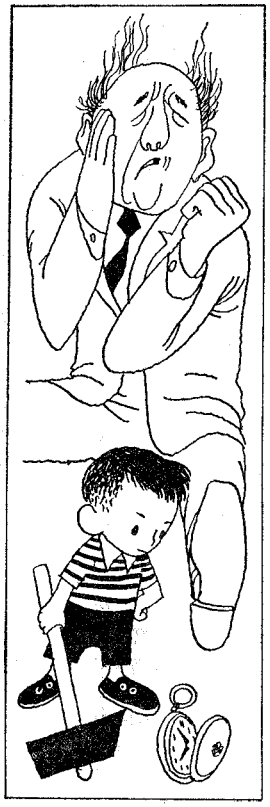
Now let us return to genetics. In order to produce a mutation a gene must evidently be changed. It was not then known what a gene was, yet it was quite clear that it could not be anything else than a chemical substance. Could a gene be affected chemically? It was not that simple. Nature had reliably protected heredity against accidental influences. A chemical could not reach the mysterious genes without undergoing changes on the way and reacting with something much closer. And then what substance was to be used if it was not known what a gene was made of?

Ionizing radiation proved to be just what was needed. The rays penetrate any obstacle, can reach any atom, and can change any substance chemically.

It is probable that the discoveries of its mutagenic effect reasoned exactly like that; and as we have seen, their conjectures proved correct. When, after a long siege, the gene fortress was bombarded with ionizing radiation, it finally surrendered.

In all the experiments many new stable hereditary mutations were obtained. Nadson and Filippov raised colonies differing in size, shape, and colour; and the biochemical properties of the yeast cells were altered. Stadler evolved plants differing in height, colour, and shape of leaves. Muller bred flies with darker or paler body colours, varied eye colours, a different arrangement of hairs on the body, twisted wings, or no wings at all.

Other scientists set about producing mutations in other organisms, with invariable success; and what was most im-



portant, the new characters we transmitted to the offspring.

The overwhelming majority of t mutations were of a negative chara ter: they lowered the viability a even caused the death of organism In Muller's experiments 'recessi lethals' were produced most freque ly; the term denotes mutations th do not affect the viability of t carrier in a heterozygous conditio but in a homozygous state cause i death, usually in the embryo stage. other words, if such a mutation present in only one chromosome, exerts little or no harmful effect, b if it is present in both homologo (identical) chromosomes, its effect quite manifest. The fact that the mutations were discovered in Mulle experiments was due to the way t experiments were carried out, whi enabled them to be determined. In t early experiments with other obje these mutations were overlooked purely technical reasons.

When an organism is irradiated, t overwhelming majority of mutatio are lethal, causing the death of th carriers. Lethals may be dominant as well as recessive, a cause death even when only one of them is present in the ce The overwhelming majority of viable mutations also pro harmful, reducing the viability of the organism to o degree or another. Only very few mutations 'improve' organism.

This is not to be wondered at, for all the organisms i habiting our planet are the product of long selection a adaptation to the environment. It is perfectly clear th accidental changes in a system as complex as a living orga ism will most probably cause it irreparable harm. It rather like asking a child, or an adult for that matter, repair a watch. The watch will most likely be worse his efforts.

Insidious Rays

The capacity of radiation to cause hereditary changes was discovered by Nadson and Filippov in 1925, but its effects on living organisms had been known much earlier.

Ionizing radiation was discovered at the end of last century. The German physicist Wilhelm Conrad Roentgen discovered invisible rays in 1895, which he called X-rays, but which are often called roentgen rays after him. In 1896 the French physicist Henri Becquerel discovered natural radioactivity. The newly discovered rays attracted universal attention, and many scientists began to use them for a variety of purposes. It is not surprising, therefore, that their biological effects were also soon discovered.

The first publication on the biological effect of X-rays was apparently the article 'Experiment with the Effect of Roentgen's X-rays on the Animal Organism' published by Ivan Tarkhanov, member of the Russian Academy in the bulletin of the St. Petersburg Biological Laboratory in 1896, only a few months after Roentgen first communicated his discovery to the scientific world. Tarkhanov had observed changes in certain physiological reactions in irradiated frogs. Shortly afterward scientists in other countries—Schober, Atkinson, Lopriore—described their experiments.

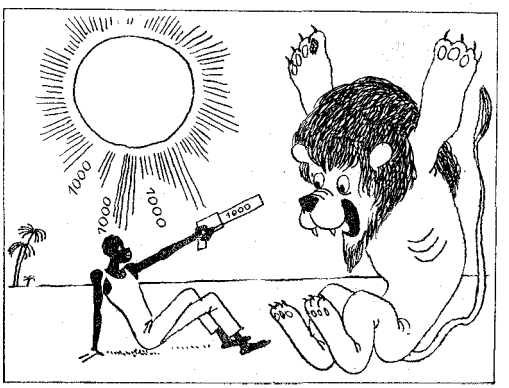
The biological effects of X-rays, however, soon came to light independently of the biologists' experiments. All the scientists who had been working with them, or had handled radioactive materials, developed skin lesions. They had felt nothing during exposure to the radiation but after a while a redness followed by persistent ulcers appeared. The 'insidious' action of the new rays proved even worse. In time more serious diseases developed, which sooner or later proved fatal for the investigators.

Almost all the pioneers of X-ray and radioactive substances became martyrs of science. In 1936 an obelisk commemorating the scientists and doctors who had died from studying X-rays was unveiled in Hamburg. They then numbered 110. Today there are many more.

The biological effects of radiation faced scientists with a difficult problem: why does it cause severe damage? To people today there is nothing surprising about it; the word 'radiation' is linked in our minds with the atom bomb,

e tragedy of Hiroshima, and megaton nuclear explosion;
hat is there strange about such tremendous energy can
ıg such great damage, you may ask. But you would b
istaken, for a considerable biological effect, even death
n be caused by an insignificant dose of radiation. Ther
nothing mysterious, of course, about the lethal effect o
diation near the epicentre of an atomic bomb explosion
ıt it is worth thinking a little about its lethal action do
ns of miles away. Let us do some simple calculation
Radiation is measured in units called roentgens. Th
periments carried out by many scientists all indicat
at the lethal dose of radiation for all species of mamma
several hundred roentgens. No mammal, without specia
eatment, can survive a dose of 1,000 roentgens and ma
no exception.

How large is a dose of several hundred roentgens? B
self it tells us nothing. To get a clearer idea of this amoun
energy, we must express it in other, more familiar, unit
Physicists know of various kinds of energy, each measu
d in its own units, e.g. heat in calories, electricity i
lowatt-hours. But all the kinds of energy can be conve
l into one another. Heat can be converted into electricity
ınd electricity into heat. And it is well-known how man
kilowatt-hours are equivalent to one calorie. The energ
of ionizing radiation can also be converted into other kind
of energy. Let us calculate what can be done with the energ
ıbsorbed by a human body exposed to an absolutely leth
dose (1,000 roentgens), if it is converted without loss in
heat or electricity. If it were used to heat a glass of wate



it would raise the temperature of the water by only one degree Centigrade. If it were converted into electric current feeding a 25-watt bulb, it would last only half a minute. Finally, if this energy were used to sustain life processes (living organisms are constantly expending energy), it would only last for six seconds.

We must stress that that applies only to ionizing radiation. Similar doses of other kinds of radiation are perfectly harmless. A sun-bather on a beach is also exposed to radiation. He will get a dose equivalent to 1,000 roentgens—but in the form of other radiation like light, heat, and ultra-violet rays—within two seconds. But people lie in the sun for hours.

These simple calculations make it clear that a lethal radiation dose is not necessarily a great amount of energy. Clearly the lethal effect of ionizing radiation is due to something specific. What do we know about it? The biological effects of ionizing radiation were discovered early, but it took a long time to ascertain their mechanism. There was no lack of theories, of course, from the very beginning, but as they all proved incorrect we shall pass them over. The first plausible theory was put forward at the beginning of the twenties. It too proved erroneous, but it contained a rational kernel that has been preserved in modern views.

Atomic Firing Range

Most biologists and doctors usually do not have sufficient knowledge of physics and mathematics. Fifty or sixty years ago the position was even worse. Ionizing radiation, however, is a physical factor whose effect on the organism cannot be seriously discussed without knowledge of physics. Many people have tried to theorize about it ignoring physics and invariably nothing good has come of it.

But in Frankfurt-on-Main there was a man who knew both medicine and biology, and physics. His name was Friedrich Dessauer. He was a very energetic man. Although his face and hands were covered with the scars left by numerous operations for radiation lesions, he never abandoned his research or practical work. He was a pioneer of roentgenology, and his name is inscribed on the obelisk in Hamburg.

Dessauer was well-versed in physics. He knew that X-rays gave up energy to a substance in the form of individual,

fairly large doses of ionization. Moreover, he was awar that the energy received by living organisms exposed t lethal doses was infinitesimal. None of these was know to his predecessors who were ignorant of physics and dis liked mathematics, or did not think them important.

As a physicist Dessauer knew that all energy is ultima tely converted into heat. It came to him that althoug the mean temperature of converted radiation energy i not great, it may be very high at individual points, fo radiation gives off energy in separate portions concentrate at definite points; and at these points temperature rise very steeply. Dessauer developed a point heat theory accord ing to which radiation heated individual points to a ver high temperature, causing coagulation of proteins whic culminated in biological damage.

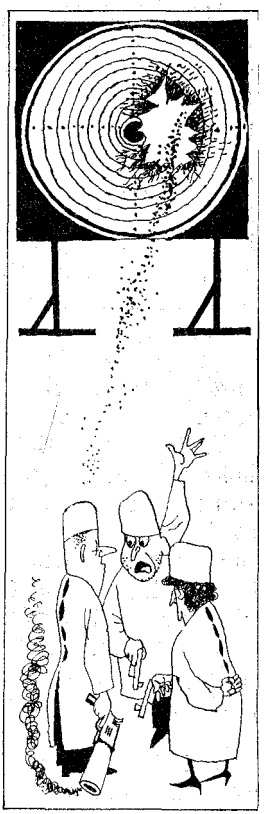
His theory, as we have already said, turned out to b wrong. It is not simply a matter of point heating. Eve if coagulation of protein actually occurred at individua points, it would not cause much damage because the pro portion of damaged molecules would be too small to produc substantial biological consequences. In addition, his phy sical calculations were not quite right, for he failed to tak account of the rate of energy dispersion. For that reaso Dessauer's theory of heat points now has only historica interest.

Nevertheless, his idea of the role of irregularities in th distribution of energy in matter proved very fruitful. In deed, the biological effects of radiation cannot be explaine by references to averages alone, ignoring its energy distri bution points, for as we know, its total energy is infini tesimal.

Dessauer's theory was discarded, but left us with wha may be called 'hit principle'. Radiant energy is absorbe by matter in the form of fairly large separate portions o 'hits'. In other words, some microscopic points receiv large portions of energy, while others may receive nothin at all. The hit principle is not a hypothesis or a theory in vented by biophysicists but a firmly established physica fact.

But of itself the fact of the irregular distribution c energy explains nothing. To understand the biological eff ects of radiation additional suppositions had to be made Inventive scientists were not slow in doing so. They pu

orward the target theory. Where there s a hit, of course, there must be a arget. If a man is hit by a bullet, it nakes a great deal of difference wheth- r it hits his little finger, say, or is heart. Similarly, during the irra- iation of cells it matters greatly hich part of the cell is hit by radiant nergy. It was supposed that a cell ad a highly sensitive 'vital centre' nd that a 'hit' there would be fatal.



When Dessauer developed his theory f heat points, he did not limit him- elf to general arguments but attemp- ed to corroborate it with a mathe- natical theory. The curves of the elationship between biological effects nd irradiation dosage have a rather eculiar form, unlike those obtained, or instance, for the effects of most oisons.

He instructed his young colleagues, lau and Altenburger, to calculate ne curves to be expected if his neory were correct. They translated s theory into the language of math- natical formulae, and then began plot the curves that followed from em. It was very interesting. They ere exactly like those obtained from the experiments. could not be a chance coincidence.

But how can that be? We know that the theory was rong. Why was there such a close correspondence? Was it rhaps a mistake to use mathematics to explain living nenomena?

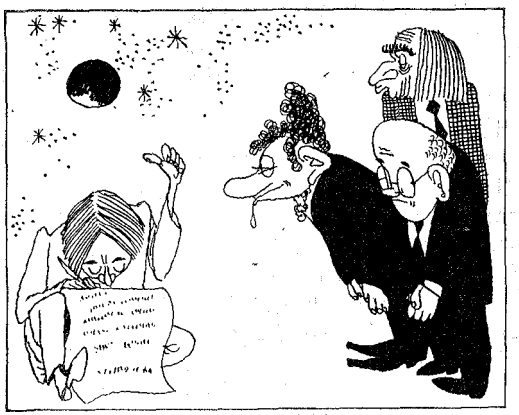
Of course, not. Blau and Altenburger's formulae had thing to do with either heat or protein molecules. They d established a link between the distribution of ioniza- on and biological effects and that part of Dessauer's eory was correct, and became our 'direct hit' principle. der formulae were also used and they, too, are quite inte- sting and help to calculate the 'size of the target' and e 'number of hits' from the curve obtained experimentally.

It seemed a tempting idea. Certain scientists made tl calculations their main work. After irradiating an object- animal, vegetable or microbiological—with different dose they plotted curves, and after analysing it predicted ho many hits were needed on a target of a certain size to evol a particular biological reaction. The conclusions were r ther naive. One paper published at the time said, for in tance, that to kill bean sprouts, i.e. to stop their growtl it was necessary to score nine 'hits' out of ten. But, as w know, a root consists of a large number of more or less idei tical cells. To kill a root, a large number of its cells mu: be destroyed, and it seems doubtful that there would l some special microscopical target in a root, a vital centr damage to which would terminate cell-division of all th cells.

Various scientists treated the figures differently. Som believed correctly that they had purely formal importanc and used them for a brief description of the shape of curv to facilitate comparison. Others, however, went much fu ther. They maintained that formal calculations were highl informative from the standpoint of the target theory, view advocated with particular zeal by the French physi cist Holveck. He maintained that our means of studyin living cells were still too limited. Some of their importan parts were so small that they could not be seen throug any microscope (the electron microscope had not then bee invented), but the target theory could help us. With i we could exactly calculate the size of vitally importan cellular structures. The target theory was the most deli cate and exact method of investigating living objects, veritable statistical microscope that would force nature t reveal its greatest secrets.

It is the dream of every theoretical scientist to repea in his own field the feat of Leverrier who discovered a ne planet by a stroke of the pen when, analysing the orbi of the planet Uranus, he predicted the discovery of th then unknown Neptune. Look at such and such a point i the heavens, he told astronomers; and they looked and dis covered.

That was Holveck's dream, too. He wanted to use sta tistical analysis to predict the discovery of unknown, vi tally important biological structures. Let the biologist to look and discover. So he made the computations, an



biologists looked, but found nothing. In rare cases the
ulations of Holveck and his successors corresponded
e or less to real structures, but usually they bore no
tion to them, and although that was a clear pointer
he imperfection and wrong application of his theory,
veck would exclaim enthusiastically that the mathema-
could not be mistaken. If the facts failed to agree with
calculations, so much the worse for the facts.
athematics, of course, is an exact science, and statis-
is a mathematical discipline. But a prominent statis-
n once likened statistics to a flour mill. If the grain
ood, he said, the mill will turn out good flour; if the
n is bad, the flour will be bad too. And if chaff is used
ead of grain, no mill, however good, can turn it into
.
very biologist, at least every young one, today is pro-
y aware of the need for thorough knowledge of gene-
The successes of molecular biology are truly specta-
r, and its consequences far reaching. But not so long
however, most biologists believed that genetics should
eft to geneticists, a view shared by many radiobiolo-
, scientists studying the biological effects of radiation.
it let us get on with our story of the great paradox
diobiology, and the dramatic event when an infinitesi-
amount of energy produces a great biological effect.
atists spent much time solving this puzzle. Many in-
ous hypotheses were advanced in the vast literature
adiobiology and still continue to crop.

For a radiobiologist familiar with genetics, however, the problem is not so puzzling. In 1928 it was already known that most of the mutations arising in irradiated cells were lethal, resulting in death of the cell, however moderate the irradiation dose. In justice to Dessauer, it should be recalled that when he was working on his theory, the genetic effects of radiation were still unknown; in contrast, when Holveck was advertizing his idea of a 'statistical ultramicroscope' radiation genetics had already become a full-fledged science.

And from there, taking the basic idea of the 'direct hit' principle, it was only a step to a theory that owed nothing to fantasy.

The 'direct hit' principle stems from the fact that radiation energy is unevenly distributed in irradiated tissue and forms what may be described as heat pockets. Its likely consequences depend on which particular point is hit. If a molecule of water or, say, some salt dissolved in the cell fluid is damaged, that, of course, will have no effect. Damage to a molecule of protein or an enzyme performing a vital function will also not have disastrous consequences. Although the protein is extremely important, the cell has many quite identical molecules performing the same function, and if 999 molecules out of 1,000 remain the cell won't feel it. For protein destruction to affect its functions the majority of these identical molecules must be damaged, for which a tremendous dose is necessary. With the doses used in biological experiments, however, it is quite impossible.

Genes owe their special role in the cell to their unique character rather than to their being more important than other substances; the cell cannot exist without many others as well. In the chromosome set each gene occurs only once. If it is destroyed or altered, there is no substitute for it. True, most body cells contain a diploid (double) number of chromosomes, so that a cell contains two genes of a kind. But the destruction of one structure out of two is a serious problem. If a centipede loses one leg, it still runs just as quickly. But if you shoot an eagle in the wing it will fall to the ground immediately. Consequently, hitting a gene is the sole case when a small change can lead to the death of a cell. It may be objected that hitting a definite gene among millions of molecules on the first attempt is a mat-

ter of luck. To make sure that it is definitely hit a large number of 'shots' has to be made, i.e. very large irradiation doses are required. All that is perfectly true, if it is a matter of changing a particular gene. But that is not the point. It is not necessary, for a cell to be affected, to hit a specified gene, because any gene will do. The cell has a great variety of genes. Therefore, the slim chance of 'hitting' a definite gene, when multiplied by the number of genes in a cell, becomes a fairly high probability of the latter's genetic death.

Now we can advance the hypothesis that the chief cause of death in irradiated cells is the mutations occurring within them. But for a hypothesis to become a theory it must be verified by exact experiments and supported with facts.

Our hypothesis looks very simple, but its simplicity is deceptive, for the problem is now solved and the answer is known. In the thirties, however, when quantitative radiation genetics was in its infancy, much of what is clear today was simply a matter of guesswork. It was after the pioneering studies of Nadson and Filippov, Muller and Stadler, which had established the fact that mutations were evoked by irradiation, that investigation of the quantitative aspect of the new phenomenon came on to the agenda.

It must be emphasized that this was not an easy task for biologists. On the one hand, these experiments which are very fine and exact required skill in experimental physics. On the other hand, processing of findings, and their theoretical evaluation, demanded a knowledge of theoretical physics and mathematics that biologists usually lacked. Today many universities train biophysicists, specialists who know both biology and physics, but in the thirties no one was training them anywhere. Success in tackling the problems of quantitative radiation genetics was therefore achieved when biologists collaborated with physicists.

The Birth of a Science

Radiation genetics had a difficult birth. Even to establish the fact of the genetic effect of ionizing radiation was not so simple.

Muller and Stadler reported their discoveries in 1927 and 1928. Nadson and Filippov in 1925. But Nadson had already written in 1920 that 'an impulse received from

radium could be transmitted by the cell through inheritance'. And in 1917 or 1918 Academician Nikolai Koltsov had instructed his young assistant Dmitry Romashov to try and produce mutations in Drosophila by means of X-rays, i.e. exactly what Muller did ten years later.

Romashov began the suggested experiments, but soon dropped them. As Koltsov had expected mutant forms were encountered in the offspring of irradiated flies, but there was no certainty that they had really been caused by the effect of radiation. They were very few, and it was known that mutations occurred without any outside influence. Moreover, the mutations might have long existed in the strain in a hidden state, and had now become manifest in the laboratory hybrids. The findings obtained were quite inconclusive.

When Gregor Mendel began his famous experiments with peas, he first checked the purity of the varieties he was planning to work on. The Moscow geneticists, having dropped their radiation experiments, also occupied themselves with studying the genetics of Drosophila. Their work was by no means a repetition of the experiments of the Morgan group. The scientific name of the species on which the Americans worked was *Drosophila melanogaster.* It does not occur around Moscow, but another species, *Drosophila funebris*, which is darker and much larger, is prolific there.

Although these species are fairly closely related, their heredity has certain essential differences. It has been found, for instance, that many genes of the darker Moscow species possess less expressivity and penetrance, and that pleiotropy is more common in it.

There is another of those damned terms. But don't be afraid. I have only used it for fun. It only means that the effect of a number of the genes of *Drosophila funebris* is not fully realized and is often weak, and that certain genes influence several characters simultaneously. This makes *Drosophila funebris* a very convenient object for investigating the action of genes but hardly suitable for quantitative experiments with mutations.

Drosophila melanogaster, however, proved very convenient on all accounts for experimenting with mutations. But it is not so simple to work with it. It is by no means enough to irradiate a pure line and examine the offspring, for the 'genotype is expressed in the phenotype only when the re-

cessive allele is in a homozygotic condition'. Most mutations are recessive, and are not, therefore, expressed in the first hybrid generation. If the experiments are limited simply to breeding flies, they may also fail to appear in the second and third generations.

It was necessary to evolve special Drosophila lines in which mutations could be detected easily and accurately. Muller and other pioneers of radiation genetics worked with such lines.

A particularly great contribution was made by the *C l B* stock, by means of which recessive sex-linked mutations (present in the sex chromosome) were detected. The experimental method is very simple. Irradiated males are mated with *C l B* females, and the second generation is examined.

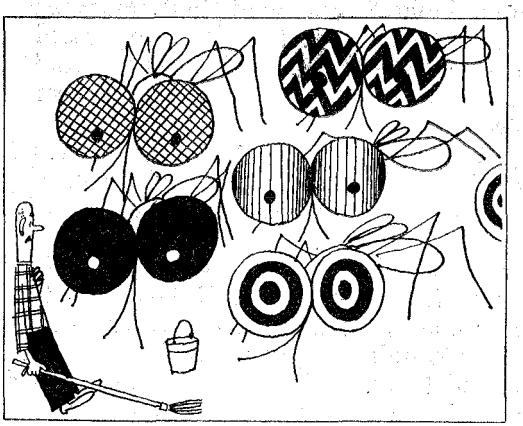
If a mutation occurs in a sex chromosome the corresponding character will be present in all the males of the second generation. There is then no doubt whether we have a mutation or simply an accidental deformity, not inheritable. If a mutation is lethal (causing the death of embryos), which occurs in most cases, there will be no males in the second generation. To use this method one need not even be experienced in Drosophila genetics.

The entire gamut of mutations can be classed in three large groups. Those we have just discussed are connected with changes in the genes themselves and are, therefore, called genic. Under the microscope no changes in the chromosomes are visible in the cells of such mutants; the molecular shifts underlying them are too delicate.

However, mutations may occur (especially frequently through the effect of radiation), that have clearly visible changes in the chromosomes. For instance, a chromosome breaks into two parts or a microscopic 'centaur' appears with the head of one chromosome and the tail of another. Mutations like these are called chromosomal.

Finally, all the chromosomes may be quite normal, but their number is changed: either there is one chromosome too many, or one is missing, or the number of all the chromosomes has doubled. Such mutations are called genomic. With radiation the number of genic and chromosomal mutations noticeably increases, but genomic ones are much less frequent.

Geneticists were faced with a host of problems. They had to find out how the number of mutations depended on



the radiation dose, on its distribution in time, on the type of radiation, on the temperature, or the accompanying chemical influences, and so on. It was necessary to experiment on a large number of animals and plants to make sure that really general laws had been found and not features peculiar to a given species. From the late twenties on almost every issue of the Russian *Journal of Biology* carried serious articles on radiation genetics, and so did the American journal *Genetics*, the German *Zeitschrift für Vehrerbungslehre* and the British *Journal of Genetics.*

It is neither necessary nor possible for us to describe the individual works or list the names of the scientists who contributed to the development of radiation genetics. We shall only mention the principal conclusions they reached toward the beginning of the forties.

Why then? Had all the problems involved in effect of radiation on heredity been already clarified by then? Of course not. Even today the problems of radiation genetics occupy scientists, and every piece of research carried out, while giving the answer to one problem, raises several other new ones. Discussion of the work would take us too far, however. The beginning of the forties was just the time when it became possible to draw the first general and partial conclusions.

Many scientists experimented with other animals and plants to check whether the conclusions inferred from Drosophila had general significance. As was to be expected

all the experiments confirmed the old truism that 'a law is a law'. Many species exhibited certain peculiar features in their reaction to irradiation, but the most general laws dealt with below are valid throughout the organic world.

Let us begin with genic mutations.

In number they are directly proportional to the irradiation dose: If we double the dose it doubles the number of mutations. Well, what of it? the layman may ask. This conclusion, however, is extremely important both for theory and for practice, and for solving certain problems not directly related to genetics.

It follows from this linear relationship that passage of a single ionizing particle through a cell is enough to induce a mutation, and that is important for understanding the mechanism of mutations. Given the form of this relationship, it is easy to calculate the effect likely to be produced by a particular dose, which is very important for drawing up safety regulations. Finally, it follows that there is no 'threshold dose' for genetic effects, there are no absolutely harmless doses. This is one of the arguments for the complete banning of nuclear tests.

The number of genic mutations induced by a definite radiation dose is not dependent on its distribution in time; the effect is the same whether exposure lasts a few minutes or several days, or is divided into several portions.

With a given dose the number of mutations has little relation to the hardness (wave length) of X-rays and gamma-rays; essential differences are observed only with radiations producing high-density ionization, that is neutrons or alpha-rays.

As for chromosomal mutations, everything is the other way round. Only the simplest changes have a linear relationship to dosage, while others increase in proportion to the square of the dose; its distribution in time has a great effect, and the dependence of mutations on the hardness of the radiation is much greater.

These few, but firmly established, facts furnished the clues to understanding the mechanism of radiation mutations. To produce a genic mutation the energy of a single ionization is sufficient. Chromosomal mutations, however, require more, though not great, energy, while to induce a chromosomal mutation, one or two particles piercing the chromosomes are enough.

The findings of radiation experiments suggested the firs conclusion about the nature of genes. By the mid-thirtie radiation geneticists were asserting that a genic mutatio was a slight chemical change, from which it followed tha the gene was chemical in nature, a molecule or part o a large molecule. Thirty years later the data of molecula genetics fully confirmed that conclusion.

Those are only the base elements of radiation genetics but they are quite enough for us to advance further. Toda radiation geneticists are interested in other problems, abov all in that of controlling the mutation process. And howe ver fantastic that may seem, it is a solvable problem t which we shall revert a little later. But now let us tak up our story where we dropped it.

A Riddle Answered

Once the foundations of quantitative radiation genetic had been laid it also became possible to investigate th role of genetic changes (mutations) in radiation damag to cells. The solution of this problem is associated, abov all, with the name of Douglas Edward Lea, one of the mos amazing figures in the history of biophysics. He lived a short but brilliant life. He was born in 1910 in Liverpool where he went to school; and in 1931 he graduated witl honours in physics from Cambridge University.

It is a tradition at Cambridge for the most brillian graduate physicists to work at the famous Cavendish La boratory. In those years the laboratory was headed by th great physicist Rutherford, and his associates include Kapitsa, Chadwick, Cockcroft, Blackett, and other renow ned celebrated physicists. Among them was one man wh did not win laurels as a physicist but later became a world famous writer—C.P. Snow. He described the Cavendis Laboratory in a novel.

Lea's work in Rutherford's laboratory was going well the young physicist was hard-working and talented. H was studying the interaction of neutrons and protons, a problem of nuclear physics that was then in its infancy One day in a physics journal he chanced to read severa articles on the irradiation of bacteria with ionizing rays.

'Interesting enough,' he said to himself. 'With a littl more physics such experiments could yield quite interesting things. Why not spend a couple of weeks on bacteria?'

That was in 1934. By the end of 1935 radiobiology fascinated him so much that he transferred to the Strangeways biological laboratory.

For all his talent and industry Lea could have done much if he had remained a pure physicist or had worked on his own. While biologists were seeking aid from physicists, Lea derived it from biologists. He wrote most of his works in collaboration with biologists. The botanist Catcheside, the geneticist Thoday, the virologists Salaman and Markham, the microbiologists Hanes and Coulson—all learned physics from Lea and helped him in their respective fields of biology. At the same time Lea did not remain a pure physicist abandoning the biological aspect of his research to his collegues. He often used the microscope, sorted out Drosophila flies, counted bacterial colonies on agar disks. That gave him a thorough knowledge of biology, and for that reason he made a bigger contribution to biophysics than many other physicists.

Lea began with bacteria. Irradiating them with X-rays of various wave lengths (on equipment of his own design), the alpha-, beta- and gamma-rays, ultra-violet light, and neutrons, he investigated the relationship between the effect and the dose, the time factor, the hardness of the radiation, and the temperature. From his results he was able to show that the loss by bacteria of their capacity for reproduction (known as inactivation) was the result of a single genic mutation.

Then followed experiments on viruses, bacteriophages, Drosophila, and pollen. The result was the same every time; the chief cause of death was the genetic changes occurring within the living cells.

Since the same conclusion was suggested by all the experiments with different material, and using all the types of ionizing radiation, it could be regarded as valid for all living things that the decisive cause of the death of irradiated cells was hereditary changes, mutations, occurring within them.

A point of explanation is probably necessary here. The word 'heredity' is associated in the minds of most people, even of many biologists, exclusively with transmission of characters and traits from parents to offspring. But that is not so. In fact, the same connection as between parents and offspring also exists between individual cells. The cells

of the organism divide, some of them dying, others taking their place; but they all possess properties inherited from other cells. There are also cells that are renewed very quickly; in certain organs their average life is only a few days.

This explanation probably makes clearer the role of genetic damage to the cells of a multicellular organism. If lethal mutations occur in many body cells, causing their death, radiation sickness develops owing to the weakening of the organs and systems affected. If the mutations are not lethal, they may lead to long-term consequences, for instance, to premature old age or the growth of tumours, and if a mutation occurs in germ cells, it will affect offspring, both near and remote descendants. These conclusions followed logically from Lea's experiments. In 1946 he published his *Action of Radiation on Living Cells*, which has been a 'must' for biologists ever since. It summed up the results of all his principal work. It was lucky for science that he succeeded in writing it, for on 16 June 1947 he was killed by an absurd accident. Absorbed in reading an article he leaned absent-mindedly against an unfastened French window and fell to his death. He was only 37. What he might not have done if he had lived.

At dawn on 7 August 1945, a glow 'brighter than a thousand suns' flared over the Japanese city of Hiroshima, and the death of a hundred thousand peaceful civilians ushered in a new era, the atomic age.

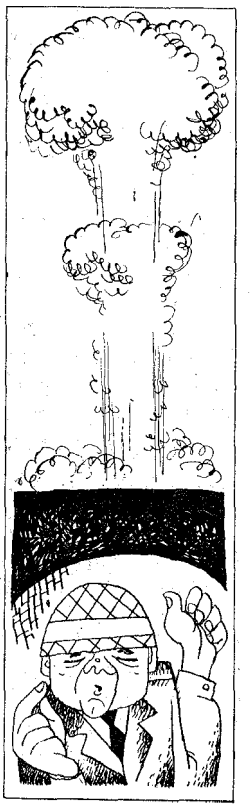
Before that the scientists occupied with atomic and radiation research had often been blamed for their neglect of urgent problems. Now the demands on radiobiologists and radiation geneticists grew tremendously.

In the second half of the forties several major works were published on the effects of radiation on cells and intracellular structures, including Lea's book mentioned above. Although they appeared after Hiroshima, they had been written earlier. Each of them reviewed the findings of radiation genetics from the standpoint of the 'direct hit' principle, and contained comprehensive bibliographies. The pre-war literature—occasional articles and works by a few enthusiasts—was scanty, but the picture it gave was quite clear.

In those years little money was given for research in radiation genetics. Time and ideas were more plentiful than opportunities for experimenting. But it's an ill wind

that blows nobody good. Only people really interested in the subject were working on it, and they had plenty of time to reflect on their findings. Each experiment was carefully thought out and 'squeezed' to yield the maximum that could be got from it.

Now the situation changed completely. Crowds of people (scarcely deserving to be called scientists) were drafted into radiobiology in general, and radiation genetics in particular, people who were not interested in the problems but were engaged in them solely because they were told to do so. And many others turned to these themes because it was easy to find jobs in this field and the pay was higher. The work was urgent and the facilities for research superb; people made one experiment after another without troubling much to think them out, to get their priorities right, or to see what followed from their results. There was no time to think.



As a result the literature on radiobiology snowballed and soon exceeded all limits. The few excellent articles were drowned in a flood of bilge. Some authors were too much guided by the 'tastes' of those who paid the piper, and played the tune expected of them with little regard for scientific truth. It is quite clear that it was useful to the Pentagon, for example, to lay down radiation hazards in order to placate the popular movement against nuclear tests. On the contrary, the Japanese, mindful of Hiroshima and Nagasaki, were inclined to exaggerate the danger. And the businessmen in science, flying in the face of the scientific facts, made the most unwarranted statements; and though there were few such pseudo-scientists, the harm they did was great.

Time, however, is the best judge. A few years went by and certain sensational works became forgotten while

unpretentious articles published by honest workers have become known to every geneticist today.

Time is also the best healer. It cured many scientist of an unhealthy weakness for sensation and quantity a the expense of quality. But we now live in the atomic age and that fact inevitably contributed to the developmen of radiation genetics. Ionizing radiation has become common feature of modern life, so we must know wha dangers are involved, how to guard against them, and ho to make this powerful force serve mankind. On the othe hand, radiation geneticists have received such opportu nities for research as they could not have dreamed of be fore the war. In those days X-ray apparatus was the mai tool at the disposal of enthusiasts; today geneticists hav neutron generators, radio isotopes, giant accelerators, an apparatus delivering the required dose in a matter of se conds or over many days. But most important of all, ever scientist working in radiation genetics is aware of th prime importance of his work and that the people expec results from it.

The work now being done deserves a special book. Bu we have still to describe such achievements of modern gen tics as the chemical nature of heredity and the decipherin of the genetic code; therefore, we must limit ourselve to the classic period of radiation genetics, its begi nings.

But are genes really changed only when hit by ionizin 'bullets'? If a gene has a chemical structure, can it nc be influenced by chemical agents? Of course it can, bu chemical ways of altering heredity were discovered lat than physical ones.

From Iodine to Yperite

Almost every scientific discovery has a long histor and that applies equally to the discovery of the effect chemicals on heredity.

In 1892 the Moscow botanist Ivan Gerasimov experimen ed on the effect of temperature on the cells of the gree alga *Spirogyra*. He noticed strange changes in some of th exposed cells. He observed cells without nuclei, cells wit two nuclei, and among the dividing cells there were som with a twice the normal number of chromosomes. Doublin of chromosome number is a hereditary change. It is no

of course, a mutation of one gene, as observed with irradiation, but a 'genomic' mutation.

Scientists had not then linked hereditary phenomena with chromosomes, so that Gerasimov's discovery was not appreciated at its true worth by his contemporaries. And he himself did not link the newly-discovered phenomenon with change of heredity. Nevertheless, he persisted with his experiments and four years later informed the scientific world of a new discovery, namely, that an effect the same as that due to a low temperature could be produced by chemical substances like chloroform or chloral hydrate.

But Gerasimov's work was gradually forgotten, and when geneticists attempted to induce mutations chemically, they had to begin from scratch.

In the early thirties Koltsov was looking for a way to make silk-worm eggs develop without fertilization. His search proved successful, and he obtained the desired result by means of hydrochloric acid, iodine, formalin, iron chloride, potassium permanganate, silver nitrate, and potassium chlorate.

When it was found that these substances actively influenced the cell nucleus, it was only a step to check whether they could induce mutations. That step was taken by one of Koltsov's associates, Vladimir Sakharov. By exposing fertilized Drosophila eggs to iodine he obtained a large number of mutations, both lethal (causing the death of the offspring) and viable (with hereditarily altered external characters). Sakharov's first work was published in 1932. But that was only the beginning. In further experiments Sakharov and his students succeeded in inducing mutations with other substances. And independently of his work, and almost simultaneously with it, chemical mutations were induced (also in experiments with Drosophila) by the young Leningrad scientist Mikhail Lobashev.

The quantitative results of these experiments were small, mutations occurring only in a very small percentage, but the possibility of inducing mutations by chemicals had been demonstrated in principle. Incidentally, the work of Sakharov and Lobashev was not only important because it established the basic facts; Sakharov's penetrating mind enabled him, even in the initial experiments, to discover specific differences between the mutations induced by radiation and those induced by certain chemicals. He then

already visualized the possibility of directed induction of mutations; today science is getting close to a solution of that problem.

Not long ago I talked with Sakharov about his old experiments. He told me that his work on the specificity of the action of various mutative factors attracted very little notice when it was published. Now that the problem of the specific action of mutagens is on the order of the day his article is cited much more often. When he told an old friend about it, she exclaimed: 'What a pity you published your work twenty years too soon.'

For his part, Lobashev had already succeeded in 1934 in formulating the guide lines for selecting chemical mutagens, that is substances that induce mutations. His principles have been put to use in our day.

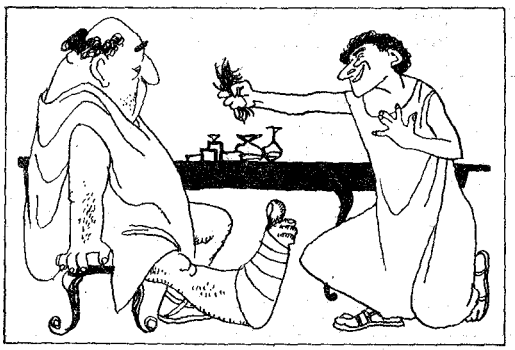
The first mutagens discovered by Sakharov and Lobashev and their co-workers were not very effective, and did not therefore interest practical workers, but within a fairly short time much more effective mutagens were found.

In 1937 the American A. F. Blakeslee discovered that colchicine, a substance derived from the autumn crocus (*Colchicum*, hence colchicine), was capable of doubling the chromosome number in plant cells. In other words, Blakeslee obtained the same effect as Gerasimov had done forty years before, using chloral hydrate and chloroform. But Blakeslee and his contemporaries were unaware of Gerasimov's work.

It should be noted that colchicine proved much more effective than the substances used by Gerasimov. Using colchicine one can be sure of success; even now, after many years of searching, nothing superior to it has been found.

Colchicine is a quite amazing substance. It was known (naturally, not in its pure form) in ancient Rome, as a common remedy for gout. Today it is employed not only to double chromosome number but also to treat certain forms of cancer. For a long time chemists were unable to determine its formula, and still do not know how to synthesize it.

The doubling (and also tripling, quadrupling, or multiplying by so many times) of chromosome number is called polyploidy. Scientists had been acquainted with it much earlier since it is not uncommon in nature. One way that new species emerge in nature is through the development of



polyploid forms. Many 'polyploid series' are known; for example, the different species of wheat have either 14 chromosomes, or 28 (twice as many), or 42 (three times as many). The 14-chromosome species include single-grain varieties, the 28-chromosome ones hard varieties, and the 42-chromosome ones soft varieties.

As a rule, polyploid forms have heightened productivity. By no means all the plants in nature are polyploids, so that colchicine and similar substances can be employed to evolve new, commercially valuable varieties artificially. And it is widely used. For instance, Sakharov developed a polyploid buckwheat. The weight of 1,000 seeds of common buckwheat ranges from 16 to 29 grams, but may be as much as 35 grams with the polyploid variety. Soviet geneticists have developed commercially valuable polyploids of millet, koksaghyz, the opium poppy, flax, peppermint, sugar beet, and other crops.

But that is only a part of the problem. Selectionists often evolve promising hybrids which, however, are sterile. Making them polyploid restores their fertility. It was in this way that A. I. Derzhavin evolved his rye-wheat hybrids, and V. A. Khizhnyak, a new forage crop known as 'agrotritic' (a hybrid of couch grass *Triticum repens* and wheat).

Substances that, like the iodine and so on used by Sakharov and Lobashev, would cause mutations of individual genes, but more effectively, had to be awaited much longer.

Agents capable of inducing a large number of genic mutations were discovered simultaneously in the Soviet Union and in Great Britain. In the Soviet Union brilliant results

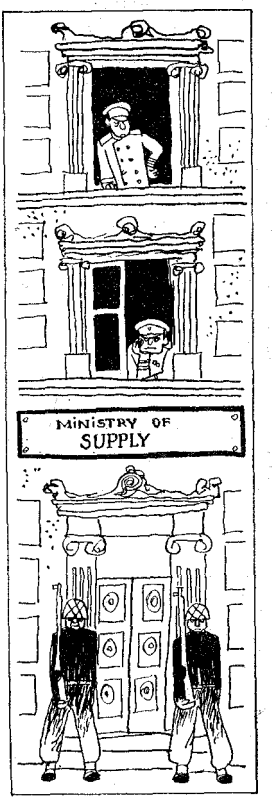
were obtained by Iosif Rapoport. Before the war he had done much work on the production of non-hereditary changes in Drosophila, resembling the mutations induced by chemicals, and wanted to uncover the chemical nature of the gene and the way characters are formed. His experiments brought him close to the discovery of chemical mutagens, but the outbreak of the war thwarted or delayed the implementation of many scientific plans.

Rapoport returned from the war disabled, but he had lost neither his passion for research nor his youthful enthusiasm. He immediately got down to work, taking up where he had left off several years before. One after another, several articles appeared describing chemicals that induced mutations not in a few of the Drosophila flies treated but in 5 to 10 per cent of them. Later he discovered even more effective agents, and in 1962 he published the results of his experiments with nitrosoethylurea. This substance worked wonders, inducing mutations in 92 per cent of the offspring of treated flies. Even irradiation gives nothing comparable.

An analogous discovery was made in Great Britain. Among other war problems the British 'supply officers' took a keen interest in the biological, and in particular genetic, action of war gases. Research into the problem was entrusted to Edinburgh University. There, to the homeland of Robert Burns, fortune had brought Charlotte Auerbach, whose name was already known to most of the world's geneticists. She had been born and educated, and begun her scientific career, in Germany; but when the raving Führer came to power, she, like many other scientists, left her fatherland forever. While doing research for the Ministry of Supply she discovered, jointly with J. M. Robson, that yperite (mustard gas) and related substances increased the percentage of mutations in Drosophila many times over. In their experiments the mutation rate reached 24 per cent compared with 0.2 per cent in the control group. It was a sensation. But Western scientists (again through ignorance of the Russian language) were long unaware that another researcher, Iosif Rapoport, living in far-away Moscow, deserved equal credit for the discovery of the mutagenic effect of mustard gas.

But why should one look for chemical mutagens when there are ionizing rays that induce mutations in adequate

numbers? Because it is necessary. Recall what Sakharov discovered in 1938, that chemical mutagens may have a specific effect. That is extremely important. It is possible to find substances that possess only those properties of ionizing rays that are required.



Study of the mutagenic effect of mustard gas led to the development of new medicines. The Soviet pharmacological industry, for example, makes a preparation known as novoembiquine, a variety of yperite. But unlike mustard gas it is not a weapon of war, but a means for treating cancer that gives spectacular results with malignant leukaemia.

Chemical mutagens have proved very helpful to plant breeding. Their uses are not limited to obtaining polyploid forms. Ionizing radiation gives rise to numerous mutations but most of them are lethal, killing all or part of the offspring. Obviously such mutations are no good for selection work. A search has to be made for the few viable mutations. Chemical mutagens, however, yield a wide variety of forms.

There are mutagens (like mustard gas) whose 'spectrum' is very close to that of radiation. Other substances produce practically no lethal mutations. Some have been discovered by Rapoport, and others by Swedish scientists. In addition, even among the viable mutants produced by various mutagens the changes, although genetically accidental, vary in character. Therefore, the more mutagens a selectionist has at his disposal, the sooner he can achieve his goal.

In speaking of the use of physical and chemical mutagens for the benefit of man, and of their application in agriculture and medicine, we have ignored the fact that mutations are in the main harmful to living organisms,

and that exposure to radiation does man no good (except when it is done specially, for medical purposes).

Is it possible to reduce the genetic effect of radiation? For a long time scientists held a pessimistic view of this question, but in recent years amazing facts have been discovered that have changed their opinion on that score.

Revival of Cells

Shortly before the Russian Revolution a rich merchant from Zlatoust built a summer residence on the shore of a lake called Bolshoe Miassovo. It had ten rooms, four covered verandahs, and large cellars. A path paved with flagstones went down to the shore. It was a mansion. The merchant's name is now forgotten, but the story goes that no sooner had he built the house than he ate himself into the grave with a gargantuan meal of dumplings. For forty years his mansion was generally vacant and deserted, and more than once was damaged by fire.

The region between lake Bolshoe Miassovo and Lake Ilmen is a natural mineralogy museum that probably has no like anywhere else in the world. Soon after the revolution Lenin signed a decree on setting up the Ilmen State Nature Reserve. Its treasures were placed under the protection of the state and began to be systematically studied.

The mansion was still standing. What had once seemed an out-of-the-way place was now within the bounds of the reserve. It was difficult to make much use of it. For a few years it housed a tourist centre, then a hospital during the war. After the war it was deserted again. So when Sverdlovsk biophysicists asked for it as a summer biological station the local authorities were glad to write it off their budget. It was soon repaired. Five small cottages for the staff were built nearby, and the new biological station began a steady ascent to fame. Each summer a full-scale laboratory conference was convened here, with leading scientists taking part. Keen young men arrived in their wake, pitching a tented camp around the station, which became the scene of heated debates on most vital scientific problems.

At one of these conferences I met Vladimir Korogodin from Moscow, then a young research worker, now a famous radiobiologist known for his experiments with yeast cells. He told me about the very interesting results of his experi-

ments. He had irradiated yeast cells with large doses of X-rays, inoculating a part of them into a growth medium immediately, and keeping the rest in tap water for 24 hours before inoculation. What happened was most amazing: the 'tap-water cells' produced many more colonies than the controls. But try as he would, he could not fathom the cause of this phenomenon.

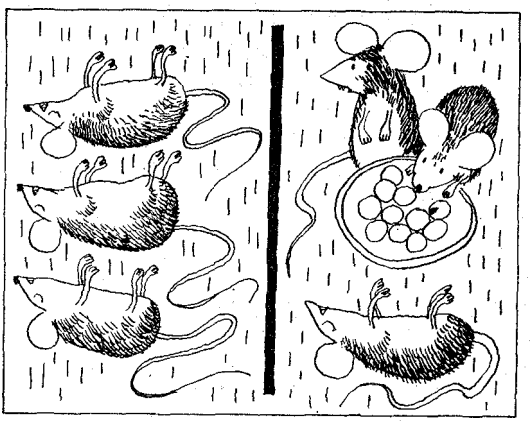
'If I didn't know it was impossible,' he reasoned, 'I would say that the cells had recovered from the damage. But everyone knows that cells lose their capacity to form colonies as the result of mutations. And it is common knowledge that mutations are irreparable.'

I laughed and told him about the results of my own experiments with peas. We had tried to irradiate dry seeds and then soaked them in various solutions. Under the influence of many substances the number of chromosomal mutations in the sprouts from irradiated seed markedly decreased. These results might also be attributed to recovery, if it were not for the prevailing view. Then he told me about other experiments yielding similar results, and I recalled my own experience to the same effect.

For over two years I had been working in collaboration with Lev Tsarapkin to find out whether cells could recover from genetic damage. The experiments that led us to this idea had been started more or less accidentally. Let me go back a little in time to describe them.

It was long taken for granted that a radiation lesion could only be healed within very, very narrow limits. But in the late forties a certain Baron and his co-workers published work that was totally unconnected with biology. They had irradiated aqueous solutions of proteins and measured how far they were damaged. When a certain amount of glutathione was added to the solution the severity of damage was very much reduced.

When I read this work I had an odd idea: what if glutathione would also protect living organisms against radiation damage? It might be fantastic, but several mice might be sacrificed to science. We had no glutathione in our laboratory, but our chemist managed to prepare cysteine, a substance that is a component of glutathione. We injected the mice with cysteine, irradiated them with a lethal dose, and waited for the results. And the amazing happened. The death rate among the mice given cysteine proved about



half that in the controls. The idea that had motivated our experiments now appeared self-evident. After the publication of Baron's article similar experiments were made in laboratories all over the world. The first to publish his results was the American Harvey Patt.

Then other substances began being used in similar experiments, and some of them yielded results like those produced by cysteine. But in all cases they were helpful only when they had been injected prior to irradiation. When injected into irradiated animals, even within a few seconds of exposure, they sometimes even raised the mortality rate instead of producing a protective effect. It was difficult to tell at the time just how much the death of the irradiated mice depended on genetic damage to cells, so we decided to make similar experiments on pea roots. When they were soaked in a cysteine solution prior to irradiation, chromosomal mutations proved much fewer in number. But when they were immersed in cysteine immediately after irradiation no effect was observed, just as in the experiments on mice.

Nevertheless, these experiments were not enough to warrant the conclusion that irradiated cells were capable of recovery from genetic damage. In those years everyone was interested in the results of Thoday and Reed. These British scientists had irradiated bean roots both in an oxygen medium and in an oxygen-free one. Growth was altered and the number of chromosome mutations increa-

sed, but in the oxygen-free medium this effect was only a third as much. That was in 1947. Two years later they repeated their experiment, using alpha-rays instead of X-rays. Oxygen had no effect on the results.

The data obtained by Thoday and Reed strongly resembled the results of irradiating water. It was firmly established that exposure of water to X-rays yielded a fairly large quantity of hydrogen peroxide, while irradiation with alpha-rays gave none. Hydrogen peroxide, it will be recalled, is a potent oxidizer and can damage cellular structures. This gave rise to what is known as the 'theory of indirect radiation effects', which received wide publicity. Its essence was that water molecules (which form the bulk of the living cell) produced active chemical products under the action of irradiation (not solely hydrogen peroxide) that had a biological effect.

From this standpoint the action of cysteine was simple to explain. It has a high affinity for the breakdown products of water, which readily combine with it, and this reduces their effect. The life of active products is measured in fractions of a second, therefore the inefficacy of cysteine after irradiation agreed with the theory.

In time, however, facts accumulated that contradicted the inordinately great role attributed to the 'indirect effect' by many radiobiologists. The effect of cysteine could then also be explained by its promotion of cell recovery from damage, while the absence of its effect after irradiation might be due to the primary damage becoming irreparable too quickly. So the fantastic idea came to us: why not use cysteine after irradiation but in conditions when there was marked slowing of the development of damage.

Resting seed in which the life processes are very slow seemed the ideal material on which to try out our idea. In it damage should seemingly also progress at a much slower rate. Although the experiments were simple to do, we put them off from day to day. People engaged in research usually have many more ideas than they have possibilities for implementing them. If we had had nothing else to do, we would probably have got on with these experiments long ago; but I must confess that, although the idea seemed good, we were very apprehensive of failure. And when at long last we did make them, it was because we were short of work.

In 1955 we moved to another town. It takes time to settle down to normal work in a new place, and having moved, we at first had nothing to irradiate. But Lev Tsarapkin, a provident man that he was, had brought along a small bag with old pea seeds that we had irradiated two years before. So we decided to check our old idea on these seeds now that we were forced to be idle. Two years, of course, seemed a very long time, even if damage had progressed very slowly in the dry seed. But we could not sit on our hands.

We took the old seeds and divided them into two groups. One lot was soaked in a solution of cysteine, the other, for comparison, in water. When we had counted the number of genetic changes in the cells, we could not believe our eyes: cysteine had reduced their number somewhat, even after two years. And when a new irradiation unit had been installed and the interval between irradiation and soaking was reduced from two years to two days, the effect was much more spectacular.

Did it mean that cells were capable somehow of recovering from radiation genetic damage? It was not as simple as that. In science any one finding can always be given more than one interpretation. Additional corroboration must always be sought. Here too we made one experiment after another, not daring to conclude that cells could recover from genetic damage. We were particularly cautious because such a conclusion would run counter to the general and long-held view.

It was then that I met Korogodin and learned that he too was tormented by similar doubts. What was particularly relevant was that he had worked on different material and made experiments of a different kind, but had reached the same conclusions. Moreover, our experiments nicely complemented each other. It is easy to study genetic changes in seeds and sprouts, as many of them can be seen directly under the microscope. But with them it is extremely difficult to follow the changes in the successive generations of irradiated cells. As for yeasts, nothing can be seen inside their cells; even the fact that their death was due to genetic changes was merely a surmise. But it is very easy to trace the fate of their cells; even accurate cell genealogies could be plotted for them, if necessary.

There, on the shore of a lake in the Urals, we finally be-

came convinced that cell recovery really was possible. We began new experiments, this time in collaboration with Korogodin, and were joined by another visitor to the biological station, Oleg Malinovsky from Leningrad. He was so fascinated by the problem of cell recovery that he is still working on it.

Danger Retreats

For years scientists had believed that genetic changes, in particular those due to irradiation, arose immediately in an irreversible form, and that it was impossible to influence the probability of their occurrence. We became convinced that this was not true. Of course, our experiments could not be put immediately to practical use. Indeed, who needs to reduce the number of mutations in pea seeds or yeast cells exposed to high doses of radiation? But the most important thing in science is to establish a possibility in principle, and that was what we had done. If genetic damage could be reduced in our laboratory experiments, then, of course, methods would be devised in time to do the same at the sick bed.

We were happy at what we thought was a contribution to the welfare of humanity. But we were in for a bitter disappointment. When we told other scientists of our findings, they did not believe us. Our findings were not questioned, but almost everybody objected to our conclusions. Indeed, the lower number of genetically damaged cells in our experiments might well be attributed simply to their death. Finally, the radiation might have altered the rate of cell-division, the number of primary injuries, and the like.

Yet we argued and argued, and carried out other experiments to dispel the doubts of our opponents. But they raised one new objection after another, as we refuted the old ones. We were very annoyed, but were convinced that we were right, especially as more and more investigators were reaching the same conclusion, that cells can recover from primary genetic damage. It was scientists of the older generation who opposed us most strongly, but their opinion was particularly important because it carried great authority. So we had to content ourselves with the aphorism of Max Planck, the famous physicist and founder of quantum theory, that new ideas have never win—it is simply that the champions of old ones gradually die out. We did not

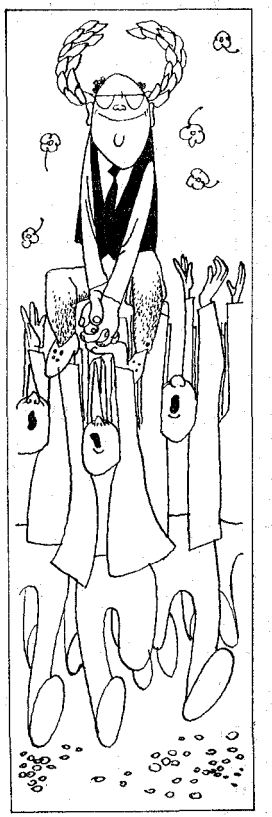
want the great ones to die, of course, but the phrase was a consolation.

Some years have passed since then. Looking back I see we had no reason to be angry with them. It was in the nature of things that our idea was not accepted immediately and that more and more evidence was required, as it was a very important matter challenging fundamental views on the mechanism of mutations. And as we ourselves had refused to believe our own eyes for a long time, what were we to expect of others? It was also a good thing that we were not believed immediately. The objections forced us to undertake new experiments and to ponder various aspects of the problem that might not otherwise have come to us.

It often happens in science that similar work is done by different scientists around the same time. So it was with the rediscovery of Mendel's laws, and the discovery of the mutagenic effect of radiation, chemical mutagens, and the possibility of chemical protection of living organisms against radiation. And the same thing happened with the discovery of the ability of cells to recover from primary genetic damage. When we were about to draw this conclusion Korogodin was in an equally difficult situation with his study of changes causing cell death. These were two sides of the same coin. But that was not all there was to it. At about the same time Sobels in the Netherlands was experimenting with Drosophila, Alper in Britain with bacteria, and Kimball in the USA with infusoria, and all of them (and certain other scientists as well) reached the same conclusion: cells could recover from primary radiation damage and, in particular, from genetic damage.

The reader may wonder what a scientist feels on learning that his discovery has been made by others besides himself. It is a difficult question. It is very nice, of course, when you have made a discovery on your own and when you immediately win recognition and are crowned with laurels. Perhaps dreams like that attract many to science. But in real life it almost never happens. Karl Baer, whom we mentioned in the previous chapter, once said: 'The lot of discoverers is usually the same; at first they are persuaded that their discovery is nonsense, then they are told that it was all known before, and some people even derive pleasure from confirming that with far-fetched arguments borrowed from the archives.'

That is just how it is. A scientist with some experience of life is attracted to science not by delusory hopes of fame but by the search for scientific truth (only those who have experienced it know the pleasure it gives), and in seeking the truth parallel discoveries are more often an encouragement than a disappointment. So long as a discovery is not confirmed its correctness is in doubt. Moreover, the solution of one problem nearly always poses several new ones to the investigator, which it is impossible to solve alone. Therefore, when a discovery is made simultaneously by several workers, it is not bad at all. The truth is established more quickly and it is merrier to work in company.



The problem of cell recovery was lucky in that respect. On the one hand, the development of science had reached a point where several scientists began similar studies independently of one another. On the other hand, as soon as the first positive results were obtained, they proved so interesting, both theoretically and practically, that many others joined the research. Thanks to that the basic problem is now clear: irradiated cells really are capable of partial recovery from primary genetic damage. And the means now exist either to reduce or to increase, as we wish, the number of genetic changes induced by a given dose of radiation. The problems of the nature of the primary changes and of the mechanisms of recovery are still not as clear, but they are being worked on with success.

The practical significance of these data need to be mentioned. The reader is already well aware that radiation has a bad effect on heredity (except where hereditary changes are induced deliberately). Therefore progressive people throughout the world will continue their fight for unconditional and total prohibition of nuclear tests.

But for all that a new factor—ionizing radiation—has appeared in the life of modern man, and it cannot be disregarded. It is one of the many unfabourable factors that man has to cope with.

A group of American scientists not long ago carried out the following experiment. They collected and condensed the exhaust fumes of motor car engines, and applied the condensate to the skin of white mice. After a time all the animals developed cancerous tumours. Then they took samples of air from the atmosphere of Los Angeles, passed them through filters, and again applied what was retained on the filters to the skin of white mice. The result was the same. Isn't it terrible? Of course, it is. Technical progress brings with it ever growing hazards to human life and health. The very air we breathe is becoming unhealthy, to say nothing of polluted rivers, cut-down forests, and much else. This is particularly characteristic of the chaotic development of capitalist economies. It was not fortuitous that it was from the air of Los Angeles that samples were taken. That city seems to hold first place for the amount of exhaust fumes in the air.

Perhaps the most alarming fact is that almost no attention is paid to most of the harmful factors surrounding man. Ionizing radiation has been 'lucky' in this respect; its danger immediately attracted attention. Wherever work is carried out with sources of ionizing radiation the strictest protective measures are taken, and everything is done to prevent radiation and radio-active wastes from escaping into the environment. But frankly speaking, man suffers much less from radiation than from road accidents.

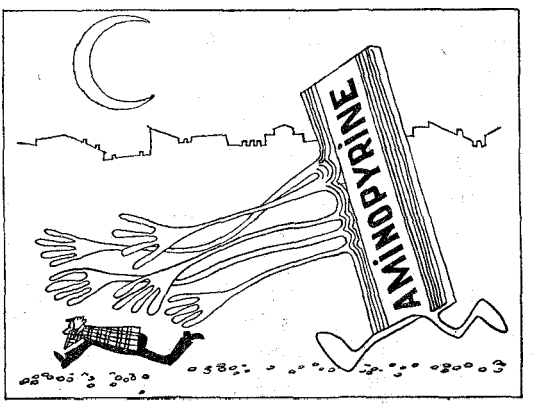
For most people radiation is surrounded with an aura of mystery and incomprehension, and many have wrong ideas about it. The people who work in research institutions suffer a special misfortune—they are inundated by letters from cranks and madmen, either unacknowledged geniuses prevented by wicked people from blessing mankind with a certain invention or sufferers from persecution complexes. Most of the letters of that kind that I have had to read over the past few years have dealt with radiation in one way or another. The writer had either invented a new kind of ray with mysterious properties of some sort, or complained of being tortured and tormented by means of rays or radio-activity. The importunate writers of these letters

are 'balmy', of course, for reasons other than radiation. Mental disorders are organic disturbances (and very often hereditary, for that matter), and anyone who goes out of his mind from an unhappy love affair does so, not because his love is so strong, but because his psyche is already sick.

But you and I, being healthy people, must take a realistic view of radiation hazards. Radiation is harmful to health; but on the other hand, it gives tremendous benefits. (Motor cars are also both useful and harmful.) What is needed is to reduce the hazards and increase the benefits as much as possible. Perfectly harmless inventions, even those that cannot be used for military purposes, are almost non-existent. That is why most medicines are not sold without a doctor's prescription. If used inexpertly, they can cause grave damage to health. For instance, aminopyrine seems perfectly innocuous (and is even sold without a prescription), yet it causes a severe and persistent disease in some people. But don't worry; if you have taken aminopyrine and not been sick, you can do so again, for only an infinitesimal percentage of people are hypersensitive to it.

Thus, the crux of the matter is the equilibrium between good and evil. People are often afraid of an X-ray examination. It is absurd. The benefits they gain from a timely and correct diagnosis far outweigh the slight probability of harm.

But let us get back to the problem of recovery from genetic damage due to irradiation. It should be clear from what we have said that the better our ability to reduce



the number of genetic changes, the wider the possible use of radiation for peaceful purposes, and the less the risk of accidents. As to the road from experiment to clinic it is not very long, and remedies found in experiments on irradiated animals and plants have already found their way to the sick room.

So far we have dealt only with the reduction of genetic damage to cells, but it is sometimes useful to increase it Do not be surprised. I have in mind such an important modern problem as the treatment of cancer.

One of the chief means of treating cancer is ionizing radiation. And small wonder. Cancer cells are cells like all others, but with slightly altered hereditary properties, owing to which their division gets out of control. It is not very difficult in principle to find a medicine that will kill harmful germs without damaging the cells of the human body, but with malignant tumours the problem is much more complicated, as it is necessary to kill sick human cells without affecting healthy ones, and they are almost identical. The chief difference between them is the quickened rate of division of cancer cells, and it is this difference that is used in the radiation therapy of cancer.

The first investigators of the biological effects of radiation noticed that the quicker cells divided, the more sensitive they were to the destructive effect of radiation. From that it was only a step to verify whether the new rays did not affect cancer cells more than the surrounding healthy ones. Experiments were made and confirmed this supposition. From then on there were only two remedies for many years for treating cancer—'the knife and radiation', i.e. either surgical excision or irradiation of the tumour, or both.

The effect of radiation on cancer cells is based on genetic damage. The irradiation of cancer cells gives rise to numerous chromosomal mutations, resulting in cell death. This makes clear the greater sensitivity of cancer cells. Since they divide faster they have less time for recovery from the genetic damage caused, which manifests itself precisely during cell division.

Radiation, however, also affects the chromosomes in normal cells as well as in cancer cells, although to a lesser extent. It is therefore very difficult to choose a radiation dose sufficient to destroy a cancer tumour and at the same

time be relatively harmless to the surrounding normal tissue, and it sometimes proves impossible. Solution of the problem can be facilitated in one of two ways: either by reducing the sensitivity of the surrounding normal cells or by increasing that of the cancer cells. That is why it is important to learn not only how to reduce the degree of damage to the genetic apparatus of cells, but also to increse it when we want to. Geneticists have made certain progress in this direction, too.

But it is not only the death of cells that is involved in the practical application of radiation genetics. And quite often the aim of attempts at inducing hereditary changes in cells is not their destruction at all.

For the Good of Man

How can that be? For we have said that the overwhelming majority of the genetic changes caused in living cells by irradiation are harmful. And that is true. But in addition to harmful changes useful changes also occur, by sheer chance, and therefore very rarely. If the use of irradiation is limited to changing hereditary characters, nothing good will come out of it. However, what we have said about the character of the changes due to irradiation applies equally to changes due to other causes or without apparent cause of any kind. The overwhelming majority of them also prove harmful; but in the course of evolution nature mercilessly wipes out the harmful changes, while the few useful changes are strengthened and reproduced in the progeny.

Man does just the same within much shorter periods, when evolving new breeds of animals and new varieties of plants. Mutations spontaneously arising in nature are used for the purpose. Their number is small, but can be increased many times over by irradiation.

In that way irradiation makes it possible to increase greatly the hereditary variations available for selection work. Scientists have established that hereditary variations in cultivated plants are increased approximately 1,000 times by irradiation. It is easy to imagine how that broadens the opportunities for selection.

That, however, is not the main advantage. The chief tool of classical selection is hybridization. In order to combine the useful properties of two varieties they are crossed. The trouble is that both varieties have a large number

of genes. As soon as they are crossed the useful combinations of genes break up (Mendelian segregation), and the hybrid offspring prove inferior to either of the parents. Almost all the efforts expended on evolving the parent stock go to waste, and the work has to be begun again.

Artificial mutations are quite another matter. It often happens that a remarkable variety lacks just one quality. For instance, a variety of wheat or barley good in every respect is apt to lodge or is not rust-resistant. Crossing it with another variety with the requisite quality might spoil it.

Now we can do it without crossing. Seed of the variety to be improved can be irradiated to produce numerous mutations. Most of them will be harmful, but one or two in a thousand may lend the plant the desirable quality, leaving the good properties of the parent stock intact. With modern methods of irradiation it is not very difficult to induce several thousand mutations to have something to choose from. At any rate the game is worth the candle.

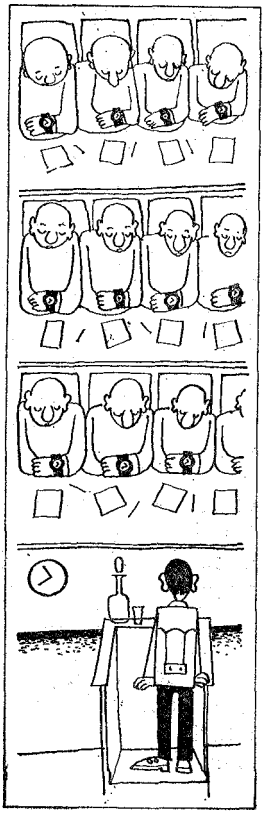
Radiation selection is a very young science. That may sound strange, since the mutagenic effect of radiation was discovered in the mid-twenties. But many scientists, knowing that most mutations were harmful, considered the application of radiation in selection quite unpromising.

The first to realize the importance of radiation selection were Soviet geneticists. Work on cultivated plants was started by A. Sapegin in Odessa and L. Delone in Kharkov as early as 1927-8. Soon the method of X-ray mutations attracted the interest of the great naturalist Ivan Michurin. Results were not long in coming. By 1938 Delone, for instance, had reported the production of hundreds of different radiomutants in wheat and barley. About the same time A. Lutkov obtained several mutational forms in barley and peas, and M. Ternovsky, of tobacco, some of which were of commercial value. Unfortunately, these experiments, so brilliantly started, were interrupted for a long time. Selection work was taken over by people who denied the existence of genes and the chromosome theory of heredity, the importance of pure lines, hybrid seed, polyploid forms, and, naturally, radiation selection. In recent years the work has been resumed and is being carried out on a broad scale at dozens of research institutions.

At the end of January 1965 Soviet geneticists assembled at Moscow University on the Lenin Hills after an interval

of many years for a symposium on experimental mutagenesis in animals, plants, and micro-organisms. The agenda was very heavy. Each speaker was allowed only ten minutes. Although the symposium was divided into three sections which met simultaneously in the morning and evening, it took six days to hear all the reports.

The abstracts of the reports give a clear idea of the problems discussed. Radiation selection was practised on all major farm crops: wheat, maize, cotton, sunflowers, buckwheat, several leguminous crops, vegetables, fruit, trees and decorative plants. It was not a matter of isolated works, either; over a dozen papers were devoted to experiments with wheat alone.

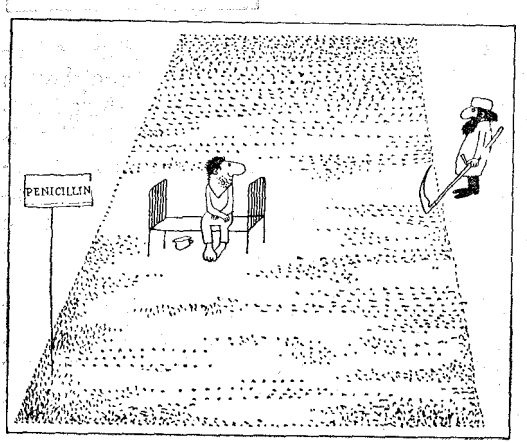


It takes several years to evolve a new variety and put it into production. It is not enough simply to induce mutations. The best of them must be selected, examined comprehensively, tested in different conditions, and reproduced in sufficient numbers. The Swedish scientist Gustafsson, whose name is now known to every geneticist and selectionist whatever his field of work, took an interest in radiation selection about the same time as Sapegin and Delone began their experiments. Over the years he acquired a large following of supporters and disciples; a number of institutions started work on the problem and, what is most important, continued it without interruption. Therefore, varieties evolved by radiation methods are already cultivated in Sweden on large areas and have great commercial importance.

There is a long list of valuable varieties of farm crops evolved by irradiation, which have a yield 5-10 per cent higher and sometimes more. But let us turn to another field, in which radiation genetics and selection have given even more spectacular results.

In 1928 the British scientist and physician Alexander Fleming made a remarkable discovery. He established that a fungus of the genus *Penicillium* produced a substance that killed germs, a substance known to everyone today under the name of penicillin. But, although it was discovered in 1928, it was only put to practical use during World War II. That was due, in particular, to the fact that the fungus discovered by Fleming produced a small quantity of penicillin, which was difficult to purify and manufacture on a commercial scale. We often say something is worth its weight in gold when we want to stress its value. The first batches of penicillin cost much more than gold, but now it is a very common medicine available to everyone.

Such rapid progress in the technology of preparing penicillin became possible by employing the techniques of radiation genetics. The first strain of penicillin discovered by Fleming had a disadvantageous property; it grew only on the surface of the nutrient medium, producing about ten international units of penicillin per cubic centimetre of medium. To obtain a million units, therefore, the amount needed for one patient, an area of 50 square metres of nutrient had to be harvested. In the end the wonderful fungus was improved, and could now be grown in the deeper layers of the medium, yielding 250 units per cubic centimetre. That was achieved by conventional selection; and despite all efforts it produced no further improvement in the qualities of the fungi.



In Cold Spring Harbour, not far from New York, there was a small genetics laboratory which was directed for many years by Milan Demerec, a Croatian, who had settled in the United States. He is now dead, and at present the laboratory is headed by one of his pupils, but at that time he was in the prime of life. Generally speaking, Demerec became world-famous for his investigations of the genetics (the radiation genetics in particular) of Drosophila, material that in itself has no commercial value.

Demerec was neither a microbiologist nor a doctor, but his experience and knowledge of radiation genetics proved more important for penicillin. He used his skill polished in experiments on Drosophila, and with the aid of X-rays evolved a new strain of fungus whose productivity was 200 per cent of the original, and for a number of years this strain was the chief industrial producer of penicillin. A 200 per cent increment of yield is unprecedented in plant selection. That is only natural, for plant breeders, for one thing, to deal with plants that have been selected for centuries and are difficult to improve considerably. Second, the selection of farm crops must be done with a view to several characters, while one character is important, as a rule, in antibiotic producers.

Work on penicillin continued. All the strains had one essential defect in common. In addition to penicillin they secreted a yellow pigment. The purification of penicillin was costly, and part of the valuable product was lost in the process. The use of ultra-violet rays helped obtain a mutation that did not produce the yellow pigment, but it yielded a smaller quantity of penicillin. However, the induction of several new mutations of this strain made it possible to reach and surpass the former productivity. Ultimately American selectionists evolved a strain yielding 3,000 units per square centimetre of medium (just compare it with the ten units produced by Fleming's original strain).

From the very outset Soviet scientists were quick to appreciate the importance of selecting antibiotic producers. A selection laboratory under the direction of Sos Alikhanian was set up at the All-Union Institute of Antibiotics. Like Demerec, Alikhanian had studied the genetics of Drosophila before the war and his experience with it proved very useful. Suffice it to say that the laboratory evolved a strain of penicillin called 'New Hybrid' (also by means

of irradiation), a strain that yielded as much as 5,000 units compared with the 3,000 of the best American strain. Alikhanian and his colleagues not only worked on penicillin but improved the qualities of most of the other fungi used to produce antibiotics. For instance, they succeeded, using X-rays, in raising the output of albomycin sixfold.

The selection of farm crops and antibiotic production are by no means the only fields where radiation genetics has given, and is still giving, impressive results. Similar work was done on the micro-organisms that produce vitamins (particularly the important vitamin B_{12}) and other valuable food and technical substances. Using the techniques of radiation genetics one can change the properties of disease-producing viruses and microbes and create 'live' vaccines. By inducing lethal mutations in agricultural pests, and then reproducing them and releasing them in the natural environment, a process of their spontaneous extinction can be set off.

These are just a few of the many prospects opened up by radiation genetics. One can already say that few discoveries have been so useful to man as those made by geneticists in the 1920s, by Muller and Stadler in the United States and by Nadson and Filippov in the Soviet Union. Although the greatest contribution of all has been made by Muller, now a Nobel Prize winner, priority in the discovery of the mutagenic effect of radiation belongs to two modest workers from Leningrad, Nadson and Filippov.

Molecules that Reproduce Themselves

An Unexpected Toast

The man was sitting on the floor. The first thing he had done on entering and greeting us was to ask Natasha, who was acting as hostess that evening: 'May I sit on the floor?' And had promptly sat down, leaning comfortably against the wall.

Natasha felt embarrassed that she hadn't even given him a newspaper to sit on. I experienced something different. I too was a guest and had a chair. The best places were on the divan, which was occupied by some professors. But a chair was more comfortable than the floor. His pose seemed a little affected to me. I knew that Americans do not always behave as we do, and if he had been plain Jimmy, it would not have bothered me. But this was Professor James Dewey Watson. The Watson!

I well remember his work on the properties of a bacteriophage exposed to X-rays, published in the *Journal of Bacteriology* in 1950. It was one of his first papers, but it had immediately attracted the attention of everyone working in related fields. That was not very much of course, because science is now so differentiated that the world fame of a scientist among his colleagues is much less than that of a provincial tenor among his admirers, to say nothing of the fame of a First Division footballer among fans. But it's not so bad to be world-famous among specialists. In 1953 Watson and Francis Crick published a short article that set the whole world talking. That also cannot be compared

to the popularity of a famous football player, yet the new work probably attracted the attention of practically all geneticists and all biochemists, and of some mathematicians and physicists. Many already now say that it was that article by Watson and Crick that began the new science of molecular genetics. Soon (in 1962) Watson would be awarded a Nobel Prize, the highest laurels in science. But just now he was sitting on the floor with a shy smile on his face.

It was in August 1961 in Moscow, during the 5th International Biochemical Congress. Some prominent Moscow scientists were entertaining eminent foreign guests informally at home. I was not a 'prominent Moscow scientist'. I was living in the Urals and had received my Candidate's degree* only the year before. It was sheer luck that, having come for the congress, I was staying with today's hosts.

Congresses, conferences, and symposia are usually disappointing because the speakers describe what they have already published in the latest issues of the journals. The 5th International Biochemical Congress was different. It was attended by Engelgardt, Belozersky, Oparin, Braunstein, Zbarsky, Watson, Crick, Jacob, Meselson, Melchers, Schramm, Fraenkel-Conrat, Doty, de Vries, Barton, Levinthal, and other stars of first magnitude, whom it was interesting just to see. Almost all the scientists you will meet later on our pages were gathered in Moscow.

The delegates did not gaze at the stars, of course; they brought along much new and interesting information. The main hero today, however, was not Watson, nor any of the other celebrities. Today, a new name was on everybody's lips—Nirenberg. Even now, a decade later, his name is pronounced with still greater respect than then, in August 1961. His report to the Congress excited geneticists and biochemists alike. That may strike you as strange, but the time when genetics and biochemistry led quite independent existences is now past, though only just.

A few years ago geneticists still studied the laws of segregation, linkage, dominance, and gene exchange without reference to the biochemical processes involved in the formation of characters. For their part, biochemists investigating the chemistry of life processes were completely un-

* Candidate of Sciences (Cand. Sc.) is the first higher degree in the USSR, roughly equivalent to the British/American Doctor of Philosophy (Ph.D.).—*Ed.*

ıterested in the hereditary conditioning of biochemical tructures and processes. Geneticists focused their attention n the gene, the material carrier of heredity, while biochemists' interest was concentrated on proteins, the bearer of ital functions.

Gradually, however, more and more facts were gleaned ıdicating that the biochemical features of living organisms ere inherited according to the laws Mendel discovered a entury ago in his experiments with crossing different varieties of peas. A new science—biochemical genetics—was orn from the union of the two, previously completely unelated sciences. And just as geneticists of the past plotted xternal characters on their gene maps—the shape of leaves r the colour of eyes—modern geneticists (and biochemists) egan to locate the genes responsible for biochemical chacteristics.

In the development of the chromosome theory of hereity the leading role was played by Drosophila, in biochemical genetics by the fungus *Neurospora*. Outwardly this ungus looks like common mould, but it can live and develop n a very simple artificial medium consisting basically of ugar and salt and a single vitamin—biotin. When exposed o radiation or chemical mutagens *Neurospora* produces mutations incapable of existing on the minimal medium, vhich means that it has lost its capacity to synthesize some ubstance indispensable for its survival. From biochemical xperiments it was learned which particular substances the ungus had 'forgotten' how to synthesize, and from crossing vhat was the genetic basis of the resulting defect.

The experiments led scientists to an amazing conclusion. To make it clear let us briefly examine a series of xperiments on *Neurospora*, experiments that are very typical of scores of others.

Many mutations have been obtained whose growth requires the addition of arginine to the medium. Arginine is n amino acid, a component of most proteins. Detailed study of these mutations made it clear that some of them required only the addition of arginine and nothing else; others vere less fastidious, permitting the addition of a closely elated substance—citrulline—but nothing else. Finally, third type of 'arginine' mutation will grow not only vhen arginine and citrulline are added, but also a third ubstance, ornithine.

In itself this would not have been so very interesting, but biochemists knew that arginine was produced from citrulline in living cells, and citrulline from ornithine, in the sequence ornithine→citrulline→arginine. It was inferred that the first group of mutations had lost the capacity to convert citrulline into arginine, the second ornithine into citrulline, and the third to produce ornithine from even simpler substances.

All the biochemical reactions in cells are governed by complex proteins known as enzymes. Each enzyme is responsible for one reaction only; for instance, one converts ornithine into citrulline while another converts citrulline into arginine. Therefore, the results of the experiments could be explained if, in each mutation, the cells had lost their capacity to produce a definite enzyme.

But a mutation is a change in a gene. Therefore, on the basis of experiments like those above, scientists made a supposition known as the 'one gene—one enzyme hypothesis', the essence of which is that it is the function of each gene to produce a particular enzyme. The hypothesis has been confirmed by numerous experiments.

Now we are approaching the crux of the matter. Since enzymes are proteins the problem of the chemical nature of heredity is one of the specific way in which a cell builds up strictly defined protein molecules. In his report to the Moscow Congress Nirenberg threw ample light on this problem. He took the first step in discovering the ABC of heredity and solving the riddle of how the plans of protein structure, in other words, the plans of all hereditary characters, are recorded in the genes.

It is impossible to pass over these works in a book on the history and progress of genetics. These are the very works that have drawn the attention of all scientists to genetics, whatever their speciality. It is these works that promise mankind delivery from incurable diseases, new species of plants, new chemical technologies, and many other benefits. But the road to them is long.

It is time we returned to the room where we left Professor Watson sitting on the floor. Everyone was now seated around the table. Meselson was telling a story about a monkey the Americans had sent into space; I was initiating the foreign guests into the fine points of Caucasian etiquet-

te and toasts. The tamada* asked Watson to propose the next toast. After a short hesitation Watson raised his glass and said: 'Here's to Russian genetics!'

'To Russian genetics!' Watson repeated, and went on to say that all young American physicists now engaged in molecular biology had been attracted to genetics by, and studied it under, Max Delbrück, a refugee from Germany. Delbrück had said more than once that the first person to analyse genetic problems from a physico-chemical approach had been the Russian Koltsov. Watson added that we probably knew better than anyone that most sensational work of today was nothing more than confirmation of the ideas Koltsov had put forward more than thirty years before. Watson said he was happy to be present among Koltsov's compatriots and drink to the Russian genetic school, and to Russian geneticists and their achievements.

Needless to say, his toast was cheered enthusiastically. Indeed, it was not just the courtesy of a distinguished guest but the simple truth.

My thought went back to the two scientists named by Watson. Max Delbrück was a member of the old German aristocracy. Several generations of his forebears had been famous statesmen and scientists. He himself became a physicist, and one of the founders of atomic physics. He was also one of the first to realize what dangers his science held for the people of the world in which he lived. He also immediately understood what Hitler's coming to power meant. As a result he left his Fatherland forever, abandoning his position of privilege, and broke with physics, in which a brilliant future awaited him. Now he was a leading microbiologist in the United States.

Nikolai Koltsov was the pride and glory of Soviet and world science; and for me he was more than the famous scientist that he was for Watson. I could not separate him from the soil on which he was raised. For me he was a member of the glorious Moscow school of zoologists.

Koltsov's teacher had been Mikhail Menzbir, professor of zoology and comparative anatomy at Moscow University and member of the Russian Academy of Sciences. Though ornithology—the study of birds—was his basic speciality, Menzbir was one of the most erudite biologists of his time,

* Georgian toastmaster.—*Ed.*

not only in Russia but in the world. He closely followed all scientific investigations and his laboratory was rightly regarded as one of the most advanced in the world. During his long life (he died in 1935 at the age of 80) he trained a whole cohort of Russian and Soviet biologists.

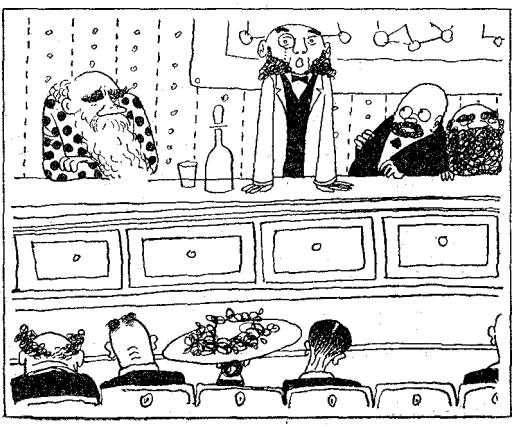
But the story does not end there, for the story of how the code of protein molecules was deciphered goes back to the time when Menzbir was a very young man.

Leo Tolstoy and the 'Things'

In the winter of 1893 more than a thousand delegates gathered in the Hall of Columns of the Nobles' Assembly Rooms (now the House of Unions) in Moscow for the 9th All-Russian Conference of Naturalists and Physicians. 'A festival of Russian science' was how Timiryazev called this forum, opening the first session with a brillant speech.

At one of the sessions a report was read by Mikhail Menzbir. On this occasion he spoke not about his favourite subject—birds—but about the latest developments in the study of living cells, and in particular, the cell nucleus, the chromosomes contained in it, and the then fashionable theories of August Weismann.

'And so, my dear colleagues,' he said, 'for all my respect for Professor Weismann, I cannot agree with his assertions. He says that all the chromosomes are identical and that each of them contains a full set of ids and determinants. It is not difficult, however, to see that he is mistaken.



Look at them through a microscope, and you will see that the chromosomes in one and the same cell are dissimilar, and vary in form and size. For all its ingenuity Herr Weismann's theory is too speculative and has too little factual evidence to support it.'

The audience listened to him with rapt attention, for he was saying what the young scientists (and most of those who filled the hall were young) were arguing about in the evenings and during the breaks between lectures, of what in fact was the last word in science.

But what was happening? The faces that had been turned toward the speaker swung round toward the entrance to the hall. Through the wide doors came an old man with unhurried gait, wearing a long beard, a coarse Russian shirt, and high boots.

Yes, it was really Leo Tolstoy. It was strange to see him there, the man who had written words that probably none of the audience agreed with. 'Botanists have found a cell, in the cell, protoplasm, in the protoplasm something else, and in this something, yet something else. There seems to be no end to them in sight because they evidently cannot have an end and that is why learned men have no time to do what people need. And that is why, since the time of Egyptian and Judian antiquity, when both wheat and barley had already been bred, to our day no plant has been added to people's food, except potatoes and these, too, not by science.'

This passage from Tolstoy's work on the destination of science and art was probably recalled with surprise by most of the delegates. Tolstoy's arrival particularly surprised a young man with a thick mane of fair hair, an ardent admirer of Menzbir and one of his favourite pupils. He was then a student and was to make a report the next day on his first piece of research 'The Development of the Pelvis in the Frog'. His name was Nikolai Koltsov, later a famous member of the Academy of Sciences. He could not understand why the celebrated author of *War and Peace*, with his known hostility to the natural sciences, should be there.

Presently Tolstoy walked over to the stage, shook hands with Professor Zinger, and took a seat next to him on the platform. Now everything fell into place, for the Tolstoys and the Zingers were known to be great friends. It was this friendship that had brought the writer to the 'alien camp',

of course, to hear his friend's paper. That the Zingers belonged to Tolstoy's circle was also only natural. The Zingers were one of the most interesting and talented Russian families of the time. Its head, now seated next to Tolstoy, was Vasily Zinger, Professor of Moscow University, a mathematician with an honorary doctorate in botany. Zinger Senior had two sons equally attracted to science: one, Nikolai, would become an eminent botanist, and the other, Alexander, a physicist whose textbooks would be studied by more than one generation of schoolboy. He would also write a famous book *Botany for Fun.*

The hall soon quietened down and again listened attentively to Menzbir. He concluded his report as follows:

'Although we absolutely disagree with Herr Weismann over the details, his main idea, however, the main idea running like a red thread through his whole hypothesis, even if he is not the first to have expressed it, is probably correct. I have in mind the view that the chromosomes are the carriers of hereditary information. Although progress in the study of chromosomes is a matter of the past few years, it is already beyond doubt that each species of animal and plant has a strictly defined number of chromosomes, that the very delicate mechanism of nuclear and cell division ensures an exceptionally accurate distribution of chromosomes among the cells; and that each embryo cell contains an equal number of paternal and maternal chromosomes.

'Like many of my colleagues, I am convinced that the chromosomes are extremely complex systems corresponding quantitatively to that of the organisms themselves but differing in quality. I am equally confident that many of those present in this hall will live to see the time when the riddle of heredity is unravelled; and I hope that some of you will contribute to the solution of that problem.'

The storm of applause did not die down for a long time. Koltsov was fascinated by the picture painted by his favourite teacher. Here really was a field of work compared with his studies on the pelvices of frogs. Though they also were necessary. 'The root of study is bitter but its fruits are sweet', as one of his teachers at school had been fond of repeating.

More and more speakers mounted the rostrum, but Koltsov had hardly recovered from Menzbir's report. But wh

was this? The speaker had taken up right where Menzbir had left off. It was Professor Kolli, a chemist. What could he say about chromosomes? Yet he said truly amazing things. Comparing the size of the head of a spermatozoon, through which all hereditary material is transmitted on the father's side, with the number of protein molecules in it, which he had calculated, he concluded that all hereditary characters were linked with a very small number of molecules.

Tolstoy had clearly chosen the wrong time for his visit. A moment ago Prof. Menzbir had spoken of the very thing in protoplasm on which he had publicly expressed his views, and now Prof. Kolli was saying they harboured still smaller things within themselves. Tolstoy frowned more and more blackly and finally walked out.

Young Koltsov also listened incredulously. Prof. Kolli was persuading the audience that the head of a spermatozoon could contain only a few protein molecules, almost as few as there were chromosomes. He did not use the term 'chromosome', of course, but that was the conclusion that suggested itself. It was impossible, however, to believe that a chromosome was nothing more than a molecule. The professor had probably made a fundamental error in his calculations. There was every ground to doubt their accuracy because far from all scientists were then even certain that molecules existed, and almost nothing was known of the structure of proteins. But for all that, the chemist had said interesting things, things that were worth thinking about. And young Koltsov thought long and intensively about them.

'Thus,' he reasoned, 'Menzbir's view that cells and their chromosomes are complex systems is counterposed to Kolli's that cells contain a few molecules, as few as there are chromosomes. Is it possible to reconcile these two views? Or is Tolstoy right to ridicule botanists whose imaginations carry them away, who try to break a cell up into bits whenever they are at a loss what to do. Would it not really be better if biologists gave up their fruitless speculations and concentrated on finding new varieties of potato and domesticating new animals?'

But Koltsov was not then inclined to follow Tolstoy's call. The contradiction between the views of the zoologist Menzbir and the chemist Kolli added to the fascination of the problem of the cell, and he was confident that its reso-

lution would guarantee the success of further, deeper research. He thought that such progress would be a surer and quicker means of obtaining valuable breeds of livestock and crops. So the student decided to dedicate his life to the problem of cell organization.

Azimov's Law

The reader may wonder how it was that someone like Tolstoy, a man of wisdom and insight, recognized the world over, could hold such deeply mistaken views of genetics.

Let us recall certain events of the distant and more recent past, and Boris Slutsky's playful verses:

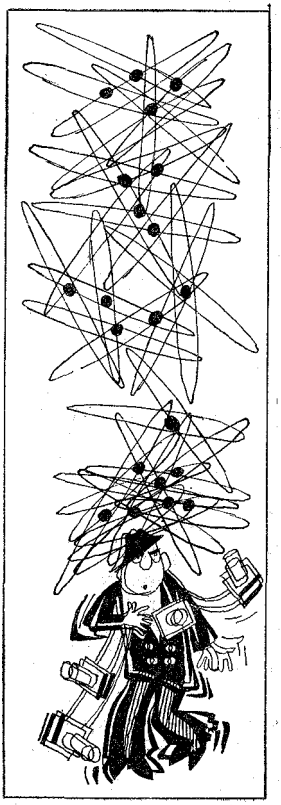
> Physicists are raised to fame,
> Lyricists are put to shame.
> It is not to be deplored,
> It is one of nature's laws.

'Physicists and lyricists' was the subject of much discussion some years ago in the USSR. An article in the youth newspaper *Komsomolskaya Pravda* signed by one Poletayev, an engineer, gave rise to heated debate, while Slutsky's verse gave a witty comment on the problem of mutual understanding between the sciences and humanities.

The most vociferous speakers in the debate were the 'lyricists' who rebelled against the one-sided technological culture. Alas! they were tilting against windmills. Scientists, particularly good scientists, always have very broad interests covering the humanities as well. They include people like Igor Poletayev, who symbolized the dry 'physicists' in the discussions. But he is quite unlike 'engineer Poletayev', who was a rather lifeless 'lyric hero', to use the literary cliché not infrequently abused by men of letters. Incidentally, this hero is not alone.

Take, for instance, what Turgenev made of his Bazarov. Isn't *Fathers and Sons* the very same as 'physicists and lyricists'? To a certain extent, at least. It is a pity, however, that it is only the astonished father-lyricists, as a rule, who write about their physicist-sons, rather than the other way round. In fact, the 'physicists' understand their 'fathers' perfectly, but they don't write. It is 'lyricists' who write for the broad public, while the profession of the 'physicists' forces them to write about quite other things for the narrow circle of their colleagues. That, indeed, is 'one of nature's laws'.

As you see, Leo Tolstoy is not alone in his views. In fact, he is one of a great many. Don't you feel how awfully modern the above quotation from his article sounds? Weren't the same words used against genetics a few years ago not only by 'lyricists'—journalists, writers and specialists in humanities—but even by reputable scientists?

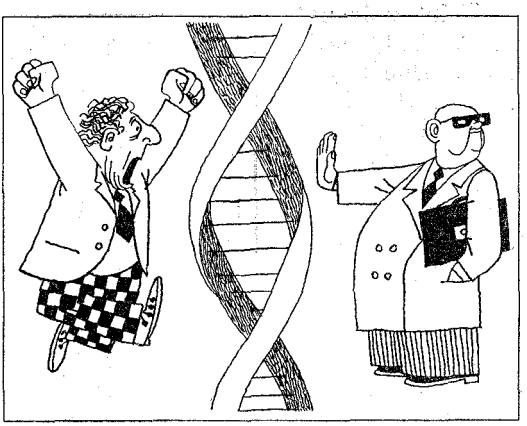


But why such a widespread opposition to genetics? Incidentally, this refers not only to genetics but to other branches of biology as well—suffice it to recall the history of Darwinism. This is a difficult problem that cannot be put in a nutshell. But it cannot be glossed over either.

Once a newspaper reporter came to a physics laboratory, where he looked, and listened, and understood nothing. Quite naturally. It is impossible for a layman to be initiated into the problems of modern science in a single day. The reporter was not ashamed of his ignorance and said so in his article. He said that it was impossible for a simple mortal to comprehend the wizardry of modern physics.

Then he came to a modern biological laboratory. The result was the same, for modern biology is just as difficult for the layman as physics. But his reaction was diametrically the opposite, and in his article he said that the biologists were engaged in such nonsense that it was quite impossible to understand anything they were doing.

One unfamiliar with higher mathematics or quantum physics would hardly call them crap for all to hear. When it comes to biology, however, many would say some nasty words about it without batting an eyelid. An ignoramus has no respect for a science that seems to be part of his daily existence. Indeed, every human being, in addition to



his other qualities, is a biological object. Biology is at first sight a simple science dealing with obvious truths. Therefore, many are apt to discuss its problems with the knowing look of an expert.

The consequences of this are especially grievous when someone from the world of science takes such an attitude. For instance, zoologists, agronomists, doctors, or philosophers no more familiar with genetics than a man in the street, however competent they may be in their own specific fields, render judgements on genetics. And that is how groundless objections and numerous false theories based on honest delusions come into being.

Thus, erroneous views of genetics among scientists have a dual cause: honest delusions due to ignorance of this very specific field, and time-serving opportunism motivated by a desire to secure personal well-being by sacrificing scientific truth.

But what about Tolstoy? Of course, he was not a naturalist. But there is another cause of misunderstandings about many sciences that are common among lay people. They don't see the difference between fundamental science and know-how. The latter truly gives immediate material benefits, any advancement in practical skills resulting in a better product quality or a bigger output. Scientific discoveries, however, give a far greater practical effect, but it comes in the long run.

Isaac Azimov, the famous American science writer, once

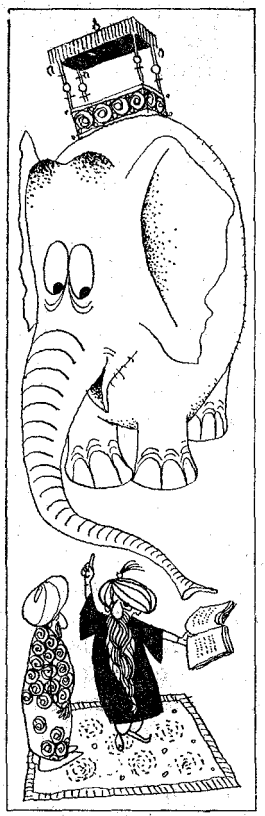
drew an interesting comparison. He found that it takes at least sixty years for a fundamental scientific discovery to yield major practical results. Incredible? But let us look at the facts.

In 1820 the Danish physicist Oersted noticed that the magnetic needle of a compass begins to move when it is brought near a wire conducting an electrical current. This was the first observation pointing to a link between electricity and magnetism. To be sure, no one then thought that the jerking needle would call into being electric motors and generators, the telegraph, and tramcars. It took a long time for that to happen. Electrification of the world did not begin in earnest until the eighties of the last century.

In 1883 Thomas Edison discovered that if a metal plate was soldered to an incandescent lamp, the latter would conduct current in one direction only. The phenomenon came to be known as the Edison effect. It is remarkable that the discovery was made not by a theoretical scientist but by Edison himself, a man with an exceptionally practical mind; but until his death Edison was unable to put his invention to practical use. And even for a long time after the invention of radio by Alexander Popov nobody conceived the idea of using the Edison effect at least to make detectors. Vacuum tubes based on this effect only began to be widely used in radio engineering in the twenties—40 years later; and 60 years had to pass before television and electronic computers were invented.

As regards aircraft and jet propulsion, however, Azimov had to run faster; he records their history from the Wright brothers' flying machine (1903) and Goddard's rockets (1926). The term turns out to be less than 60 years and in order to preserve the balance Azimov takes our day as the era of 'practical' aeronautics, and puts the 'practical introduction' of rocketry into the future. But Alexander Mozhaisky tried out a heavier-than-air machine at the beginning of the eighties, and Konstantin Tsiolkovsky suggested a liquid-fuel jet engine for space flight in 1903. It is difficult to name the birthday of the aircraft industry exactly, but the first man to be lifted into space, Yuri Gagarin, performed his feat in 1961.

One cannot, of course, take 'Azimov's law' as strictly true. The term may be more than 60 years, or less. A number of discoveries could be picked out that would suggest



another period. Then I catch myse thinking that I am writing this boo in Obninsk, where the first atom power station in the world bega operation in 1954. The atomic a began with Henri Becquerel's disc very of radioactivity. When was tha In 1896. It seems almost like witc craft.

We shall assume that Azimov approximately right. Then whe should we place the beginning of th 'unlocking' of the cell? Not, of cours in the time of Weismann and Tolsto The structure of desoxyribonucle acid—the 'material of heredity'—wa determined by Watson and Crick i 1953, while Nirenberg's first work o cracking the genetic code dates fro 1961. Judging by Azimov's law w may expect wide practical applicatio of the results of knowledge of the me chanism of heredity in the early twe ty-first century, around 2013 or 2021- it doesn't matter much which.

Such a perspective will hardl gladden anyone. Some readers ma recall what is perhaps the olde anecdote in the world known alread in the days of Babylon, about how someone promise a king to teach an elephant to read and write in 6 years, counting on one of the three—the king, the ele phant, or himself—to be dead before the time was up But let us not talk of the future, but rather look bac in time again. I don't think anyone needs convincing tha Gagarin's historic flight would not have been possible i 1961 if it had not been for the selfless work of Tsiolkovsk in Kaluga at the turn of the century; and it was not acci dental that the flight was accomplished in Tsiolkovsky' own country.

But what would have happened if Tsiolkovsky had neve lived? That is easy to answer. Man is so built, and scienc so developed, that someone else would sooner or later hav

tackled the problems as Tsiolkovsky had done, problems strange and unreal to his contemporaries. And man would have flown into outer space all the same, though later.

Incidentally, I am an optimist, and I think Azimov is wrong. The tempo of scientific development is gathering speed. What would have taken 60 years in the last century, or a couple of centuries in the Middle Ages, in our day takes—but let us refrain from rash forecasts. At any rate I think you and I will live to see the fruits reaped from the present progress in genetics.

As for Leo Tolstoy, from the standpoint of modern genetics, he lived in prehistoric times. But even for his own time he was not quite right; indeed, when he was publicly mocking the 'things' in the protoplasm, not far from him, in the town of Kozlov, wonderful new varieties of plants had been already evolved by Ivan Michurin. And Michurin, moreover, took a deep interest in these 'things', fully realizing what their investigation might yield in control of heredity.

Form and Substance

Nikolai Koltsov also understood the importance of these 'things'. Here, on the boundary between biology and the physico-chemical sciences, he saw the richest field of scientific activity, although it was then a veritable terra incognita. In one of the books of the famous physicist, Oswald, the youthful Koltsov read words that remained stamped on his mind for the rest of his life. Oswald compared the individual sciences to continents and archipelagoes scattered in an ocean of ignorance. The naturalist's loftiest ideal, he wrote, was to connect these separate pieces of land by firm isthmuses. This ideal Koltsov made his own aim. What could be more fascinating than to offer a physico-chemical explanation of the chief forms and phenomena of life? But it was a fantastically difficult task; the very posing of the problem ran counter to prevailing views.

Koltsov recalled the history of cell theory. At first, strange as it may seem, the link between form and substance appeared clearer. For Schleiden a plant cell was really a cell; he considered the membrane, which gave it the shape of a building brick, its chief member. Schwann thought that cells precipitated out of the ground substance like crystals from a saturated solution. These were primitive views,

needless to say, but one has to admit their inner logic: that the concept of form is inseparable from that of substance.

Then began study of the cell itself; the nucleus was discovered, finer and finer details were investigated, and the chemical composition of the cell body given more detailed explanation. That, of course, was a tremendous advance for science, but it was bought at the great price of a dichotomy between the problems of form and substance. For example, Max Schultze developed the theory of protoplasm as the carrier of all life properties, discarding the cell membrane and even the nucleus as something quite unessential. Does that seem preposterous? But don't forget that fifty odd years—and what a half-century—have passed since then. Then there was Chambers, who suggested (and practised what he preached) that it was best to observe and study protoplasm, 'living matter', with all cytoplasmic inclusions removed by centrifugation. The structureless colloidal solution that remained, he alleged, was the basis of life.

That was the background on which Nikolai Koltsov decided to unite the concepts of substance and form, but on a higher plane that it had been possible in the time of Schleiden and Schwann. He was a very hard-working man. By 1904 he had put forward a theory explaining the form of cells by the physico-chemical properties of their constituents. It would be extremely interesting to tell you about this theory, the research that underlay it, the recognition it gradually won, at first abroad and then in Russia (alas! as too often happens). But that would take us too far from our main concern.

We shall have to skip this long and very brilliant period in Koltsov's life, a rich, eventful life that still awaits its biographer. We shall pass over his work at the major laboratories of Europe, his progress from student to reader at Moscow University, and how, in February 1911, he abandoned his university career, so brilliantly begun, when together with other progressive members of the faculty, he resigned in protest against the notorious purge carried out at the University by the reactionary minister Kasso. We must also pass over his brilliant series of monographs *Investigations of the Form of Cells*, his work on the physiological series of cations, on phagocytosis, artificial parthenogenesis, etc. But his activities after the Russian Revolution deserve a few words.

Koltsov had long cherished the dream of setting up a biological research institute. Such institutions did not then exist in Russia; research was carried out only in connection with university teaching. Koltsov realized his dream immediately after the Revolution; the Institute of Experimental Biology was founded in 1917 itself. From 1 January 1920 it became part of the research network of the Ministry of Health. As its basic task Koltsov wanted the Institute to concentrate on the frontiers of science, in a field where Russia's progress had been slow. This field was genetics, which still had not gained wide recognition in Russia. Biologists of the older generation had been hostile to it, stock-breeding was soaked in long outmoded Lamarckian views, and none of the higher schools gave a course in general genetics. Although a whole decade had passed since Morganism was born, it was almost unknown.

Koltsov coped with the task brilliantly. The new institute quickly won itself a world reputation. Most of the leading Soviet geneticists of the older generation were trained there. Through its activities the Soviet Union, along with the United States, had moved into a leading place in world genetics on the eve of World War II. That period was the Institute's heyday and the happiest period of its director's life.

In those years genetics had long passed its infancy, where it was at the time of the Congress of naturalists and physicians where Koltsov as a student had avidly drunk in every word of Menzbir's and Kolli's reports. The many outstanding events that you already know about from our earlier chapters had taken place. Mendel's laws had been rediscovered, and that, in effect had begun modern genetics, and cytogenetics and the chromosome theory had been developed; the basic facts on cell structure and division described in Menzbir's paper were now to be found in every textbook; the external structure of the chromosomes was fairly familiar. The problem of the material foundations of heredity and the physico-chemical nature of the hereditary material were on the order of the day.

Self-replicating Molecules?

It was in Leningrad, on 12 December 1927, at the formal opening of the 3rd All-Union Congress of Zoologists, Anatomists, and Histologists. Koltsov had been asked to speak.

The subject he had chosen was 'The Physico-chemical Foundations of Morphology'. And just as he and other young men had once listened with bated breath to Menzbir, now a new generation of young people strained to catch his every word. He mounted the rostrum and began his famous speech.

'Mr. Chairman, and colleagues, let me first express my appreciation to the Organization Committee for doing me the honour of inviting me to address this opening session of our congress. It is a great pleasure for me. After this session the work of the congress will begin, and delegates will report the results of their own special investigations. But now we can all leave our specific fields for a moment and take a look at the wider problems of biology. I will try to bridge the gap between the great physico-chemical mainland and the archipelago of biological islands. At times I may run out of building material; allow me then to use a boat or even to fly over the waters on the aeroplane of natural philosophy. The problem of the association between physical chemistry and biology is so wide that the building of a continuous bridge between them is still beyond our powers at present.'

Koltsov made a long and inspiring speech, presenting calculations, formulae, and photomicrographs, corroborating his statements with numerous facts.

In winding up, he spoke about the structure of protein, about which we knew almost nothing then. It is amazing how close some of the views he expressed then were to the truth. He spoke, in particular, of the multiform variety of protein molecules. He quite correctly conjectured that their structure was based on polypeptide chains of amino acids, and as an illustration he presented the formula of heptakaidecapeptide—a chain of 17 different amino acids.

The properties of protein molecules depend both on their general composition and on the mutual disposition of their parts in the same way as the meaning of a word depends not only on the letters that make it up but also on their sequence. For instance, the words BAT and TAB, FLOW and WOLF mean quite different things although they are composed of the same letters. Koltsov had calculated just how many different molecules (known as isomers) could be obtained simply by reshuffling a chain of 17 amino acids. The result was staggering—around a million million.

It is impossible to imagine a million million. Koltsov illustrated it as follows. If the formulae of a million million isomers of heptakaidecapeptide were printed in their simplest form, designating each amino acid by a single letter, it would take all the world's printing works, and an annual rate of 50,000 volumes of 100 printer's sheets in each, taking as many years to complete the job as the number of years since the Archean period, which is the oldest in the geological history of the Earth.

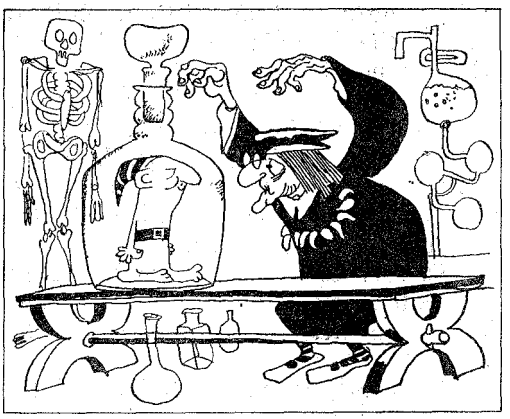
For his calculations Koltsov took a small molecule by present standards. Most proteins contain hundreds of amino acids rather than 17, a complexity that poses a gigantic task before scientists.

If you drop acid on to metal, it will bubble, and the liquid will evaporate, leaving a film. A salt is formed, and hydrogen liberated. Why? Why this reaction and not some other? Science gives a clear and simple answer: a chemical reaction produces substances with the least free energy.

But that happens only in very simple cases. It can be that different substances are produced with an identical energy rate. When sugar is produced chemically, a mixture of two varieties, or isomers, is formed; they behave differently in polarized light, and produce crystals of different form. But when this same sugar is produced in a living cell, only one of the isomers is formed. Living cells have substances of a protein type—enzymes—that guide a reaction in one definite direction.

How are such intricate molecules as proteins formed? That was a hard nut to crack. If their structure depended on energy conditions alone, a fantastic variety of molecules would result. It would be impossible to find two identical ones in the whole world. Perhaps enzymes would help? Unfortunately, no. If it were so, every enzyme (for it too is a protein) would require another enzyme in the cell to form it, and so on *ad infinitum*. The number of molecules in a living cell would be infinitely large, which is an obvious absurdity.

How was the problem to be solved then? It is easy to see that it amounts to unravelling the mystery of life in general. Is that why it is so difficult? Nature jealously guards its most treasured secrets. Then Nikolai Koltsov puts forward an unusually bold hypothesis. To get an idea



of its place in the history of science we have to go back in time 300 years.

The ancients believed in the spontaneous generation of life. Flies were thought to be generated by rotten meat, and mice by dirty linen. Alchemists said they knew the way to make a tiny human being or homunculus, and were believed. And why not? There was the authority of the Bible, where it was written that bees were borne from a dead lion's entrails. And for the few who put the authority of science above that of the Church there was the fact that Aristotle had believed in self-generation (these superstitions were so tenacious that some have survived to this day in popular beliefs and in certain pseudo-scientific theories of recent date).

The theory of spontaneous generation only began to falter in the seventeenth century. The Florentine physician Francesco Redi, a friend of the famous physicist Torricelli, doubted what had been believed for centuries, that flies were generated by rotten meat. To test it he did what now seems quite natural but was quite unusual then. He experimented. And he found that, if meat was protected against flies, 'worms' did not come into being in it. Redi's work on the meat fly appeared in 1668 and made his name famous forever. Scientific papers were then written in Latin. Redi formulated his views in this laconic Latin phrase *Omne vivum ex vivo* (all life comes from life). In time his dictum was universally acknowledged; Pasteur later extended it

to the world of invisible living things or microbes. Redi's dictum was that the living could not be generated by the non-living; but how, precisely, did the living generate the living?

At the time when Redi lived and worked a fascinating book appeared entitled *Exercitationes de generatione animalium* (The Generation of Animals). Its title page was ornamented with an allegorical picture of Zeus the Thunderer seated on a throne and holding in his hand an egg from which were emerging a spider, a butterfly, a serpent, a bird, a fish, and a child. The egg bore the inscription *Omne vivum ex ovo* (all life comes from an egg). A very essential supplement to Redi's formula. The author of the book was William Harvey, the same Harvey who some years before had discovered and described the circulation of the blood. The works of Redi and Harvey belong to the golden treasury of science, and every scientist knows their views on the origin of life. Although no one any longer writes up his work in Latin, scientists in the last century, when they discovered first cell division and then karyokinesis (division of the cell nucleus), formulated their conclusions in the same manner—*Omnis cellula ex cellula* (every cell from a cell) and *Omnis nucleus ex nucleo* (every nucleus from a nucleus).

Koltsov meditated on how protein, and not just any protein but the one needed, was formed in cells. He drew on all the data available not only to biology but also to chemistry and physics—sciences he was thoroughly familiar with—and turned over all the known mechanisms in his mind; and each time came to the same conclusion. It was impossible!

But if it was impossible, how could life exist and develop on our planet? Where did organisms get the proteins they needed? At that point Koltsov arrived at his famous hypothesis, the only one possible and the only valid one. In order to avoid the need for unrealistic selection complex molecules must be built on the pattern of existing ones. Koltsov compared the process to that of crystallization. Just as the sodium and chloride ions dispersed in a solution of common salt lined up in a regular pattern about a growing crystal, so amino acids also had points of 'affinity' in contact with similar points on an already existing protein molecule with corresponding amino acids. That

was the solution, at long last! Although its correctness had yet to be proved in experiments, it was the first explanation ever given of the mysterious process.

All this was the climax of Koltsov's report. Then he unfolded yet another far-reaching conclusion to his spellbound audience.

'If assimilation really boils down to crystallization,' he said, 'it follows that protein molecules share a quality of the greatest significance with organisms, a quality that has hitherto been regarded as the distinguishing feature of living organisms. It took much time to establish that an organism is generated only from another organism, from an egg: *Omne vivum ex ovo, Omnis cellula ex cellula, Omnis nucleus ex nucleo.*

'Now we can add yet another dictum: every protein molecule arises in nature from another, similar protein molecule. Through the crystallization about it of amino acids and other protein rudiments dispersed in the solution—*Omnis molecula ex molecula* (every molecule from a molecule).'

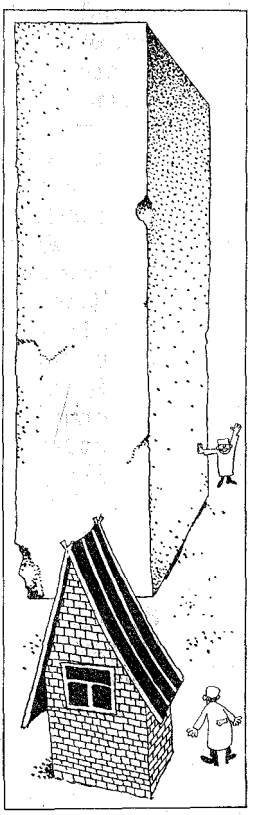
That meant that multiplication (replication) was not the exclusive property of living organisms; it was the most probable mode of generating all complex vectorial systems in nature.

We cannot expound the whole of Koltsov's report here, but you already have the essence of it—self-replicating molecules. It sounds most improbable, doesn't it? Without a doubt. And that is why few agreed with him then and there. Those inclined to fantasy were delighted by his 'mad hypothesis'. Others took a sceptical view. But however mad the hypothesis seemed, it gave a plausible answer to the question posed, and the sceptics could offer no other explanation. Koltsov's supporters set about trying to corroborate his hypothesis with a considerable number of experiments.

Suspicion Falls on Nucleic Acid

To corroborate Koltsov's hypothesis was not so simple, for protein chemistry was still in an embryonic state. But facts—very few, it is true—accumulated that seemed to support it. Certain facts on the conversion of zymogens into enzymes were particularly striking confirmation. Enzymes are biologically active substances of a protein cha-

ıcter, while zymogens are their ›rototypes', i.e. the material from 'hich enzymes are produced.



Particularly interesting were the ata regarding the formation of tryp-n, one of the digestive enzymes. It produced from trypsinogen. The most ıteresting fact was this: inactive 'ypsinogen is converted into active 'ypsin in the presence of trypsin self. Didn't that seem brilliant ›nfirmation of Koltsov's hypothe-s?—trypsin building new molecules om trypsinogen in its own image.

Alas! special experiments showed ıat it was not so. The trypsins various animals differ slightly om one another; bovine, for example, ffers from pig's, and pig's from ıeep's. Experiments were made. Bo-ne trypsin and pig's trypsinogen ere put into a test-tube; the trypsino-›n was converted into trypsin. But ıere is nothing special about that, ıt when the trypsin formed was exa-ined in detail it turned out to be g's trypsin. That meant that the emplate' (bovine trypsin) had not ıssed on its specific character, and g's trypsin was obtained from a pattern that was not esent in the experiment. At first it seemed inexplicable. 'hen the size of the molecules was determined, however, ıat of trypsinogen proved bigger than that of trypsin. he 'brick' proved bigger than the house. It seemed that ypsin was not built up from trypsinogen, but resulted om its partial breakdown.

The process is now known in adequate detail. Although e enzyme molecules are very big, their functioning de-›nds on 'active groups' of very small size. Imagine a ›w with a very taut string. If the string is broken the ›w will straighten out. If you can imagine a bow bent so ırd that its ends touch, you will have a model of the ypsinogen molecule. The active group is at one end of

the bow, and cannot operate because it is connected to the other end, which cuts it off, preventing its contact with the substance it must act on. If a definite part (the 'string') is torn from such a molecule, the latter will straighten out; the active group will be released, and the inactive trypsinogen converted into the active trypsin. Clearly it has nothing to do with Koltsov's hypothesis.

There were other cases, though not many, when it seemed that Koltsov's hypothesis of self-replicating molecules had been confirmed, but each time deeper study showed that it was not so.

What we have said applies to proteins. And that is extremely important. The hereditary information that must be stored in molecular structures is immense. Therefore it can be carried only by substances whose molecules occur in very great variety. Only among them was it worth looking for 'self-replicating' molecules. Of all the substances known proteins had the requisite variety. They were literally *hors de concours*.

However, in the middle of the forties a new challenger appeared—nucleic acid. It had been known a very long time. Back in 1868 a young chemist Friedrich Miescher, who had just embarked on his scientific career at Hoppe-Seiler's famous laboratory in Tübingen, was examining soiled dressings. A strange and obnoxious object for study, wasn't it? An established scientist would hardly bother with such work, but a young probationer must do what he is told. The most thankless jobs fell to Miescher's lot. He evidently did not hit it off with his professor, if he was given the chemical composition of pus as the subject of his independent research.

Miescher, however, was persistent and hard-working. Why not pus, after all? He pinched his nose and scraped the grey substance from the dressings, isolated the cells from the mass, and the nuclei from the cells, and began analysing the nuclei. What he obtained was quite unexpected; one of the substances isolated was like nothing hitherto known to chemists. Miescher repeated his experiments again and again, and each time obtained the same results. Finally he ventured to approach his chief. 'Herr Professor,' he said timidly, 'the cells of pus seem to contain some unknown substance. It contains quite a lot of phosphorus, is soluble in water, and is precipitated by alcohol.'

Hoppe-Seiler checked his pupil's analyses. Yes, he was right. A new substance had been discovered. Since it had been isolated from cell nuclei, they christened it nuclein.

Miescher moved to Basel, where he took up independent research; but from time to time he turned back to his youthful work. His attempts to isolate nuclein from cell nuclei of various origin were each time successful. It was evidently an indispensable constituent of the cell nucleus. In 1872 he succeeded in breaking nuclein down into two components—an acid and a base. The acid part is now known as nucleic acid. The base Miescher himself referred to as protamine.

Although the discovery of nucleic acid in the cell nucleus seemed certain to attract interest, chemists treated it like Cinderella for many years. Few took any note of it. What was known of it, of course, could hardly excite special interest. It was thought to consist of small molecules (small, that is, in comparison with protein), absolutely identical. Most scientists ascribed a merely auxiliary role to it. It was supposed, for instance, that it protected the chromosomes against harmful external influences by forming a sheath around them, an attitude shared by Koltsov among others.

But slowly, very slowly, evidence accumulated pointing to its participation in more important processes. Before the war the Belgian Brachet and the Swede Caspersson, working independently of each other, noticed that the more intensive protein synthesis was in a cell, the more nucleic acid it contained. They became convinced that nucleic acid played a role in the synthesis of protein, but few people shared their view. There were also other facts, but they too impressed few people.

It was not until 1944 that work was published that made scientists believe in nucleic acid as capable of something more than forming a sheath for chromosomes.

There are several varieties of pneumococci, the bacteria that cause pneumonia. They have a capsule of a special substance related to sugars, but some forms have not. When this kind is cultivated on a solid nutrient it produces 'rough' colonies, whereas normal pneumococci, with a capsule, give neat, 'smooth' colonies. Both are stable, hereditary forms; smooth types always produce smooth offspring, and rough types rough ones.

In 1928 a group of scientists had obtained surprising

results, the like of which had never been observed before They had killed normal 'smooth' bacteria by heat and mixed them with live 'rough' ones. In the culture live 'smooth' pneumococci were discovered. There was no doubt that all the original 'smooth' bacteria had been killed; that had been checked carefully and repeatedly. Consequently, one of two things had happened: either the killed 'smooth' bacteria had been restored to life by the company of the live 'roughs' or, even more amazing, the 'roughs' had acquired the capacity from the dead 'smooths' of building a capsule around themselves. The transformation proved to be stable; all the descendants of the transformed pneumococci were also 'smooth'.

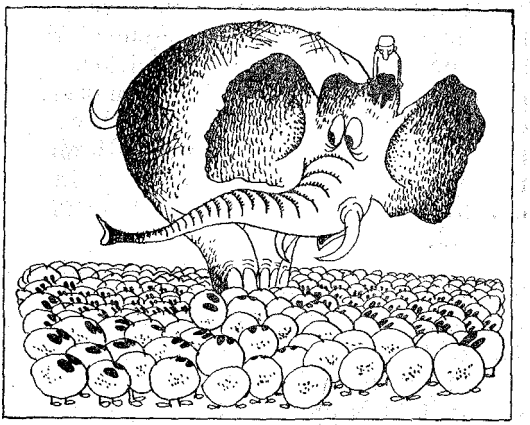
In 1931 the same results were obtained using a cell-free extract instead of killed bacteria. When an extract from 'smooth' bacteria was added to the medium on which 'rough' bacteria were developing, the same transformation took place. Hence bacteria must contain some amazing substance (which was called PTF or pneumococci transformation factor) capable of causing directed changes in the hereditary properties of other bacteria. But what was the substance?

Scientists were unable to answer that question for a long time; but in 1944 Oswald Avery and his associates succeeded in isolating the enigmatic PTF. After long and intricate separation and purification they finally recovered a definite substance that had the same effect as a whole extract. It turned out to be nucleic acid.

Evidence Piles Up

Avery's findings were so persuasive that many took serious note of nucleic acid. One investigator after another began to come up with similar evidence. I shall only describe two trends in their research.

The first trend related to the reproduction of bacteriophages, that is to bacterial viruses, the most minute of parasites. They cannot be seen through an ordinary microscope; an electron microscope is needed. Bacteriophages, or phages as they are called for short, have a fairly simple structure, a long thread of nucleic acid rolled up in a ball and covered with protein. A single particle of a phage is quite enough to infect a bacterium. Events then develop truly dramatically. Within a half-hour or so the bacterium dies,



its membrane bursts, and about a hundred new, fully developed phages emerge into the surrounding medium.

The phenomenon fascinates many scientists. They hope, with good reason, that study of bacteriophages will help them solve some of the major riddles of life. The laws of nature are the same for all living organisms, and it is easier to study them on the simplest objects (and what can be simpler than viruses and phages, particles that lie on the border between dead and living matter?). On the other hand, the process of phage proliferation and development is extremely fast. What can be studied on bacteriophages in one working day would take centuries on elephants.

In order to explain the details of the process of bacterial infection, it was necessary to learn what penetrates the bacterium, the whole phage or only part of it? Which constituent of the phage was required for its proliferation? Two Americans, Hershey and Chase, among others, racked their brains over this riddle. And it was far from easy. Under the microscope even bacteria appear as tiny dots, spirals and rods. It is rarely possible to discern any details. As for bacterial parasites, to say nothing of their individual details, even an electron microscope does not help. In Koltsov's time (not to speak of Mendel's) the problem was simply insoluble. But in our day biologists are aided by the other sciences. Hershey and Chase were helped by physics.

the atom that have the same chemical properties but differ in their physical ones. Physicists are now able to obtain radio-active isotopes of any element artificially. These atoms emit radio-active radiation and are easily detected by special instruments that are available in any modern laboratory. And what is particularly important, they can be detected in smaller quantities than is possible by any other method.

Since the isotopes of an element behave identically a small quantity of a radio-isotope, added to its conventional form, will behave exactly like the bulk of the substance, but will continually send out radio-active signals by which it can be located wherever it is, thus giving information on what is happening to the substance as a whole. These radio-active atoms ('labelled' atoms as they are figuratively called) have proved invaluable to modern science, so we shall meet them again later. It was 'labelled' atoms that helped solve the riddle we are considering now.

The idea was simple, to 'label' the different parts of a bacteriophage with radio-isotopes. As we know, a phage consists of nucleic acid and protein. The latter contains a fairly large quantity of sulphur and practically no phosphorus. Nucleic acid contains much phosphorus and no sulphur. Therefore, if radiophosphorus is introduced into a bacteriophage, it will be taken up into nucleic acid and emit radio-active signals by which it can be followed. In exactly the same way radiosulphur can be used to trace what happens to protein.

But how can a bacteriophage be 'labelled'? Ordinary bacteria not infected by bacteriophages were reproduced on a nutrient medium rich in radiophosphorus or radiosulphur. As a result they were loaded with a large number of 'labelled' atoms. They were then infected by a bacteriophage. The bacteriophages obtained from a labelled bacterium naturally had a radio-active tag. If radiophosphorus was used, only the nucleic acid was labelled, and if radiosulphur was used the tag was on the protein.

The decisive experiment could then be started. Labelled bacteriophages were introduced into a culture with normal unlabelled bacteria. After a time, long enough for the bacteria to become infected, they were extracted from the culture, taking every precaution to ward off free bacterio-

phage, and put under a counter capable of detecting radio-active particles. It was found that they emitted signals only when the bacteriophages had been labelled with radiophosphorus. Radiosulphur did not get into a bacterium. Hence only nucleic acid penetrated bacteria during infection, the protein coat of the bacteriophage remaining outside.

But the most surprising thing was that a fully mature phage containing a specific phage protein was formed inside the bacterium, yet none of the proteins of the bacterial cell was known to have the properties of phage protein. Was it possible that nucleic acid built a specific protein? However surprising that conclusion might seem no other explained the facts obtained. These experiments, carried out in 1952, no less clearly than those with pneumococci, pointed to a genetic role of nucleic acid.

It is also worth telling about the experiments with the virus of tobacco mosaic. This virus (TMV for short) was the first to be discovered; it was discovered by Dmitry Ivanovsky in 1892. But, besides being the first virus found, it turned out to be an exceptionally convenient object for research, and became the first virus to be obtained in crystalline form. The first living thing produced artificially in a laboratory was this same TMV. And that is what we shall now tell about.

Just like phages, TMV is nucleic acid with a protein coat. In 1955 Fraenkel-Conrat succeeded in breaking TMV down into its components, protein and nucleic acid. Two pure chemical substances were thereby obtained. Of course, they were not synthesized, but taken from nature. Then scientists mixed the substances and applied the mixture to tobacco leaves. The plant developed the characteristic symptoms of mosaic disease. Thus a primitive living organism was created for the first time from two chemical substances in laboratory conditions.

The next step was to take protein from one TMV and nucleic acid from another (there are several varieties of TMV). The experiments were a success, but if you were to think that in these experiments, as with Mendel's crossing of peas, the progeny of the phages had the characters of both 'parents', you would be mistaken. In all cases the virus obtained had the character of the parent from which nucleic acid had been taken. In addition, this was true

of the properties of the virus prote... as well. In other words the experiments suggested the same conclusions as the previous ones. It is interesting that another scientist, Gerhardt Schramm, soon succeeded in obtaining TMV by painting tobacco leaves with pure nucleic acid containing not even a trace of protein, i.e. achieved the same results with TMV as Hershey and Chase had with bacteriophages.

Thus more and more data came to light that suggested that nucleic acid played an exceptionally important genetic role. Some scientists felt it was the very substance of heredity from which the mysterious genes were made; but how could that be reconciled with the concept of nucleic acid being made up of small molecules as like as the match sticks in a single box. But scientists were not embarrassed by that.

They were not embarrassed because chemists too now took a quite different view of nucleic acid than in the times of Miescher and Koltsov. But we need to know how it was constructed, and for that we must make an excursion into the field of chemistry.

Before we try to understand the structure of nucleic acid, let us recall how proteins are built up. Just as houses are made of bricks, and written words are formed from letters, proteins consist of simpler molecules, amino acids. The comparison with words is perhaps the more convenient of the two. Bricks are all the same, while letters are all different. Amino acids are also different, and proteins are made up of combinations of 20 different ones—almost as many as there are letters in the alphabet. And just like letters, amino acids are arranged in a linear sequence, one after the other. The amino acid composition of various proteins differs; however, it is not only their composition that is important but also the order of the amino acids in the sequence. It will be perfectly clear that just as a practically infinite number of words can be made up from the letters of the alphabet, so an infinite variety of proteins can be built up from 20 amino acids.

As for nucleic acid, it also consists of simpler molecules, known as nucleotides. But whereas a protein is made up of 20 amino acids, there are only four nucleotides, and what is more, all nucleic acids have roughly the same composition. Nucleic acid contains all the nucleotides in approximately equal proportions, though analyses have

never yielded exactly 25 per cent, but that could have been due to the error likely to happen with the inaccurate methods initially used. So, for a long time the tetranucleotide hypothesis that a molecule of nucleic acid consists of four nucleotides, one of each kind, was universally accepted.

It became clear in time that the molecule of nucleic acid was much larger than had been originally thought. Little by little it became bigger and bigger. Nucleic acid is easily destroyed, and originally chemists had been working only with its fragments. That is how they came to believe that large molecules were made up of a multitude of identical 'fours'.

We said that all the molecules of nucleic acid were thought originally to be identical; but that is not quite the case. Or rather it is true only of nucleic acid obtained from the cell nucleus. Nucleic acid is present in other parts of the cell, besides the nucleus, but there it has a rather different composition, which was clear from the very beginning.

The nucleotides from which nucleic acids are built are themselves quite complex. Each of them consists of a residue of phosphoric acid, a sugar molecule, and another molecule called a base. All the molecules of phosphoric acid and sugar in nuclear nucleic acid are identical. Nucleotides differ in containing one of four different bases.

Cytoplasmatic nucleic acid differs from nuclear nucleic acid only in that it contains another type of sugar and that one of the four bases is slightly altered (the other three are the same in both types of acid). Nuclear nucleic acid is now known as desoxyribonucleic acid, or DNA for short, while the cytoplasmatic form is called ribonucleic acid, or RNA.

Any nucleic acid—be it DNA or RNA—contains a roughly equal number of all four nucleotides. As methods of analysis improved, ever newer figures were obtained, but the correlation of nucleotides remained only approximately equal. Even when the accuracy of analysis had become so high as to give quite exact rather than approximate figures, the ratios continued to vary.

The most strangest thing, however, was that workers in different laboratories seemed to make the same errors. Working, say, on the same bacterium, known as *Aerobacter aerogenes*, one scientist finds that its content of adenine (one of the four bases) is 20.5 per cent instead of the 25 per cent expected. Repeating his experiments, another obtains 21.3 per cent, a third, 21.2 per cent, a fourth, 20.3 per cent.

(I have not invented these figures but taken them from research papers.) The figures vary, of course; but they are always around 21 per cent, with an error always of less than one per cent. The deviation from 25 per cent therefore cannot be explained as a chance occurrence.

Two scientists took a particularly keen interest in the variations in the composition of nucleic acids, or to be more precise, of desoxyribonucleic acid (DNA). One was Professor Andrei Belozersky, of Moscow University, the other, Professor Erwin Chargaff, of Columbia University in New York. Each of them examined tremendous numbers of samples of the most varied origin, using the most accurate methods of chemical analysis. And each concluded that nucleic acids have type specificity.

Every species contains a nucleic acid of an exactly defined composition. No matter from what organ it is isolated, for example the liver, spleen, brain, or muscles of a guinea-pig, it always has the same composition. Analysis of the nucleic acid of rats gives rather different figures, but again they are identical for all organs. This means that nucleic acids (now we must use the plural) may be quite varied. But what about the tetranucleotide hypothesis? It had to be discarded as contradicting the facts.

Consequently, by the time Avery, Hershey, Schramm, and the others had obtained their amazing findings pointing to a genetic role for nucleic acids, their conclusions no longer contradicted the chemical data. Chemists now knew of two groups of organic substances that had a very great variety: nucleic acids as well as proteins.

It is easy to argue from hind sight. Thumbing the pages of old journals, you will occasionally find data on the genetic role of nucleic acids, and it is much simpler now to appreciate them at their true worth.

We can now draw the same conclusion even from facts of 70 years ago. In 1896 the German chemist Albrecht Kossel examined the composition of salmon milt. Its cell nuclei contained DNA and protein, as Miescher had found earlier. But the protein content was 50 per cent less, and it was a peculiar protein. Its molecules were small and consisted to 80-90 per cent of a single amino acid, arginine. It was a really surprising finding, especially as it was made on the milt that fertilizes spawn and transmits all the hereditary characters on the father's side.

The hereditary substance, if it exists, must be present in milt. But the proteins Kossel discovered in them were little suited for such a responsible role. Indeed, such a uniform composition of protamines (to use Miescher's name for them) could not ensure much variety of protein molecules and so the transmission of a large quantity of hereditary information.

Indeed, if we imagine a chain of ten different amino acids, we can get 3,628,800 different permutations from it; but if eight of the ten are identical, the number of permutations drops to 90. It follows that the protamines in milt can only store 1/40,000th of the amount of information stored in ordinary proteins. Beyond doubt, very strange. And the nuclei of other cells not involved in the reproduction of progeny contained other proteins, known as histones, of a much more intricate composition, instead of protamines. In those distant days it was impossible on the basis of these facts alone to deny the role of proteins in the transmission of hereditary characters and attribute that role to nucleic acids.

Now, looking back, we take a different view of many things. It was known from the very outset that DNA was contained only in the cell nucleus (hence the name nucleic acid); later it was found to be present only in the chromosomes. If genes are located in the chromosomes does that not suggest that DNA has something in common with them? The law of the constant quantity of DNA in a cell was formulated a long time ago; all diploid cells of a given organism contain a strictly determined quantity of DNA. And that is a property that the hereditary material must possess.

But all that only now seems suggestive. During the long reign of the tetranucleotide theory nucleic acid seemed uninteresting material. For biochemists it was a Cinderella, while geneticists were not concerned with biochemistry, let alone nucleic acids.

By the beginning of the fifties, however, enough evidence had accumulated for nucleic acid to be considered no less important genetically than proteins. I say 'no less' because there were few who dared to affirm that they were more important. To say that it was necessary to elucidate the structure of nucleic acids and to learn more about their functions in the organism. But many realized that a period of great discoveries was in the offing for genetics.

Cinderella Becomes a Princess

Molecules Duplicate Themselves

A herd of cows was grazing on a green meadow bathed in sunshine. A little away lay a group of men dressed in jackets and ties. The cows were busy with their own affairs—nibbling the grass, chewing their cuds—and not paying the least attention to the people. And the people were watching the cows because they had nothing else to do. They were resting. They had just broken off a discussion of the most complicated problems of modern physics, in which Niels Bohr himself had taken part, and had gone to the nearest meadow to lie on the spring grass. Beyond a nearby copse they could see the roofs of Copenhagen, as they basked in the sun, smoking and joking. They watched the cows with interest, because townsmen and arm-chair scientists do not often get the chance to see them so close. The cows went on chewing with concentration.

'Gentlemen!' one of the physicists exclaimed. 'Look how they chew. They don't move the lower jaw from up and down like us but from left to right.'

'I beg to disagree,' his neighbour retorted. 'Your definition is incomplete. That one over there with the crumpled horn is chewing from right to left.'

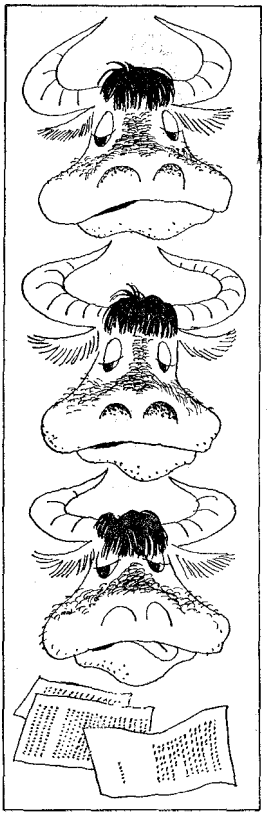
The scientists began wise-cracking. 'No, that's not a scientific approach. You haven't collected sufficient material or processed it statistically.'

'Hasn't it something to do with stereo-isometry and the optical effect of organic substances?'

'Work it out and you'll get one to three, the usual Mendelian segregation.'

They got up and strolled back toward Copenhagen and their discussion of physical problems.

Some time passed. One of those present, the well-known physicist Pascual Jordan, wrote a quasi-scientific article about 'left- and right-turning' cows when he got back home. He round up by saying that his conclusions were ten-



because their validity had been proved for cows of Danish nality. He showed it to his ls, and they laughed heartily. he had a mischievous idea: ıot send it to a scientific jour- Would they print it or not? ıere to send it? Jordan did esitate long. In London there he famous scientific journal *re*, one of the oldest in the , a weekly with a huge circu- ı, read by scientists of every ılity. The main thing, how- was that it had 'Letters to]ditor' section in which brief ts on recent discoveries were ɔd. Every issue carried a ote disclaiming the editors' nsibility for the content of s. What more suitable place? ll Jordan was very soon sur- l to see his letter printed. Then nt the editor (then Lord Aston, nventor of the mass-spectro- ') a saucy letter, advising him ɔk through his journal once in ile. To which Aston replied true British sang-froid: 'I read nonsense'.

is practical joke did not in the least undermine the al's authority. Today, too, when a scientist wants ake a discovery known to as many colleagues as pos- he writes a brief article and sends it as a letter to]ditor of *Nature*. Readers all over the world open each issue at the *Letters to the Editor* page. One can often much of interest there.

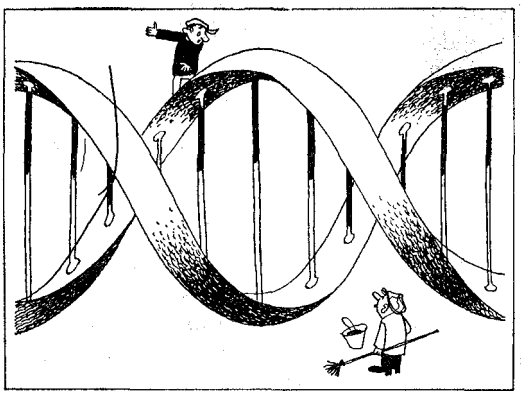
1953, an issue of Volume 171 of *Nature* carried a re- short like all letters to the Editor, on the macro- cular structure of desoxyribonucleic acid by F.H.C. and J. D. Watson. This brief communication, less than ge long, immediately made their names known to all tists interested in problems of heredity or nucleic acids.

Why was the article so famous and what had its authors accomplished? As the title suggests, it dealt with the structure of DNA. To describe to a layman briefly how it was done is impossible. But the procedure was essentially as follows. When X-rays are passed through a crystal they produce a pattern of spots on a photographic plate arranged according to the position of the atoms in the crystal. But the picture obtained is far from a 'portrait' of the molecule. To decipher an X-ray picture and determine the arrangement of the atoms from it requires complicated calculations, wide and deep special knowledge, and a good deal of imagination. But with DNA, the very process of making the pictures involves a number of specific difficulties.

The first attempts to decipher the structure of the DNA molecule by means of X-ray diffraction date from the first half of the forties, but the pictures then turned out so unintelligible as to make definite conclusions impossible. The Englishmen Wilkins and a group of associates, however, succeeded then in making excellent photographs after long and painstaking efforts, but were unable to decipher them. Although past masters at making X-ray diffraction pictures they were not experts in deciphering them, and no wonder for the degree of specialization in modern science is so great. It was Watson and Crick who were to decipher the pictures.

How, in their view, did the DNA molecule look? It can best be compared to a ladder twisted into a helix. We already know that nucleic acids are made of nucleotides, while each nucleotide consists of three parts, a sugar, phosphate, and a base. Nucleotides are linked in long chains so that the main strand of this chain consists of alternating molecules of sugar and phosphate, while the bases jut out to one side. Continuing the comparison with a spiral ladder, the sugar-phosphate chains represent the stiles or uprights, while the bases of the two chains linked to each other form the rungs. That, in general outline, is how the DNA molecule is constructed.

But the most interesting point is something else. The X-ray diffraction picture not only showed DNA to be a double helix but also revealed its diameter, the distance between the coils—in a word, very fine measurement. As chemists already then knew how the individual atoms



making up DNA were linked to one another, the chemical data now had to be brought into line with the X-ray diffraction picture.

If they coincided, it meant the structure of DNA had been described correctly; discrepancies would mean that the model did not correspond to the facts. But to fit all the atoms into this 'ladder' was not a simple task. Atoms can form chemical bonds only when they are a definite distance from one another, and the chemical bonds must form quite definite angles. Such are the laws of the structure of matter. And nature demands observance of its laws. These distances and angles can vary only within very narrow limits.

Crick and Watson arranged the atoms in their 'ladder' in accordance with the laws of nature. At first all went well. All the atoms fitted accurately into the 'stiles', but when it came to the 'rungs' an obstacle arose.

Here we must turn back to chemistry again. As we already know there are four sorts of base in DNA. Their formulae are fairly complicated, but there is no need for us to examine them in detail. The important thing is that they differ in size. Two of the bases, thymine and cytosine (called T and C for short), belong to what is called the pyrimidine group and are relatively small. The other two—adenine (A) and guanine (G)—belong to the purine group and are almost twice as big as their pyrimidine fellows.

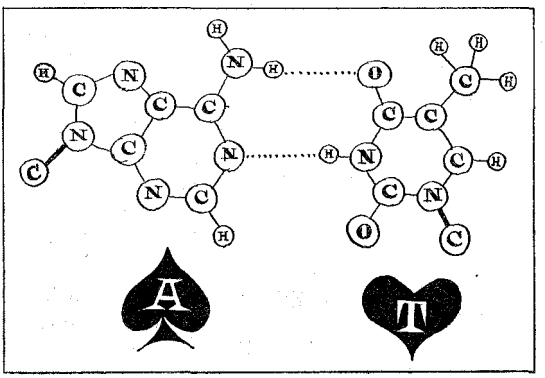
Although I am trying to write as simply as possible, it is unlikely, if you are not a chemist, that you will take

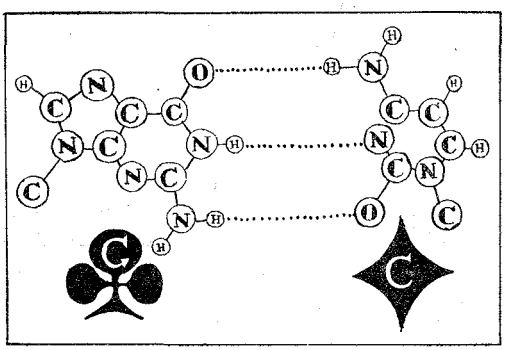
in at once everything I have just said. But if you want to understand what is to come you will have to remember it. As a matter of fact, it is enough to remember that two bases are large and two are small. Sometimes the four bases are compared with the four suits in cards, the blacks (spades and clubs) and the reds (hearts and diamonds).

In Greek mythology there is a fable about the robber Damastes, nicknamed Procrustes, who lived where the highway crossed the river Kethis. He used to capture travellers and lay them on his bed. If it was too long for the prisoner, Procrustes would stretch him, breaking his bones; but if it was shorter than his 'guest' the robber would cut a piece off him. Only the famous son of Aegeus, king of Athens, and Aethra, Theseus, was able to overpower him. The expression 'Procrustean bed' is still used when we want to describe artificial conformity to an arbitrary standard.

The double helix proved a veritable Procrustean bed for purines and pyrimidines. Each rung of the ladder had to be made up of a pair of linked bases. Almost none of the pairs, however, was suitable. There was not enough room inside the helix for the two purines ('black suits'), while the two pyrimidines ('red suits') proved so far apart that they could not form a chemical bond. Only when one purine and one pyrimidine were taken, did their size prove to correspond exactly to the spiral diameter. And then, the atoms to be linked turned out in half the cases to be at opposite ends of the molecule and so were unable to form a bond. Only two pairs met all the requirements: A and T ('spades' and 'hearts') and G and C ('clubs' and 'diamonds'). That might have seemed incredible if it had not agreed with the chemical data. In the experiments of Belozersky and Chargaff, mentioned above, it was found that the level of A in all DNA specimens was equal to T and of G to C. In spite of all the difficulties everything was a perfect fit, and Crick and Watson were sure they were right.

Everything we have described here is very important and very interesting (at least for specialists). But if Crick and Watson had limited themselves to that alone, their names would not have become as famous as they are today. Quite a few people were busy deciphering X-ray diffraction pictures, but each of them did not receive a Nobel Prize.





It went to Crick and Watson, and to Wilkins who did the photography.

To understand the full importance of their work let us reason as follows (never forgetting that in the double helix of DNA A must always be opposite T and G opposite C). Imagine a certain sequence of bases in a chain of DNA, for instance A—G—C—T—T—G—G. Recalling the rule for the formation of pairs, we can say immediately that the sequence of bases in the other chain will be as follows: T—C—G—A—A—C—C. Hence the corresponding portion of the molecule must look like this:

A—G—C—T—T—G—G
T—C—G—A—A—C—C

Let us now assume that the double helix has unwound into separate coils, and a new helix has begun to form near

each of them. What will happen then? It is easy to see that we shall have the following combination (to distinguish between old chains and the new ones we shall designate the new bases by lower-case letters, although there is no difference in fact between them and the old ones):

A—G—C—T—T—G—G
t—c—g—a—a—c—c
a—g—c—t—t—g—g
T—C—G—A—A—C—C

What have we got here? Two molecules, each exactly like the initial one. Do you grasp what that means? These are the very same replicating molecules that Koltsov predicted back in 1927. Of course, he thought they were proteins, for the nucleic acids were then 'beyond suspicion'. But the discovery of such a property in DNA did not come as a surprise in 1953 after what had been learned about it, and the very structure of its molecule now suggested its possible amazing ability for self-duplication. But it remained to prove it.

Watson and Crick cannot be reproached for underestimating their discovery. All the conclusions we have mentioned (and some others) were contained in their short letter to the Editor of *Nature*.

Checking the Hypothesis

We have talked a great deal about molecules; isn't it time we talked about people? For it was people who made those discoveries.

Every nationality has its own typical image. The Englishman is level-headed, cool, and rather stiff. The German is pedantic, disciplined, and thrifty. And so on. But we live in times of change and mixing. The British are rapidly becoming Americanized and more and more informal, calling each other John or Michael rather than 'sir' or 'mister'. When I first met Britishers they were quite unlike the characters of 'English' anecdotes or Dickens' novels. The first Englishman to conform to my childhood picture was Francis Harry Compton Crick.

I saw a man above average height, dressed in a neat dark suit, examining some photographs, with mild features framed by short reddish sideburns, a gentle smile, and kind, clever eyes. He was courteous and amiable, but very

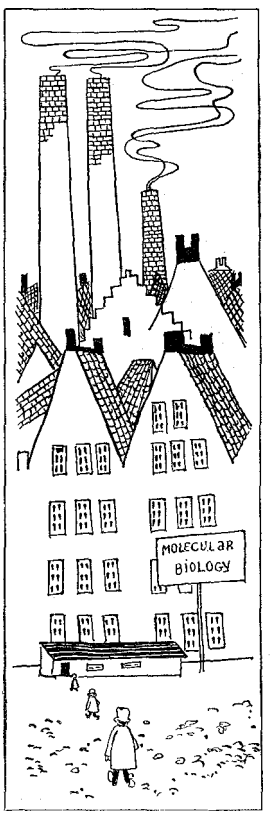
reserved as befits an Englishman. He seemed older than his 45 years (it was in 1961), because of his grave looks and early baldness that made his forehead seem very high. His companion, a Russian lady who spoke quite good English, was explaining something to him about the photographs. Suddenly Crick asked her to repeat what she had said.

'What, isn't it said that way?' Olga asked in surprise.

'Yes, it is, but it is American, not English'.

Most Englishmen intersperse their speech with Americanisms, but I have never heard Crick use them. His countrymen say his manners are Edwardian.

Like most scientists Crick had an outwardly uneventful life. He studied at London and Cambridge, and during the last war served with the Admiralty, developing instruments to locate U-boats. When the war was over he, in his own words, fell to 'reading and thinking'. The end result was that he joined the Laboratory of Molecular Biology of the Medical Research Council. 'Laboratory' is too grand a term, really, for what did not even have a place of its own. Crick fixed himself up a corner in the Cavendish Laboratory while his associates were scattered over a dozen other places. It was not until Crick and Watson had made their discovery that the Laboratory of Molecular Biology obtained premises of its own, a small building near the Cavendish Laboratory lent them by the University Department of Metallurgy. When Crick and his colleagues wanted to mount big experiments they had to use a room in the neighbouring Zoology Museum.



It would be wrong to think that the Cambridge MRC Laboratory of Molecular Biology owed its fame to Crick alone. It was directed by

Max Perutz, famous as the first (with John Kendrew) describe the structure of haemoglobin. Four of the 30 so staff researchers of the laboratory were Nobel Pr winners.

I specially emphasize that they were staff workers. T point is that in many countries scientists are very of (much more frequently than in the USSR) taken on te porarily at laboratories other than their own. In 1953 young American physicist Jimmy Watson was one of th scientists. He had recently graduated in his own coun and had come to Europe to work in laboratories there. was while he was at Cambridge, working with Crick, t they made their famous discovery.

While Crick is a typical Englishman, Watson cannot called a typical American. His free-and-easy manners member his sitting on the floor in Natasha's flat), his bro smile ('keep smiling', Americans are told from childhoo and the bright tie decorated with a double helix (Cr would never wear a tie like that) cannot conceal his inn self-consciousness. He does not feel very sure of hims in company, but does not put on airs since his rise (so you to fame.

Both Crick and Watson steadfastly avoided the bl of publicity that fell on them (though I have heard t Watson has now fully overcome the shyness that stru one so in Moscow).

Molecular genetics is one of the youngest and most p mising fields of modern science. Its development has c minated in a great victory for human intelligence, deciphering of the genetic code and the establishment the molecular ABC of heredity. The day Crick and W son's article appeared in *Nature* is often taken as its bir day.

The ABC of heredity was sorted out because it agita the minds of very many different people—geneticists, b chemists, crystallographers, mathematicians and so on— Great Britain, the USSR, France, the USA, Germa Japan, and other countries.

The breaking of the code of living molecules might ha been different if it were not for an eccentric astrophysic living in Boulder, a small town in the state of Colora in the USA. His house on Sixth Street was quite unl those of his neighbours. The lop-sided chimney stick

cture of DNA, was it not there that the power to determi the structure of complex protein molecules lay?

DNA molecules have a much simpler structure than p teins, of course. The proteins are made up of 20 'lette or amino acids, while DNA has only four 'suits' or n leotides. But what of that? It is possible to use the Mo code of dots and dashes to transmit any message writt in the letters of the alphabet. The same relationship m exist here—perhaps several nucleotides could code one a no acid?

But can DNA give adequate variety? Gamow took his model a DNA molecule of medium length and calcu ted just how many such different molecules there could The result proved more than sufficient. Indeed, the num of possible combinations is much greater than the num of atoms in that part of the Universe that can be s through the largest modern telescope. It is easy to guess t the comparison was made by Gamow himself: he was astrophysicist.

Gamow carefully examined the structure described the article. Two circumstances caught his attention. T distance between neighbouring 'rungs' was 3.4 Ångstr units (one Ångström equals one hundred-millionth o centimetre). But that was the same as the distance tween neighbouring amino acids in proteins. It could a chance coincidence. On the other hand, if a protein ch were arranged along the DNA chain there would be nucleotide (four kinds) for one amino acid (twenty kin Clearly, with a ratio of 1 : 1 DNA could only code f amino acids.

The way out was found quite easily. In essence it as follows. Take three three-letter words, say PAT, E EMU; and write them together PATEAREMU. Now l at them closely; if we take any three consecutive let we can make words from them: PAT, ATE, TEA, E ARE, REM, EMU. Amino acids must also apparently coded in the same way, i.e. with 'overlapping'.

Gamow went on to examine the second helix and nc another peculiarity. If we take both the bases that m up a 'rung', one base from below it, and one from ab it, we get a rhombic 'hole' consisting of four bases same distance apart as the amino acids in protein. number of 'rhombi' that DNA can yield is exactly 20,

same as the number of amino acids in protein. Another coincidence? More probably that is how it really is.

But if everything were really as Gamow supposed then the deciphering of the genetic code, the law governing the relationship between the 'suits' of DNA and the 'letters' of proteins, would not be so very difficult. Let us arrange our three-letter words in another sequence, for instance EARPATEMU. What do we get then? Before any three consecutive letters formed a word; now they often make nonsense—ARP, RPA, TEM. There are no such words in English. Hence, with such an overlapping code, there must be permitted and forbidden neighbourhoods for amino acids. To decode it we would simply need to take a few proteins and see what amino acids did or did not occur side by side. Then, having found the rules for the disposition of amino acids, it would be possible to crack the code.

But that was easier said than done. It was then 1954, a short time after Frederick Sanger's discovery of a method for determining the sequence of amino acids in proteins. He was then working on the sequence of amino acids in insulin. Only tentative, by no means complete results had been published: but that was better than nothing. Gamow took what was available and seemed to be getting somewhere; but there were too few facts. He had to wait—not, however, for long. Sanger's method had been taken up in many laboratories which were working feverishly on protein analysis. In 1957 Sydney Brenner, one of Crick's talented colleagues, having assembled all the published data, succeeded in drawing the final inference—that the rhombic code suggested by Gamow, and any other overlapping code, was contrary to the facts. There were no forbidden zones in proteins.

Gamow had made a mistake. Nevertheless his work was of fundamental importance, although for him it was largely a side line. Once I wrote to him asking whether he had any new work not known to me on the problem of the genetic code. He replied: 'I'm not really a biologist but a physicist, and the problem of the genetic code only happened to fascinate me as an interesting mathematical puzzle. Now I've fallen behind and work more in astrophysics and cosmology.'

Another eminent Russian theoretical physicist, Igor Tamm, living not on Sixth Street but on the Gorky Embank-

ment in Moscow, who was also interested in the genetic code, once said that Gamow's hypothesis was good precisely because it proved easy to disprove. Gamow's work was important not merely because he raised the problem of cracking the code (important as that was), but also because he formulated a hypothesis that could be checked. As a result it was found not only that the rhombic code was wrong, but also that the code itself was not overlapping.

The Theoreticians Take Over

The deciphering of the genetic code is often compared to the interpreting of mysterious inscriptions. In fact, there is a similarity between them that is more than superficial. Furthermore, comparison of the task posed by Gamow with the deciphering of inscriptions can be quite instructive.

We often have to decipher inscriptions. Baffling rebuses are to be found in every 'puzzle corner'. People are engaged professionally with ciphers in the armed forces, in the theory and practice of communications, in historical research and archaelogy, and so on. All the problems can be divided into two groups: those when the language of the inscription is known, and those in which it is not. In the second group it is not a question of deliberate coding; rather it is one of deciphering the language itself, as has to be done in order to read ancient forgotten languages. The first group embraces all other types. It must be said that, strange as it may seem at first glance, inscriptions that have been deliberately ciphered (the first group) are much easier to decode than writings in an unknown language with no attempt at concealing the meaning. Completely different methods are used to solve the two groups.

Let us start with the first group. Take no notice of the simple puzzles you will find in children's newspapers. They are intended for 12-year-olds, and use transposition and garbling of letters (for instance, mirror reflection, anagrams, and so on). When codes are made deliberately to baffle strangers the letters are replaced by others or by symbols of some sort, so that a 'key' is needed to read them. Such a replacement as, say, using the next letter of the alphabet, is too simple and also belongs to the category of 'schoolboy' codes.

Let us assume that someone has invented a secret alphabet, ciphering each letter with a cunning symbol, and

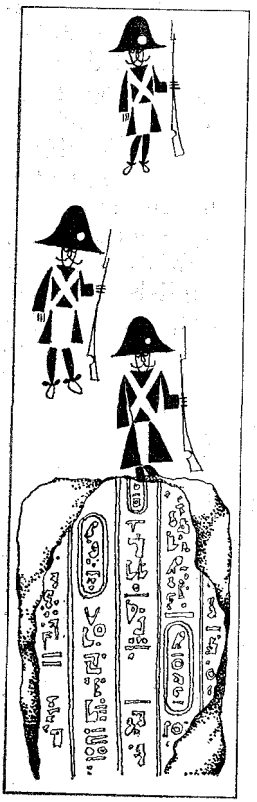
is confident no living soul will understand his coded messages without the paper on which he recorded the cipher (that is, without the key). But he is deeply deluded. Such ciphers are generally not difficult to break. All one needs is a sufficiently long message coded in it.

The way it is done was fascinatingly described in Edgar Allan Poe's famous story *The Gold Bug*. It concerned a note indicating the site of hidden treasure by means of mysterious symbols. The hero of the story counted how often the same symbols occurred. Since it was known beforehand that the message was written in English, in which the letter 'e' is that most frequently used, he assumed that the most frequent symbol stood for the 'e'. Another reason for his conjecture was the frequent occurrence of two of these symbols together: the combination 'ee' is also fairly common in English. After several letters had been deciphered by this statistical method certain words became understandable although some of their letters were missing, and once words were recognized the missing letters could be guessed. Carrying on like that, he soon succeeded in reading the note, and then found the treasure.

That is exactly how such codes are deciphered in principle, utilizing the frequency of letters in words, their most common combinations, etc.

The most difficult cipher in the first group is what may be called the 'book cipher'. Let us suppose we have agreed to exchange coded messages. We take two absolutely identical books and agree to write, instead of a letter, the number of the page and the place where it is found. Therefore, the same letter should now be represented by one, now another, combination of figures. The chief difficulty in deciphering such messages is that the same letter may be coded differently. This type of cipher is called degenerate. It also can be solved without a key; only a much longer piece of ciphered text is required. Generally, the longer a text is, the easier it is to decipher. That, in particular, is a reason why keys are changed from time to time.

But how are texts in an unknown language deciphered? The best known example is that of ancient Egyptian hieroglyphics. Inscriptions were widely known and attracted much attention. For centuries scholars had tried in vain to penetrate their mystery, and had finally concluded that it was impossible. In 1802 one of the specialists wrote



that all hope of deciphering the hieroglyphics some time had been abandoned. But he proved a poor prophet. In 1822 a young Frenchman, Jean François Champollion, made the historic announcement: 'I have done it!'

This centuries-old riddle had been solved thanks to a remarkable find. During Napoleon's Egyptian campaign, more exactly on 2nd Fructidor, year VII of the Republic (2 August 1799), Bouchard, an officer of the General Staff, ordered his men to repair the fortifications of Fort Julien, seven kilometres from Rashid (Rosetta). The spade of one of the soldiers struck something hard. When the 'something' was unearthed it was seen to be a slab or stele of black basalt all covered with symbols. On closer scrutiny it was found that there were three inscriptions on the stele (which came to be known as the Rosetta stone). The top inscription was in the long-known but still mysterious hieroglyphics; the middle one was quite unknown, and the bottom one was in Greek.

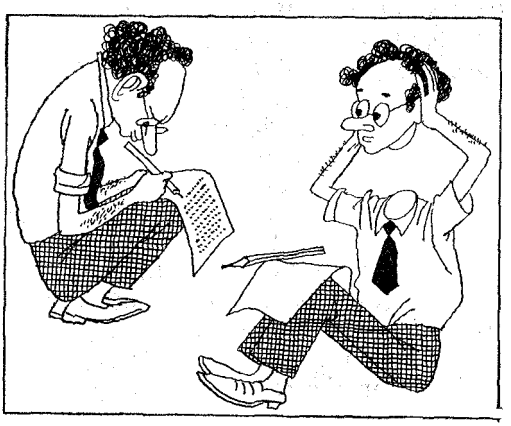
Some of Napoleon's officers knew Greek quite well, and were able to read the third inscription at once. It was a decree of 196 B.C. in which the priests of Memphis, in gratitude for benefits accorded to their temples by Ptolemy V Epiphanes, 'multiplied the honorary rights granted in Egyptian sanctuaries to the King and his ancestors'. It also said that the decree was to be inscribed on a memorial stone in the old writing of the men of religion, and in the writing of the country, and in Greek. That meant that all three inscriptions had the same meaning. It was something scholars had dreamed of for centuries. A bilingual text is a parallel text in two languages, one of which is known. Here was a case not of bilingualism but of trilingualism; but even then it was far from simple to decipher

the hieroglyphics with its aid. I shall not recount the story of the deciphering of the Rosetta stone and then of the Egyptian hieroglyphics. All we need to remember is that it was made possible by the discovery of the Rosetta stone.

The story of the deciphering has been described many times. Today many other unknown ancient writings have been deciphered: ancient Persian, Mesopotamian cuneiform writing, Hittite hieroglyphics, the languages of Ugarit and Byblos, the Cypriotic syllabary, the Creto-Mycenaean linear inscriptions, etc. And if we turn to the history of their deciphering, we shall find that the discovery of a bilingual text nearly always provided the key.

Thus, to decipher writing in a known language statistical analysis is used, based on the rules of language structure; but to decipher inscriptions in an unknown language a bilingual text is sought. The problem of the genetic code clearly belongs to the second group, because we do not know the 'language' of DNA. Consequently, we need a bilingual text. That could be provided by data on the sequence of amino acids in proteins and on the sequence of the nucleotides in DNA that codes it. Easier said than done! At the time about which we speak the order of amino acids in proteins was just beginning to be determined, but we did not know the order of nucleotides in nucleic acids. It was not until 1964 that the first work appeared that deciphered the sequence of nucleotides in a relatively small molecule for which almost all known methods had had to be used in combination. Afterwards other works on deciphering the sequence of nucleotides were published. Unfortunately, however, all the molecules studied so far cannot serve as a bilingual text because it is precisely these molecules (a rare case!) that do not code the structure of proteins.

A bilingual text was needed to decipher the genetic code, and since one was not available the time had not yet come to solve it. But the mind of man is so built that he cannot wait for an answer to come by itself. As soon as it was found that a genetic code existed, and that there was a link between the sequence of nucleotides and that of amino acids, scientists have not relaxed their efforts to decipher it. And the impossible has been achieved. Although we still cannot read what is written in nucleic acid, the genetic code has been deciphered.



Success did not come overnight. Scores of people had to work like galley slaves to prepare the ground for the great discovery, both experimenters and theoreticians.

The theoreticians got down to business first. They needed nothing except pencil and paper (and a head on their shoulders, of course). They reasoned as follows. Since a bilingual text is not available and the language is unknown the code must be approached as if the language were known. One only needs something to get hold of and to guess the 'grammar' in which nucleic acids give their commands to the 'workers' building proteins.

That is precisely what Gamow did in the work we already know. He 'clung' to the fact that the distances between the neighbouring 'bricks' from which both proteins and nucleic acids are built are identical and that the number of the 'rhombi' he had postulated was exactly what was needed—20. Then he set about deciphering the code by the same methods as were used by the hero of Poe's *The Gold Bug*, or by intelligence officers who have intercepted an enemy radio message.

Gamow had been mistaken; but his example proved infectious, and work based on the same principle sprang up like mushrooms after rain. None of them solved the problem, but none was wasted, because each one came closer to the target. I shall describe only one of these efforts, one that played a particularly important role—both positive and negative.

Gamow's followers, like himself, were mistaken. The code proved to consist of elements that did not overlap. Neighbouring amino acids are coded by unrelated groups of nucleotides. That gave rise to another difficulty. How many nucleotides were needed to code one amino acid? There are four nucleotides, and twenty amino acids. If we take one nucleotide, only four amino acids can be coded. If we take two nucleotides for one amino acid, we will get sixteen possible combinations, which is not enough. If we take three nucleotides, however, the number of combinations will be quite sufficient—64. That means that each amino acid is specified by at least three nucleotides (the 'triplet' as scientists call it).

A nucleotide 'triplet', however, takes up three times as much space as an amino acid. If triplets do not overlap, amino acids are too far apart to be able to join up in a protein chain. Again the problem of the Procrustean bed arose. In 1957 a work appeared suggesting a solution. Its authors were Crick himself and two of his colleagues, Griffith and Orgel. It was a simple solution. They suggested that amino acids had nothing to do with triplets directly, and that there must be special molecules ('adaptors') with one end attached to the amino acids from which a protein was built, and the other to the nucleic acid, in which the triplets were arranged in a definite order. For that the 'adaptors' would, of course, require to be oblong in shape.

Within a year the hypothesis of 'adaptors' was confirmed. A new variety of nucleic acid was discovered, which was first called soluble RNA, and today is commonly called transfer RNA. It was found that the molecules of transfer RNA performed exactly the function Crick and his colleagues ascribed to their hypothetical 'adaptors'.

The same article gave the answer to another question that followed directly from the solution of the first. Let us just recall the code proposed by Gamow, which I explained by the letter sequence PATEAREMU.

The rhombic code was an overlapping one. Every triplet in the sequence had meaning, and the row of letters contained seven words: PAT, ATE, TEA, EAR, ARE, REM, EMU. Now one had to admit that this sequence contained only three words: PAT, EAR, EMU, which posed substantial difficulties for an 'adaptor' might hook on at the wrong place, for instance, to the letters A, T, or E,

which would change the meaning. A different protein to the one required would be built, or one might not be built at all. For instance, if one 'adaptor' became attached to the letters A, T, E, and another to R, E, M, there would be a solitary letter A between them, to which nothing could become attached. The protein will break in two.

What was the way out? It was perhaps simplest to suppose the existence of some kind of punctuation marks ('commas') indicating where one triplet ended and another began. But the chemical data unfortunately were against the existence of 'commas'. The work of Crick, Griffith, and Orgel dealt with the 'code without commas'. To explain the single meaning of the information coded in nucleic acid, they put forward the following idea. The code must be so built as to make incorrect reading impossible, so that any 'word' composed of the end of one triplet and the beginning of another would be nonsense. Let us take, for instance, the words OAK, TEA, DAM. If we write them as one word (in any order), the sequence will contain only three meaningful words. Check it yourself and you will see it is so.

Calculations have shown that such a code can be designed. It is particularly interesting that one gets a 'vocabulary' of exactly twenty words (just as many as are needed). The hypothesis seemed very plausible, and Crick's standing was then at its height, and when the hypothesis of 'adaptors' had been corroborated, became greater still. But the hypothesis proved mistaken, and its acceptance naturally steered a number of other works in the wrong direction.

Though there was much theoretical work it alone could not solve the problem. It was for the experimenters to have their say. It was necessary to demonstrate even such basic propositions that DNA was capable of self-duplication, and that it determined the structure of proteins. In addition, experimental ways had to be found for deciphering the code.

Man-made Nucleic Acids

Do you know who the Basques are? Probably not. There are only about a million of them, descendents of the ancient population of the Iberian Peninsula. In the post-war period a representative of this freedom-loving people

vas destined to make several vital contributions to molecular biology.

His name was Severo Ochoa. He was born in 1905 in the village of Luarca, in the province of Asturias in the north of Spain. Until 1936 he had worked in his homeland where he had become head of the physiology department of Madrid University. When General Franco's fascist revolt began he left his country for good. At first he went to Germany, where he had already worked earlier, but this time to Meyerhof's laboratory in Heidelberg; in 1938 he moved to Great Britain, and in 1940 he went to the United States. In spite of his hardships Ochoa did exceptionally valuable work, and long retained his vigour and enthusiasm. We shall pass over most of his work, since it is too specialized, and begin in 1955, when he was already famous and his name was pronounced with respect by all biochemists.

No natural phenomenon can be considered fully understood until man himself can reproduce it. As far as nucleic acids were concerned progress was very slow. The honour of producing nucleic acid synthetically fell to Severo Ochoa. In 1955, working in collaboration with a young French woman, Marianne Grunberg-Manago, who had joined his laboratory, he succeeded in isolating a new, hitherto unknown enzyme from bacterial cells. The enzyme possessed astonishing properties; in its presence individual nucleotides joined into long chains and the resulting polymers were absolutely identical with natural RNA. Of course they had to take rather uncommon nucleotides for this purpose, and a fairly large amount of energy was required to join them. In the course of life processes energy is most commonly stored in the form of phosphorous bonds, and nucleotides with additional phosphorous groups are employed to produce RNA. The required energy is generated when they break off.

This, of course, was an outstanding victory since it marked the first step in man's active mastery of nucleic acids. The discovery won Ochoa a Nobel Prize in 1959. But the importance of his work went beyond what we have said. A little later, as you will see, it played an exceptional part in the deciphering of the genetic code.

Further research showed that the enzyme discovered was not solely contained in the bacteria from which it had originally been isolated. That was to be expected, since the

laws of nature are, as a rule, universal. But it was only a matter of RNA; attempts at synthesizing DNA in this way failed. But we did not have long to wait before DNA was also produced in a test-tube. The method was more or less like that used for RNA, but one of its details was different in principle and highly important. To bring about the assembly of new DNA molecules, priming in the form of existing DNA was needed. Without it synthesis did not occur, but the addition of even a tiny amount triggered off the synthesis.

Do you remember the Crick-Watson hypothesis? They conjectured that DNA molecules could replicate themselves; but the priming might play some other role. Arthur Kornberg, who developed this method with his colleagues, examined the end product very thoroughly and found that the new DNA had all the properties of the priming.

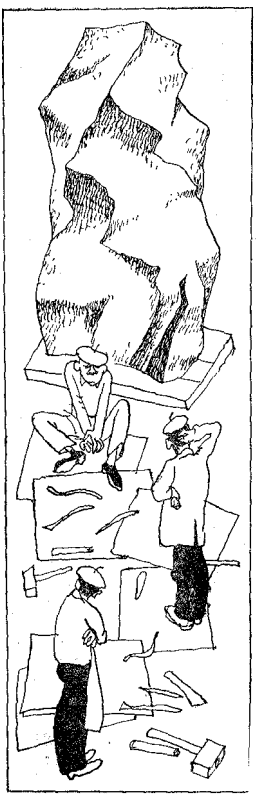
In that way it was finally proved by experiment that replicating molecules did, after all, exist. It happened almost thirty years after Koltsov had enunciated his famous proposition 'Every molecule comes from a molecule', and three years after Watson and Crick had suspected that DNA possessed this remarkable property and was the source of the phenomenon of life.

Thus one of the predictions of the theoreticians had been directly confirmed by experiment. It had been shown that DNA was capable of replication; now it remained to prove that nucleic acids actually determined the specific character of protein molecules. That, however, took longer, though many scientists continued to obtain 'clues' of various kinds to the role of nucleic acids in the synthesis of proteins. But these were not proof, and it was not until 1961 that indisputable evidence was obtained; then the world heard of two independent pieces of evidence.

I had the luck, by a whim of chance, to be among the first to learn of these discoveries. Both were first reported to the International Biochemical Congress in Moscow which I also attended.

Monuments are not merely erected to real people; there are monuments to Sherlock Holmes, and to Tom Sawyer and Huckleberry Finn. Pavlov sponsored the erection of a monument to the Dog, the laboratory animal that helped develop the theory of higher nervous activity. Geneticists often talk of putting one up to Drosophila. That is pos-

sible, too, but it would be hard to carve a monument to the 'heroes' of molecular genetics. One would have to portray the shape of the tobacco mosaic virus or of the intestinal bacillus (*E. coli*) in marble or bronze.



Tobacco mosaic virus long attracted the interest of many investigators, and in particular of the German botanist Melchers who began to study it before the war at the Institute of Biology at Dahlem, a suburb of Berlin. In 1942 he described an interesting mutation of this virus, and later, with the chemist Gerhardt Schramm (who later succeeded in inducing mosaic disease by means of pure nucleic acid), studied the mechanism of its reproduction. Using radiophosphorus as a label, they tried to find just how the virus took its building materials from the cells of the tobacco plant. That was only the beginning, however; after the war Melchers and Schramm settled in the small medieval town Tübingen, and although they were working at different institutes, they resumed their joint research. Schramm, working with a young colleague Gierer, investigated th action of nitrous acid on RNA. Nitrous acid is a ver simple substance, so that it was fairly easy to ana lyse the way it acted. It proved to have very little effec on RNA; through its action one of the 'suits'—know as cytosine—was ultimately converted into uracil, whil another 'suit'—adenine—was converted into guanine. N thing else can happen to RNA exposed to nitrous aci that is a precise chemical fact.

It was also interesting to see just what would happe to tobacco mosaic virus, whose major component is RN when exposed to nitrous acid. The experiments were mac and showed that the virulence of the virus was great reduced and, even more interesting, that a fairly large nur

ber of mutants arose, viruses with altered hereditary properties. It appeared that a change in RNA changed the hereditary properties of the virus.

The nature of these changes was studied in Melchers' laboratory and required much effort, but, as the saying goes, the game was worth the candle. Melchers had entrusted the research to H. G. Wittmann, a young physicist on his staff, or rather, an ex-physicist like most contemporary molecular biologists. Tobacco mosaic virus (or the RNA isolated from it) was treated with nitrous acid and used to infect tobacco plants. The variegated mottled spots, from which the disease takes its name, developed on the leaves. Although these spots were visible to the naked eye, each of them arose from a single virus particle, therefore, all the virus particles in one spot were absolutely identical. As a result of mutation the virus caused altered lesions. Each of these changed spots was cut out and then, after repeated infection of plants, a sufficient quantity of the altered virus was collected to be subjected to detailed chemical analysis to find the exact arrangement of amino acids in the virus protein. But there are as many as 158 in the molecules of this protein, so you can imagine that it was a devil of a job. But the results were extremely gratifying.

It was found that the protein in viruses with changed hereditary properties was altered, the change usually affecting a single amino acid. In normal virus protein, for instance, the amino acid threonine occupies place No. 59; in one of the mutations this place is taken by isoleucine, while all the other 157 are absolutely identical in both types. That fact alone suggested several important conclusions.

First, the experiments showed that a hereditary change was associated with a change in both types of virus. Second, a very slight change in a protein molecule was enough to induce a change in the external characters. Third, and most important, it followed that the sequence of amino acids in proteins was determined by the sequence of nucleotides in nucleic acid, since certain 'suits' were replaced in RNA by others, as a result of exposure to nitrous acid, and that led to a change in the protein. Thus Gamow's hypothesis was corroborated experimentally.

The attentive reader may note that Gamow's hypothesis

was not concerned with RNA but with DNA. But surely, there was talk of the cells of higher organisms having chromosomes consisting of DNA and protein. Viruses are the most primitive of living things, not even cells, standing on the borderline between living and inanimate matter. Naturally they have neither nucleus nor chromosomes. The role of chromosomes is played in them by individual molecules of nucleic acid; most vegetable viruses do not contain any DNA, and RNA plays the same function in them as DNA in other organisms.

It was these highly important experiments with tobacco mosaic viruses that Wittmann reported to the Moscow Congress.

At the congress I met Melchers, Wittmann's teacher and chief. Our talk naturally revolved around problems of interest to us both—genes, mutations, RNA, and DNA. We did not agree on every point, of course. I told him about my experiments in inducing plant mutations by radiation. Melchers agreed that my findings had a certain interest but hinted in general that I should give it up. It was difficult to argue with him. Just imagine a strapping fellow who would be the pride of any basketball team and brimming with energy. Even when he talked in undertones every word was clearly audible in the next room, and when he argued—well just imagine the rumpus he raised! Melchers was completely convinced that all geneticists should now switch to work with viruses, preferably tobacco mosaic virus, of course, and induce mutations exclusively by chemical means (of which nitrous acid, naturally, was best).

'Did you hear Wittmann's report?' he roared. 'It's stupendous. Could you ever have got such results from Drosophila or peas? Or can you get such clear findings from X-rays or gamma-rays? Incidentally, what he told us today is just the beginning. Just you watch. We'll crack the genetic code if we carry on along these lines.'

When you argue with Melchers it is best to keep quiet, but I could not contain myself. 'Well, it's all very interesting and instructive, but I don't see how we can possibly break the code by such experiments.'

'Of course nothing will be solved with what has been done so far. But we already have something. We know, for instance, that proline can be changed into leucine by nitrous acid. On the other hand, we know it causes C to change

to U and A to G in RNA. That surely means (as we can already say) that the triplet coding proline includes either C or A, while the triplet coding leucine includes either U or G. When we find another few substances of equally specific action like nitrous acid and analyse a few hundred mutations for each of them, it will then be a simple mathematical problem to decipher the code.'

'But that would take two hundred people a century to do,' I ventured to disagree.

'One scientist with a half-dozen lab assistants will do. We have already set up automatic amino-acid analysers to check one mutation after another round the clock. Give me your address. Within six months you'll receive an article from us on this problem. We won't know everything about the code in half a year, of course, but we'll have made a start.'

It was hard to believe him, of course, but I listened with bated breath.

Nirenberg's Triumph

Melchers and Wittmann were out of luck at the Moscow Congress, like many others, incidentally. They had brought with them their latest, most interesting findings, still not known to other scientists, hoping to cause a sensation that would put their names on all lips. And so they would, if it had not been for Nirenberg.

In 1957 Andrei Belozersky, the man who disproved the tetranucleotide hypothesis of the structure of nucleic acids (who by that time had become a member of the Soviet Academy of Sciences), began to take an interest himself in the comparative analysis of DNA and RNA. He entrusted the work to his talented, 26-year-old pupil Alexander Spirin. After examining a large number of bacteria Spirin established that while the composition of DNA varied quite widely, the RNA in all of them was almost identical—almost, but not quite. In addition, there was a certain resemblance in the composition of DNA and RNA in the same bacteria. But why?

Belozersky and Spirin explained their findings as follows. The RNA they had analysed was a mixture; the greater part was identical in all bacteria, while the smaller part corresponded in composition to DNA. It seemed extremely interesting. Indeed, if there was RNA with the same com-

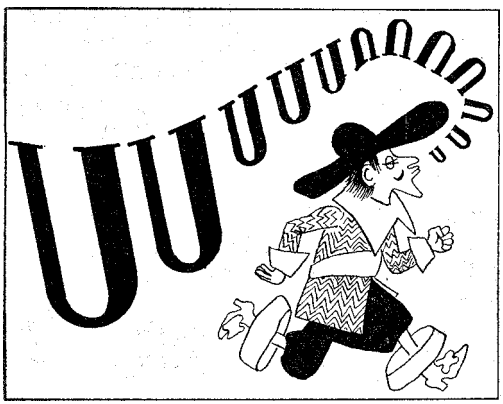
position as DNA, then perhaps it played the role of a messenger carrying information from the nucleus to the cytoplasm. The point is that the chromosomes containing DNA are in the nucleus, while protein is built in the cytoplasm. It was puzzling; but if there were such a carrier everything would be clear.

The Belozersky-Spirin hypothesis was soon corroborated. In 1961 it was proved beyond doubt that an RNA was formed in the nucleus that copied the composition and order of nucleotides in DNA. It was called information or messenger RNA.

Now the general features of protein synthesis in the living cell began to be sketched in. The structure of protein is coded in the DNA contained in the chromosomes and 'recorded' as a sequence of its component nucleotides. This information is conveyed by messenger RNA to the cytoplasm; the RNA molecules leave the nucleus and attach themselves to minute, special particles known as ribosomes, on which the protein is assembled from amino acids. As for the amino acids, they are first 'activated' by the charge of energy required to join them together, and are then attached to the molecules of transfer RNA, which puts each of them in the place where it should go. In 1961 all that seemed very probable, though no decisive evidence of the process exactly as described was available.

Nirenberg attempted to simulate, outside the living cell, the conditions required for protein synthesis. He took a full complement of amino acids, transfer RNA, the necessary enzymes, sources of chemical energy, and ribosomes, but however long the mixture was kept at a constant temperature, protein failed to form; however, as soon as large RNA molecules were added the building of protein rapidly began. When virus or yeast RNA was used, uniformly good results were obtained. It was a brilliant success. It alone was enough to start everyone talking about the new star of biochemistry.

That was not all, however, that Nirenberg described in his report. Biochemists were then already able to obtain RNA synthetically using Ochoa's method. Nirenberg decided to add synthetic RNA to his mixture instead of natural RNA. The result was unbelievable; protein was formed in the presence of 'home-made' RNA. It should be noted that the synthetic RNA was quite unlike any



occurring in nature. Natural RNA contains an approx
tely equal quantity of all four nucleotides, while Nire
experimented with polyuridylic acid, i.e. an RNA co
ing nucleotides of only one kind, uracil (U). In other w
the 'emissary' that he sent to the point of protein synt
carried rather monotonous information, something
this—UUUUUUUUUUUUUU... Nevertheless, protei
being built.

What kind of protein was it? It was just as uniform a
information supplied—and consisted of absolutely id
al amino acids, although the test-tube contained all t
any of which could have been chosen. But this time,
one amino acid—phenylalanine—was required. When
tein formulae are written down it is usual to indicat
amino acids by three letters, separated by hyphens.* T
fore, the formula of the new protein produced in Nire
and Matthaei's experiments was as follows: phe-phe-phe
phe...

Nothing like that exists in nature just as there is no
like the monotonous UUUUUUU....

One need not be a genius to understand that suc
periments make it possible to decipher the genetic
not by guesswork but by accurate clues. Indeed, the re

* For instance, alanine is designated 'ala', threonine 'thr
cine 'gly', cysteine 'cys', phenylalanine 'phe', etc. The fo
of a protein consisting of alanine, glycine and cysteine is w
ala-gly-cys.

The ABC of Heredity

After the Ball

'That will cost him a pretty penny,' blonde Svetlana, the operator at the international telephone exchange, remarked to her mate, nodding toward a booth in which an excited young man was shouting something in English. His call was to New York.

'Perhaps he's calling his girl,' Tamara replied glumly.

'Sure he is. That's love!'

Both girls would have been surprised and disappointed to learn that the young man was talking not to his sweetheart, and not to his wife, but to a 56-year-old man, Professor Severo Ochoa.

Prof. Ochoa was not at the Moscow Biochemical Congress. His colleagues said that he was so overworked that instead of coming overseas he had decided to take a holiday and go sailing.

When Nirenberg described how he had deciphered the first triplet (by means of synthetic RNA produced by Ochoa's method), one of the workers from the biochemistry department of New York University rushed to phone his chief and tell him the staggering news.

There is no knowing whether or not this story is true, but it was quite popular among delegates at the Congress and no wonder. Nirenberg's report made many scientists either change their research plans or alter their interests.

I too was impressed. Of course I was not working on deciphering the code. Our laboratory was quite unsuitable for that, and I was then too old to begin work in a new field. If I had been ten or fifteen years younger I might have thought of switching my job. But my interest in molecular genetics, already great, now grew to tremendous proportions. I no longer missed a single article whose title contained the letters DNA. In fact, any geneticist or biophysicist (and I considered myself both to some extent) is now obliged to be familiar with this field.

Francis Crick attended the Congress but did not make a report. No one was surprised. He had done so much al-

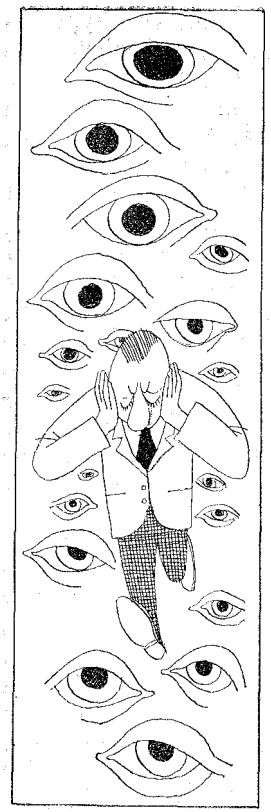
ready—the macromolecular structure of DNA, the hypothesis of 'adaptors', the code without commas, and what have you. But after returning home he made his colleagues a nice New Year present of a new article written in collaboration with L. Barnett, S. Brenner, and R. J. Watts-Tobin and published in *Nature* for 31 December 1961.

When I saw that issue in the library I read it avidly but failed to understand anything. It was long and abstruse, but its conclusions were extremely interesting. They told the 'inside story' of the genetic code. The meaning of the triplets was not discussed but that was not very important, for it was so far no more than a conjecture that phenylalanine was coded by the UUU triplet. There were almost as good grounds for concluding from Nirenberg and Matthaei's experiments that it was coded by a UU doublet, or a UUUU quadruplet, or some other number of U's. The hypothesis of triplets was the most probable one, but it still had to be proved.

Crick and his colleagues affirmed that they had proved it. But that was not the heart of the matter. They also concluded that the code was not overlapping (you already know what that means; Gamow's code, for example, was overlapping), and what is more degenerate, that is to say, one amino acid could be coded by several different triplets rather than by one alone. Finally, they talked of the way a single-valued read-out from nucleic acids was ensured. Crick had already given an answer to that problem earlier in his code without commas, but now, in this work, that hypothesis was discarded.

His discarding of the code without commas is perhaps Crick's greatest contribution to science. Unfortunately, scientists very often cling too tenaciously to what they have once said. Though it happens that the advance of science completely refutes some hypothesis, its author continues to swear by it in defiance of all evidence to the contrary.

The psychology of it is understandable. Such a scientist probably thinks that if his hypothesis proves wrong he will immediately be taken for a fool. He seems to begin to think that people in the street are laughing at him, saying 'Look, there goes the scientist whose theory was proved wrong'. But it seems like that only to him. It is common knowledge that the history of science is the history



of the collapse of innumerable theories. The hypothesis advanced by this scientist was necessary and progressive in its time and helped advance science by its very existence. It was something that could be checked and proved or disproved, and so helped science to take a step forward. That is quite clear to the outsider, but false pride sometimes prevents the scientist himself from realizing it. Then his colleagues really do begin to mock him and finally to avoid any serious discussion or argument with him because it is a waste of time. He has fallen behind.

A scientist's honour demands objective appraisal of himself and of others. I would even say that one needs to be more critical of one's self, for that is the surest guarantee against failure. And when a scientist says 'I was wrong', it is the acme of scientific honesty. Anyone who does so deserves to be called a real scientist. Linus Carl Pauling, a very great physical chemist and famous peace worker, is such a one. He had decoded the structure of DNA molecules a few months before Watson and Crick, and had published his work. His model differed substantially from theirs, and if any dispute had arisen, his standing was so high that he would probably have been given more credence than his opponents. But he promptly announced in the press that the Watson-Crick model was more correct than his one. Needless to say, no one considered him any the less a great scientist for that, rather the contrary. Now Crick was doing the same thing.

As a matter of fact the problem of read-out was simpler to solve than it had seemed. Imagine that this book was printed without intervals between words. Wouldd ifferen-treadersreadthissentencedifferently? It is difficult to read,

of course, without practice, but nobody will make a mistake. Why? Because we read it from the beginning and in normal succession. And that is how the problem of protein synthesis was solved; the information was read consecutively in groups of definite length, beginning at a definite starting point.

Those were only their conclusions. What about the article itself? I took it home and sat up late reading it very carefully. When I had finally got to the core of it, I was beside myself with delight. It fascinated me by its impeccable logic and the ingenious planning of the experiments and the explanation of the results. Unfortunately, I can give you no more than the gist of it here. It was intended for specialists and took about twenty pages of this size; and even a specialist would find it hard to grasp its meaning immediately because of its brevity. I shall only tell you this, that the code was shown to be a triplet one.

The method employed by Crick and his co-workers consisted essentially in inducing mutations in a bacteriophage using the chemical proflavine, which is known to have a rather peculiar effect on RNA. Unlike nitrous acid, which converts one 'suit' into another, proflavine causes mutations through the 'deletion' or 'insertion' of individual nucleotides.

When Crick and Co. had obtained a large number of mutations within one and the same gene and began to cross them with one another, they obtained most interesting findings. Sometimes two mutations of absolutely identical action produced outwardly perfectly normal offspring when crossed; but at other times nothing was observed. How was that to be explained?

It will be simpler if we begin at the end, and assume that the triplet nature of the code has been proved, in other words that all the 'words' (or codons) in the 'language' are three-letter ones. Such a language would certainly be a funny one, and would yield sentences rather like this: DAD WAS BAD AND MUM WAS SAD or OUR SON TOM WAS TOO BIG FOR HIS BED. These examples will help you to understand the essence of what Crick and his co-workers did.

One must keep in mind that the mutations induced by proflavine have certain letters missing or inserted. Take the sentence DAD WAS BAD AND MUM WAS SAD. Its

mutations might look something like this: DAD ASB ADA NDM UMW ASS AD (deletion), or DDW ASB ADA NDM UMW ASS AD (another deletion), or DAD WAP SBA DAN DMU MWA SSA D (insertion). Absolute nonsense results, although only the letter W was deleted in the first case and A in the second, and P added in the third.

The absurdity arises because we divided the row of letters in each case into three-letter words from left to right. That is what Crick's new idea amounted to; the code was to be read from left to right in the same way as we read books.

What would happen if we combined two mutations in one molecule of DNA? First, however, what is 'combination'? It is a process absolutely analogous to crossing-over in chromosomes, but taking place at the level of the DNA molecule. The new molecule incorporates the 'head' of one molecule and the 'tail' of another, the crossing-over occurring in the interval between two 'misprints'. Combination of the first two mutations given above would produce this: DDA SBA DAN DMU MWA SSA D. Nonsense, as before. And in the case of genes, the gene would not work, of course, either before or after combination.

Now let us combine the first mutation with the third: DAD APS BAD AND MUM WAS SAD. Although this sentence is not absolutely identical with the original one, it is intelligible, and has a certain meaning. In this case a protein will be built that will differ slightly from the original one but will look very much like it.

On these grounds it was considered that there was a return to normal when two 'mutations' were combined if one of them had an 'insert' and the other is a deletion. If both 'mutations' are insertions or deletions their combination will produce the same altered bacteriophage as each taken separately.

But what would happen (if this interpretation of the experimental results is correct, and the code is really a triplet one) if three insertions are combined. It is easy to guess, without using a diagram, that an extra triplet will be added, and most of the text will make sense. If the code were a quadruplet one, however, that is, if each word consists of four letters, a combination of four insertions would produce a return to normal, but one of three would not. And that also applies to deletions.

Experiments were carried out, and it was found that

combination of three insertions or three deletions produced a bacteriophage of perfectly normal appearance. The triplet character of the genetic code was proved beyond doubt.

At the same time, the experiments confirmed Crick's new idea of the 'text' being read in succession in groups of definite length. With the same ingenuity it was shown that the text was read from a definite starting point.

I would like to tell you how it was proved that reading of the triplets began from a definite point (just like sentences after full stops). Let us take two sentences of three-letter words as an example.

DAD WAS BAD, OLD AND SAD. DID YOU SEE TOM AND ANN.

It is necessary to prove that they are really separated by a full stop, in other words, that the second is read independently of the first. These sentences, of course, symbolize two neighbouring genes in the bacteriophage with which Crick and his co-workers experimented.

Indirect evidence of the existence of a 'full stop' was the fact that mutations arising in the first gene did not affect the functioning of the second. But that was not enough. The scientists decided to make a more direct experiment, for which they used a mutation lacking a large piece covering the end of the first gene and the beginning of the second, i.e. something like this: DAD WAS BAD, OLD AID YOU SEE TOM AND ANN. A piece ND SAD D was left out. It consisted of six letters, a number divisible by three, so the rest were meaningful. But what if the first gene had an insertion or a deletion? DDW ASB ADO LDA IDY OUS EET OMA NDA NN. One letter A is deleted, and both sentences are nonsensical; but if a letter is now inserted in the first gene the meaning of the most of the text will be restored.

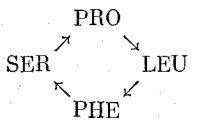
More experiments were made and so it turned out. Any acridine mutation in the first gene completely excluded the second. Combination of two mutations, of which one was an insertion and the other a deletion, did not disturb its activity. The existence of points from which the triplets must be counted was demonstrated.

I shall not recount the whole of this remarkable work. Two examples are enough to illustrate the brilliance of the experiments and the clarity of the conclusions. The article

contained conclusions on the majority of the basic properties of the genetic code. Although no triplet had been deciphered, it provided the foundation for drawing up the 'alphabet of heredity'. The dictionary was still non-existent (only one triplet—UUU—had been deciphered by Nirenberg), but the 'grammar' was already there.

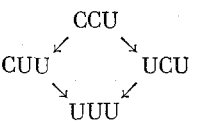
A Sensation

George Melchers kept his word. Early in 1962 I received a reprint from him of an article (published in the last issue of another journal for 1961). The article, contributed by Melchers' co-worker Wittmann, also dealt with possible ways of deciphering the genetic code. Several triplets were deciphered in it, but not only on the basis of Wittmann's own experiments. He took as his starting point Nirenberg's data to the effect that phenylalanine is coded by the UUU triplet. In experiments with inducing mutations with nitrous acid (which, as we know, converts C into U and A into G) serine and leucine were replaced by phenylalanine, and proline by serine and leucine. Reverse changes were not observed. Schematically this can be presented as follows:



But we know, on the one hand, that phenylalanine is coded by the UUU triplet and, on the other hand, that in experiments with nitrous acid U can only be produced from C. Consequently, each of the triplets coding serine and leucine must consist of one C and two U's in different order.

Reasoning further along this line, it can be asserted that proline is coded by a triplet consisting of two C's and one U. In short, the depicted above scheme of mutual transitions for amino acids should be explicable as follows:



The sequence of the letters in the triplets, of course, is arbitrary. Altogether the composition of triplets for nine

amino acids was indicated in Wittmann's article. A start had been made. It could be hoped that triplets for all the amino acids would be found within a few years.

But we did not have to wait that long.

In our day the progress of science is so rapid that the rate of publication is becoming a major problem. Scientists feel that too much time passes between delivery of a manuscript to the editor and its publication. It is not so surprising therefore that the first report on the discovery of triplets for all amino acids was published in a non-scientific periodical.

New York Times for 3 February 1962 frontpaged the news that progress in biology was such that disclosure of chemical secrets of genetics could be expected that year. The issue devoted more than a page to molecular genetics. The highlight was a table of the genetic code, in which triplets for each of the twenty amino acids were indicated; for three of them several triplets were even given.

The problem was nearly solved. It remained only to find the sequence of the 'letters' in the triplets, which it was hoped would be achieved that same year.

Scientific journals later described just how this success had been achieved.

In his first early experiments Nirenberg had used very uniform, 'home-made' RNA consisting either of U's alone or of C's. RNA with a UUUUUUU... composition put phenylalanine into the protein, while CCCCCC... introduced proline but in such a smaller degree that it could be attributed to an error; the other two forms of 'home-made' RNA had no influence on protein synthesis. CCC, AAA, and GGG apparently did not code amino acids.

Nirenberg's work was continued simultaneously at several laboratories, but success came first to the workers of Ochoa's laboratory, for they knew best how to prepare artificial RNA.

What needed to be done after Nirenberg's first experiments? It was clear that RNA of a more complex composition was required. As in the first experiments a mixture was made whose main constituents were ribosomes (the particles on which protein is assembled from amino acids), a full complement of amino acids, a full complement of transfer RNA (delivering amino acids to ribosomes), and a priming in the form of 'home-made' RNA of appropriate

composition. The experiment, it must be said, is conducted on such a microscopic scale that protein synthesis can only be analysed by means of labelled atoms. For that purpose, every experiment is carried out in twenty variants, in each of which one labelled amino acid is used while the others are normal ('cold'). After keeping this mixture at a constant temperature for a certain time the proteins are precipitated by trichloracetic acid. At the same time free amino acids remain in the solution. Variants in which the precipitate is radio-active indicate which amino acids have been taken up into the protein and in what proportions.

Let us examine, as an example, one of the first experiments made by Ochoa and his co-workers. They took as priming an artificial RNA consisting of five U's and one C. Before considering their results let us see what was to be expected. The sequence of 'letters' in artificial RNA is not known and is believed to be haphazard.

When we need to deal with chance events we have to resort to the theory of probability, which says that the incidence of triplets containing 3, 2, 1 and nil U must be proportional to 5^3, 5^2, 5^1, and 5^0. In other words, for every 100 triplets of UUU composition there should be 20 triplets consisting of 2U, and 1C (i.e. 20 CUU, 20 UCU and 20 UUC triplets), four triplets consisting of 1U and 2C, and only one CCC triplet (or rather 0.8).

What did the experiment show? Taking the phenylalanine inclusion as 100 per cent the results were as follows: phenylalanine 100 per cent; serine 25 per cent; leucine 20 per cent; proline 8 per cent.

That was just what had been expected. The figures were not exactly the same, of course; the accuracy of the measurements was low, and any experiment was likely to yield errors. But as the results could only be 100, 20, 4, and 0.8 per cent, we can say that the figure of 8 per cent is closest to the expected 4 per cent. Examining the figures obtained it is easy to see that phe=UUU (as we already know); ser= =2U, 1C; leu=2U, 1C; pro=1U, 2C. I took this experiment for consideration deliberately. If you go back a few pages you will see that Wittmann drew exactly the same conclusions from his experiments in inducing mutations in tobacco mosaic virus with nitrous acid. It was remarkable. When two different methods yield the same result it can definitely be trusted. The composition of the triplets coding

all 20 amino acids was determined in exactly the same way, using other 'home-made' RNAs.

The little table compiled by Ochoa and his co-workers was immediately taken up by the world scientific press. Needless to say, there was good reason for jubilation. The triplets for all the amino acids had been found. It only remained to determine the sequence of the 'letters' within them. Since the composition of triplets had been found in a matter of months, it was to be hoped that the sequence would also be clarified before the year was out. The problem of the genetic code would then be finally solved.

I Look for a Pattern

Through the open window came the sound of birds and children's voices. The first spring rain had washed the world and it was shining with bursting buds, young emerald grass, the first coltsfoot flowers, and radiant faces. It was a season when it is a chore to look into a microscope for hours on end. One's thoughts wonder far away.

I switched off the light, removed the slide from the stage of the microscope, and went to the library. It was better to look through the latest journals on a day like that. But now I wish I had never gone up to the fourth floor to the library on that day in May 1962. A few minutes after I entered the reading room spring ended. I entered a never-never land where time did not exist, and days and hours pass as in a dream. That happens if one is absorbed in one's work. When I was again aware of my surroundings, it was already the scorching dusty summer of a large industrial city.

I took a dozen newly-received journals from the rack, sat at a table, and thumbed leisurely through the pale-green March issue of *Proceedings of the National Academy of Sciences* (USA). Suddenly an article by Severo Ochoa and associates caught my eye. They described at length and in great detail the experiments that had produced the table published in the *New York Times.*

When you read a good research paper, you sometimes, frankly, experience a feeling of 'Why didn't I do that'. But this article, like Crick's on his experiments with bacteriophages, and Wittmann's about tobacco mosaic virus, caused admiration rather than envy. I felt like shouting like a boy at a football match.

I slowly and carefully reread the article, and in the findings reported by the American biochemists, to my surprise, I began to notice certain patterns the authors had passed over. It would have been worth their while. Now that the composition of all the triplets had been determined (as it then seemed) it then remained (as again it seemed) only to determine the sequence of the 'letters' in the 'words'. And the patterns that caught my eye seemed to help solve the problem.

I went on turning the pages, and had another surprise. There was another article on deciphering the genetic code. Its authors were Jeoffrey Zubay and Henry Quastler. I knew Quastler's name quite well. It seemed to me he was one of the most interesting of American scientists; and he was working on many of the problems that I was engaged on. But hitherto he had not done anything connected with the genetic code. Now he had made a most ingenious attempt to decipher it on the basis of data on the substitution of amino acids in proteins during mutations. Wittmann had attempted to do the same using his findings from experiments in inducing mutations in viruses with nitrous acid. But there were other data in addition to Wittmann's that might prove useful. Zubay and Quastler had collected them and deciphered the code.

By the irony of fate they had deciphered the code 'by themselves', before the results obtained in Ochoa's laboratory became known; and both articles appeared in the same issue of the journal. When they were compared it became clear that Zubay and Quastler's deciphering of the code was utterly wrong. Nevertheless, they had done a remarkable job. They had profound ideas and beautiful methods. It was not their fault that they had not solved the problem; they simply had not had enough material.

But I had! For if one took the data adduced in both papers and analysed them together, one might, possibly, determine the sequence of 'letters' in the triplets. It all amounted to a simple mathematical problem that could be solved in an evening.

I went to bed very late that day, at dawn, in fact, but I had not solved the problem. It took two weeks of continuous painstaking work. The data in the two articles I had found in the library proved insufficient, and new evidence had to be sought. During the analysis I came up against hidden

obstacles I had not suspected. But I finally solved the problem.

I was as happy as can be for in Severo Ochoa's article was stated in black and white that for final deciphering the genetic code it remained only to determine the sequence of the 'letters' and it had fallen to me to solve this final problem of the chemical foundation of heredity. My delight, alas, was premature.

First, I found I had rivals. My article on the determination of the sequence of 'letters' was published quite soon. But at approximately the same time several other almost analogous articles appeared. The Czech Rychlik, the American Smith, and others had had the same ideas, which is not surprising. Apparently, they were self-evident if they occurred to me, a man who had never before actively tackled the problem of the genetic code.

Second, the problem turned out to be by far less simple than it seemed at first glance.

Further Difficulties

The problem of the genetic code is so important that everyone who had the opportunity to check Nirenberg's and Ochoa's experiments got down to the job. First of all, of course, Nirenberg and his co-workers published an article on deciphering the triplets for all the amino acids. The work had apparently been started in Nirenberg's laboratory even earlier than in Ochoa's (which was better equipped for the purpose) but was completed rather later. The results of both investigations were almost identical. That, of course, was a good omen: coincidence of scientific findings is evidence in favour of their validity.

Other authors also made the same experiments. When they fully adopted the methods suggested by Nirenberg, they obtained the same results; but when their methods were different, the results were also sometimes quite different. That was too bad.

For example, the American scientists Davis, Gilbert, and Gorini repeated Nirenberg's experiments with one difference: as a preliminary they treated the ribosomes with streptomycin. It is hard to say why they did so; perhaps, they simply wanted to see what would come of it. The results proved quite interesting, indeed. They began with the simplest experiment, putting polyuridylic acid

(UUUUUUU...) into the test-tube as priming. You will remember that in these conditions protein is synthesized from only one amino acid—phenylalanine. But here, in addition to phenylalanine, inclusions of isoleucine, serine, and leucine were found, and sometimes there was even more isoleucine than phenylalanine.

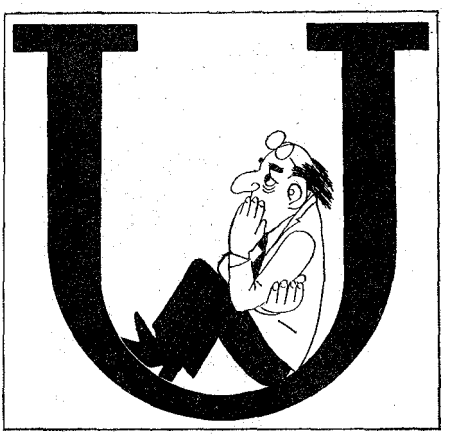
Streptomycin is a well-known antibiotic, a substance preventing the reproduction of bacteria. There are also microbial strain resistant to it. The scientists also tested ribosomes obtained from streptomycin-resistant microbes; no errors were then noted—only phenylalanine was taken up.

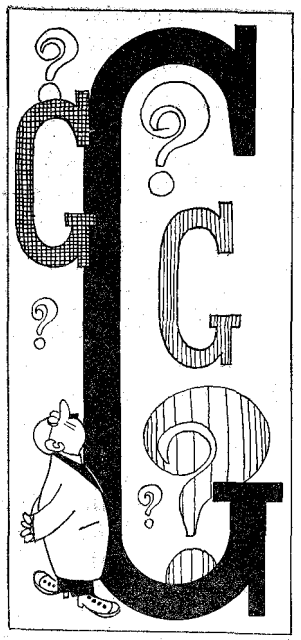
Interesting, isn't it? Indeed, this may be the basis of the therapeutic effect of streptomycin. Perhaps.... But we were none the wiser for that. If, in definite conditions, the reading of information occurs in different ways, what guarantee is there that the conditions in the living cell have really been created in the test-tube experiments? It would not be so bad if similar results were only obtained with such a potent drug as streptomycin, but new experiments showed that the meaning of triplets was influenced by such very ordinary factors as the adding of certain salts, changes in the acidity of the medium, temperature, etc. And one might well think that the conditions in a cell-free system differ much more widely from natural conditions than different variants of these new experiments. There was good reason for pessimism.

These results alone were enough to throw doubt on all the work carried out on Nirenberg's lines. The euphoria evoked by the sensational and truly great discovery gave way to sober-minded appraisal. Some were particularly sceptical. About a year after publication of the first papers on deciphering the genetic code, Wittmann summed up the situation as it then was. Speaking of Nirenberg's methods, he adduced about a dozen arguments that threw doubt on the validity of the results. A few months later, Crick himself made a similar survey. By that time he had become the accepted 'pontiff' on molecular genetics and his opinion carried great weight. He divided all the triplets then known (a triplet was known for every amino acid, and for some several) into three groups: probable, possible, and doubtful. (He had no 'authentic' group at all.) Only eight of the 24 were 'probable'.

The biochemists went on with their experiments. Quite often they produced results that made the theoreticians renounce the hypotheses they had only just developed.

The reader will remember, of course, that synthetic RNA containing only uracil (UUUUUUU...) stimulated the building of protein incorporating phenylalanine molecules, while other polymers of equally uniform composition (CCCCC..., AAAAA..., and GGGGG...) proved ineffectual. The first (CCCCC...) seemed to stimulate the incorporation of some proline, but that could very well be attributed to experimental error. Interestingly, too, all the other triplets for all the amino acids contained at least one U. That could hardly be accidental. The theoreticians thought hard over why it was U and not another letter. Why was U preferred? It was not difficult to find an explanation. Indeed, the DNA in the chromosomes (which is passive carrier of hereditary information), and the RNA transmitting this information and taking a direct part in protein synthesis, contain rather different sets of nitrous bases ('letters'). In DNA they are adenine (A), guanine (G), cytosine (C), and thymine (T). RNA, however, while containing the same A, G, and C, contains U instead of T, that same U whose meaning we are pondering. If U were a 'letter' present in RNA and absent in DNA, it was not surprising that its role in coding was so important. The theory could be developed further, but we shall not do so, because all these conjectures proved futile.





After a time polymers that had previously been quite inactive also began to work. Polycytidylic acid (CCCCC...) began to stimulate the incorporation of proline very actively where it had formerly been almost idle, and polyadenylic acid (AAAAA...) began to stimulate incorporation of lysine. Many new triplets not containing U were found—all because of certain changes in technique. In the first experiments a relatively mild solution of trichloracetic acid had been used to precipitate the synthesized protein. It soon became apparent that in these conditions proteins containing much phenylalanine were precipitated. And such proteins could only be built in the presence of a large quantity of U. When other methods were used, other proteins previously not noted by investigators also began to be precipitated, too. Things proved much simpler than theoreticians had thought them to be.

But when the problem of U had been settled, the question of G arose, because polyguanylic acid (GGGGG...) still did not work, while there were fewer triplets containing G than any others. And that was the result whatever the technique of precipitation. It was another brain-teaser. I will not tell you what theoreticians thought of it; for it again proved to be connected with causes that had nothing to do with the genetic code. Portions containing a large quantity of G are capable of forming a double helix with one another like that of DNA; and that being so, the corresponding parts of RNA become blocked and cannot take part in protein synthesis.

There is no point in listing all the difficulties and doubts that arose in solving the problem of the genetic code. Two things are clear. First, the universal assertion that the problem would be solved in a matter of months proved overoptimistic. Second, it became obvious that Nirenberg's

method by itself was inadequate for full deciphering the chemical ABC of heredity. Little by little scientists reached the conclusion that the correct solution lay on one of three roads.

The Three Roads

Nirenberg's method had two shortcomings. First, the system was artificial and did not fully guarantee that the synthesis of protein was governed by the same laws as in the living cell. Second, as you will recall from what was said about the technique of deciphering unknown languages, a bilingual parallel text is required. Nirenberg's methods gave bilinguals, but they were inadequate. In the synthetic RNA produced by Ochoa's method the bases were combined at random, and their sequence remained unknown. Continuing the metaphor of inscriptions, the 'protein text' was not full enough, and as for the 'nucleic acid inscriptions' all that was known was how many letters it included and which. You will agree that such a comparison is not very reliable.

In view of that we can outline the roads to be followed.

First and foremost, it was necessary to find ways of deciphering the genetic code not only on the basis of a cell-free system but also by means of experiments on living cells. It would be best, of course, to find a method quite independent of Nirenberg's data. At worst it might be sufficient just to compare the code available with the results of experiments on living systems.

The other two methods are based on obtaining an adequate bilingual text in which the sequence of the letters is known. On the one hand, one might attempt to synthesize RNA with a quite definite sequence of 'letters'. On the other hand, we might learn how to unite and discover the amino acids in very short RNA chains, say, in individual triplets (chemists have long known how to obtain such chains).

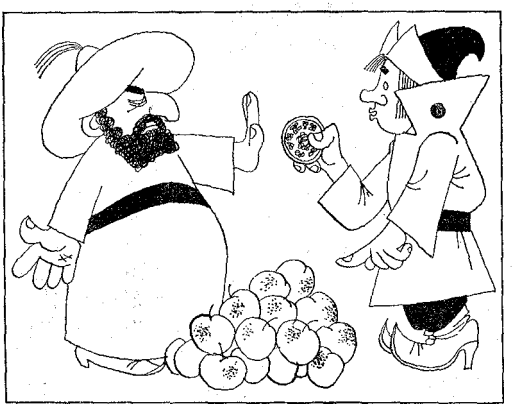
And finally, one might learn how to determine the sequence of 'letters' in natural RNA; but that is very difficult, and no early solution of the problem could be expected along that road.

I must say outright without any diversion, that research was carried out in all three directions and was crowned with success in all three. It is simply amazing how quickly

all the difficulties were overcome. This is the second edition of our book, and it did not require any substantial amendments. But I had to rewrite this chapter, so great was the progress made in the two years since the first edition. True, no cardinal changes were made in the picture painted two years earlier, but it had become clearer and more authentic. As to the first of the roads mentioned above I myself did a good deal of work along it.

If you have ever been interested in old coins, you may have come across 18th-century Russian copper coins with a picture of two martens holding a shield with the inscription 'Siberian Mint'. The inscription did not mean that they were for circulation only in Siberia, for, in fact, they were to be found everywhere in Russia. But they were smaller than ordinary coins, because the copper from the Kolyvan mine, from which the coins were minted, contained a sizable admixture of silver. With the standard of metallurgy prevailing in Russia at that time it was not profitable to remove the silver. So the coins struck from copper with a silver admixture were of a correspondingly lower weight. The copper coins of other mints also contained silver but in a smaller quantity, which was disregarded. It is said that certain British merchants made fortunes out of these Siberian coins, buying them in quantity to resmelt them in England and extract the silver at a profit.

I acted in roughly the same way. The data cited by the authors of most experimental works contained a sizable portion of 'silver'—information they themselves had not taken note of, mainly as regards the mathematical aspects of their research. Although it is known that any exact science largely depends on mathematics, certain scientists unfortunately, are slow to adopt its methods, particularly in biology and chemistry. Because of the neglect of mathematics in these sciences conclusions that should be drawn from the experimental data are distorted or overlooked. Data required for deciphering the genetic code were mostly biochemical. I am not a professional mathematician; I like it, but I don't know it well enough. As the saying goes, however, 'in the kingdom of the blind the one-eyed man is king', and many biologists consider me an expert. At any rate, for the level at which the biochemical research was conducted my modest knowledge of mathematics was sufficient to extract the 'silver'.



There is no need to describe the work I did. It was concerned with too many problems and was mainly mathematical, which does not make for interesting reading. The crux of the matter was that I succeeded in working out methods for deciphering the code without using data obtained from cell-free systems. And what was particularly important from my point of view was that the experiments required for application of my method had already been carried out and their results published. In this way I was able to make an independent and almost complete deciphering of the genetic code. Its results practically coincided with those of Nirenberg and Ochoa.

Other theoreticians were engaged on much less imposing tasks. They were comparing the results obtained from living systems with the Nirenberg-Ochoa code. Correspondence would mean that the code had been deciphered correctly and that protein synthesis in cell-free systems was governed by the same laws as in living cells.

But that was not enough. They only confirmed the correctness of the Nirenberg-Ochoa code, which had not yet been deciphered in full. Consequently, it was necessary to wait for the discovery of new biochemical routes. We did not have long to wait.

Many people believe in 'paired chances' or other coincidences, affirming that they take place more often than follows from the theory of probability. True, nobody has ever attempted to calculate what actually must be expec-

ted from the theory of probability, for it is rather difficult to do. But willy-nilly, we are always impressed by coincidences.

We began our story of the chemical foundations of heredity at the 5th International Biochemical Congress where Nirenberg's report on polyphenylalanine synthesis in the presence of polyuridylic acid was the chief sensation. Four years later the next, 6th International Biochemical Congress was held in New York. Both the theory of probability and the general situation in the field of research indicated that no important news about the genetic code would be reported at this congress, just as none had been broken at the international genetic congress held shortly before.

I did not attend the 6th Congress, nor did I hasten to learn the news. What was I to expect from it after what had happened at the 5th?

Then I received a letter from a colleague saying that the chief sensation at the 6th Congress had been the new successes in deciphering the genetic code. And they have been achieved... by Nirenberg. It was a surprise but fact. The information in the letter, however, was too scanty and I had to muster my patience and wait until Nirenberg wrote an article and it was published.

Fortunately, I did not have to wait very long, for literally within a few days I received a thick package from the USA with the name M. W. Nirenberg in the upper left-hand corner.

In our day science is developing faster and faster, and requires increasingly rapid exchange of information. Special journals have been founded for early publication of papers. In the USSR for example, we have *Transactions of the USSR Academy of Sciences* (*Doklady AN SSSR*). With certain journals only two or three weeks pass between receipt of the manuscript and its publication. Yet even that is not short enough; besides there are not many of these 'express' journals, and they print only short notices.

So scientists have devised a new form of information exchange—' preprints'. A 'preprint' is a copy of a manuscript circulated before its publication. Various techniques of reproduction are used—duplication, photography, carbon copies. The periods also vary. Some authors mail preprints simultaneously with posting the article to the press,

fearing plagiarists. Others distribute them much earlier so as to collect criticisms and introduce amendments.

The package from Nirenberg contained preprints of two new, still unpublished articles, that he had sent to two different journals. Both articles, of course, are now in print as I write and are well known to every specialist. One—'RNA Code Words and Protein Synthesis' lies on my desk and has become very familiar to me. It deals with the influence of trinucleotides on the attachment of soluble RNA to ribosomes. The authors are Philip Leder and Marshall Nirenberg. Is it clear what it is about? I am afraid that it probably is not and that you still do not know quite what I am driving at. It needs more detailed explanation.

First, let us recall the methods of the earlier experiments of Nirenberg, Ochoa, and others. They were indirect. Synthetic RNA of known composition but with an unknown sequence of 'letters'—bases—was used as a template to assemble protein from amino acids. Therefore, they were forced to compare only the general composition and analyse the results statistically, which was very difficult and tedious. In addition, only quite long chains of amino acids, such as are precipitated by trichloracetic or tungsten acid, can be analysed in this way.

The idea behind Nirenberg's new experiments was to learn to control the process earlier—before the protein chain separates from the ribosome and not after. It would then be possible, of course, to determine the attachment of amino acids to the quite short molecules of messenger RNA. The idea had not only occurred to Nirenberg, and many had tried it but failed. At least a dozen papers were published describing the attachment of transfer RNA to ribosomes, but the mechanics of the process remained obscure.

Nirenberg and Leder's work showed no trace of the numerous trials and errors that led up to the final analysis. But it was clear that their success had not been easy. The full description of the methods used takes on six typewritten pages in telegraphic style. Their essence is simple enough.

At first everything went as in Nirenberg's earlier experiments. Labelled amino acids became attached to their 'carriers' (transfer RNA) and mixed with ribosomes loaded with messenger RNA. The amino acids began to hook on to ribosomes. That was just the right moment to find out what happened. But how?

They were probably helped by chance (at any rate no theoretical explanation of the method so far exists). When the incubation mixture is filtered through cellulose nitrate, both the ribosomes and the carriers with amino acids settle on the filter. Although filters were used here, filtration is apparently not essential, as filters with meshes a hundred times bigger than ribosomes can be employed. Probably adsorption, i.e. adherence of particles to the filter material, takes place. The ribosomes adhere most strongly. When the filter is washed in a saline solution, the transfer RNA and free amino acids are removed, while the ribosomes remain in place. It is then easy to learn which particular amino acids have been bound by the ribosomes, if at all, for the amino acids carry a radio-active label.

Nirenberg began with the same polyuridylic acid with which he had carried out his initial experiments. But it was now unnecessary to obtain long chains. The binding of even a single amino acid to each of the ribosomes would make itself known by radio-active signals. The scientists tried taking chains differing in length, and obtained a remarkable result: chains two nucleotides long produced no effect, but trinucleotides (UUU) stimulated intensive attachment of phenylalanine to the ribosomes; chains four and five U's long had the same effect as a triplet. This was the first concrete proof that the genetic code was a triplet one. Up to then various authors had adduced much evidence in favour of a triplet code but it had all been indirect.

Identical experiments were made with chains consisting of only A's or C's, and yielded the same results. It was shown that AAA coded lysine, and CCC coded proline.

That alone was a remarkable discovery. The second preprint dealt with a triplet made up of different 'letters'. The scientists had obtained all the three variants of a trinucleotide consisting of one G and two U's: GUU, UGU and UUG—and had tested them in analogous experiments. They studied the attachment of the amino acid valine and found that it was bound only in the presence of GUU. The two other variants were quite inactive.

Further discoveries were a matter of technique, now that a broad, new path had been opened up. Nirenberg and his co-workers carried out one experiment after another, testing all the possible triplets consecutively.

But it was not long before another method was found for

direct deciphering of the genetic code: scientists succeeded in constructing synthetic RNA with a quite definite sequence of 'letters'. True, the longest way round proved to be the shortest here.

The American chemist Khorana and a group of colleagues had been making a comprehensive study for some years of DNA (rather than RNA, be it noted) and its components. And in the end they found a way of joining nucleotides in whatever sequence they wanted. Once he could do that, he might as well try to imitate nature.

You well remember, of course, that DNA is a double helix; the two strands forming the helix are different and, as it were, supplement each other. Only a two-chain molecule is biologically active, so Khorana began by building chains of two sorts, with their 'letters' so arranged as to supplement each other accurately. When these chains were mixed in appropriate conditions, they joined into double helices!

In that way, a synthetic DNA molecule was produced in which the order of 'letters' was exactly known. By that time biochemists already knew how to reproduce the synthesis of RNA or DNA in a test-tube. (The order of 'letters' in RNA accurately repeats that of the DNA priming.) So that is what Khorana did.

When RNA molecules were obtained in which not only the 'letters' forming them but also their sequence were known, it only remained to test them in exactly the same experiments that Nirenberg had reported in Moscow in 1961. The experiments were a brilliant success. And just as Nirenberg tested the coding properties of different triplets, so Khorana set about investigating proteins built in the presence of different chains of RNA.

Research was carried on in both directions and fairly quickly. The general result was that Nirenberg's first and second methods and Khorana's methods suggested the same conclusions on the coding properties of triplets, and these were the same as those drawn from analysis of the results of experiments on living systems.

That was not the end of it. All the first experiments had been made on a cell-free system obtained from intestinal (*E. coli*) bacteria. Now experiments began to be made on systems isolated from other cells, in particular from those of higher animals. The genetic code proved universal for

both the vegetable and animal kingdoms of our planet Or, speaking with greater caution, no deviation from the universality of the genetic code has so far been discovered.

The genetic code has been practically deciphered. A total of 64 different triplets is possible; 61 of them determine the incorporation of quite definite amino acids into protein. But only 20 different amino acids take part in protein synthesis, so it is clear that most amino acids are coded by several triplets. The number of triplets encoding each amino acid varies; only two have one triplet each. It is an easy guess that these amino acids—methionine and tryptophane—are among the rarest ones. Some of the most common ones, like serine, arginine, and leucine, are coded by six different triplets.

But these are only 61 of the 64 triplets. What about the remaining three? Is their meaning still not known? For two of them it has been determined with perfect clarity; they are 'nonsense', i.e. meaningless, triplets. They are meaningless, of course, only as regards coding amino acids; in fact, they are quite meaningful as they serve as 'punctuation marks', coding the beginning and end of the protein chain. The last triplet (UGA) is still uncertain, but all the evidence available indicates that it is probably also nonsense.

That is all. One of Nature's greatest mysteries—the secret of the chemical basis of heredity—has been unravelled.

'What comes next?' you may ask. I leave the answer to your imagination. The discovery of the chemical basis of heredity is on a par with the greatest scientific discoveries in history and is compara to the discovery of the structu of the atomic nucleus, the perio system of elements, the theory

relativity, etc. And it is perfectly clear that the progress of genetics will be important for the most varied aspects of man's activity.

The importance of smaller discoveries is easier to see—their consequences are nearer in time and more tangible, yet less significant. With great discoveries, however, 'Azimov's law' comes into force. Now we can list only some of the spheres where knowledge of the mechanism of heredity may bring about truly fantastic results.

In medicine there is the treatment of diseases that nearly defy the efforts of doctors, like virus infections, cancer, and related maladies, for these diseases are associated with a derangement in the chromosomal apparatus of the cell. And of course we can hope for control of hereditary diseases, and general amelioration of the health of mankind.

As regards agriculture, we can expect the evolvement of new breeds and varieties by more efficient methods than before, and perhaps the creation of novel species, most likely among the lower organisms, yielding valuable nutritive substances.

And finally, in industry, there will be reconstruction of chemical technologies, for the living cell builds most complex substances mainly from water and air at normal temperature and pressure. What great advantages that offers, compared with the methods used today. It holds promise of absolutely novel types of production, above all, of foodstuffs, for example, the synthesis of proteins, fats, sugars, vitamins, medicines, etc., from inorganic raw materials.

That is enough for a start. A more detailed description of the possibilities opened up by control of heredity is the prerogative of science fiction. But these are not wild fancies but solid forecasts. It goes without saying that much depends on how the great genetic discoveries are utilized by future generations. They can be used to fight viruses or to create new viruses for germ warfare. I hope that by the time that humanity has learned to reap the harvest of today's discoveries good will and common sense will have prevailed.

Why I'm Like Dad, After All?

Three Effective Principles

The reader may feel he has been taken in. We are clos to the end of the book, yet nothing has so far been said wh he is like, or unlike, as the case may be, his father. Ou book, however, is devoted not to human genetics but t the science of heredity in general. As for the laws of here dity, we have stressed time and again that they are unive sal in character, and that what is valid for a pea or a frui fly is fully valid for man.

In addition to general genetics, however, there is a larg separate study—human genetics. Many thick books an countless special articles have been devoted to it. And i could make the subject of another popular science boo like this one.

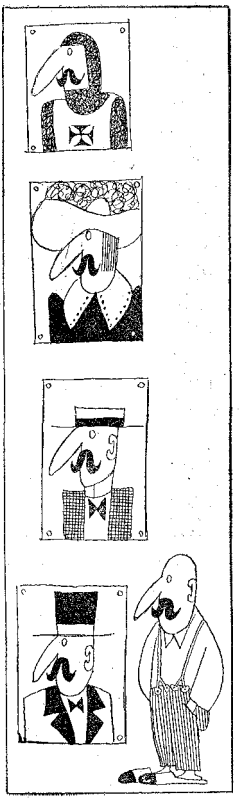
It could start, for instance, with a story of one of th final events of the Hundred Years' War—the Battle c Castillon in 1453. I would write of how the general of th English army, John Talbot, on whom the King had con ferred the title of Earl of Shrewsbury several years before was killed in action and fell into the arms of his sword bearers. He was buried with full pomp and ceremony i his family vault in Shrewsbury Cathedral and left to res there for almost 500 years.

In 1914 when the cathedral was undergoing repairs th vault was opened, and an amazing find was made. Th man in charge of the repair work was one of John Talbot' descendants. He had symphalangia, accretion of the firs and second phalanges of the fingers. This is a hereditary defect which he had inherited from his father. But th scant remains of his distant ancestor also had its finge phalanges accreted. The defect had been transmitted un altered through fourteen generations.

That, of course, is a spectacular case that will amaz anyone. Yet we are not surprised to see identical traits say, in dogs of the same breed, but here we have a rar hereditary character in a human being. If we think abou

it we can conclude that symphalangia is the result of dominant mutation.

But the book could be started in another way, taking the reader not to past centuries but to far-away lands.



In Brazil there are colonies of Russians, descendants of dissenters, or Old Believers, from the Orthodox Church. All religions are intolerant of dissenters, and the Russian Orthodox Church which was the official religion in Russia before the Revolution was no exception. In the seventeenth century Patriarch Nikon, the head of the Russian Orthodox Church, introduced certain alterations in the Service. Many people clung to the old ways, however, and were subjected to hard persecution that went on for centuries. The most intransigent Old Believers emigrated to other countries where they were free from persecution. In that way Russian colonies sprang up in Turkey, Canada, Australia, Brazil, and other places.

But before we visit the Old Believers in Brazil, first cross your arms on your chest. Note how you do it. One arm is placed over the other. Now cross them the other way round. You will probably feel a bit awkward. And if you cross your arms without thinking about it, you will always put the same arm above the other. Is it a habit, or what?

But now we are in Brazil. Strolling along the streets of Rio de Janeiro, we can see local people who cross their arms either way. But if we go to the Old Believers and ask them to cross their arms, they will all do it in exactly the same way. Is it a sign of the old faith? For they crossed themselves differently from other Orthodox Christians. But if you ask them about it, they will tell you that it is simply that it is easier to cross their arms that way. Does

that mean that the way a person crosses his arms is inhe
ted? It is, in fact. Apparently it was a hereditary charac
of those stubborn Russian peasants who went overseas
the last century and founded a Russian colony there,
Brazil.

Either story could make a good beginning for a bo
on human genetics. They are striking illustrations of
force of heredity. But both concern unessential characte
The way one crosses his arms is quite unimportant, wh
symphalangia, although involving a certain inconvenien
is quite rare. It is not difficult, however, to give an exam
illustrating a very common character of extremely gr
consequence.

Doctors have long known about sickle cell anaemia
severe disease in which the red blood cells or erythrocy
assume a sickle- or crescent-shape. In certain individu
the disease is innocuous and they feel normal, but in oth
it becomes a very serious sickness that usually causes de
in infancy. Survivors have severe anaemia, are physica
underdeveloped, and suffer from severe pains in the join
muscles, and abdomen, and not infrequently from para
sis. It is a hereditary disease that is associated, as resea
has shown, with a change in a single gene, and consequen
is transmitted from one generation to another in exact c
formity with Mendel's first law. Homozygotes with
sickle cell gene develop the severe disease, but in hete
zygotes only the shape of the erythrocytes is affected. T
disease is very common.

You are surprised? You have never had any friends v
suffered from this illness. And now that you have read
the earlier chapters of our book it must be clear to
that such a harmful gene would have been nearly wi
out by omnipotent natural selection. And that is true
temperate climates; but this disease is common in
tropics.

Individuals heterozygous for the sickle cell gene,
those who feel well, prove resistant to tropical fever,
scourge of the local population. Nature prefers to sacri
some individuals in order to save the others. And natu
selection, which keeps sickle cell anaemia in check in
climate, promotes its spread in the tropics.

Incidentally, it is fortunate that sickle cell anae
was the first hereditary disease to be studied not only

the biochemical but also at the molecular level. The biochemical basis of the disease is the changed properties of haemoglobin, a protein substance entering into the composition of erythrocytes. Detailed study of haemoglobin revealed a very slight difference between the normal and abnormal forms: in one of its chains, consisting of some 150 amino acids, in the place where a residue of glutamic acid is present, a valine residue was found. A glance at the genetic code makes it clear that the cause of the mutation is the replacement of a single base in one of the molecules of nucleic acid. Such a small change leads to such dramatic consequences!

But enough of examples. It is clear as it is that hereditary phenomena in man are based on the laws described in the preceding chapters and which are valid for all living things on Earth. It is more important to describe, even if briefly, the methods used to study human genetics, the problems it is concerned with, and its importance for modern society.

Knight's Move

If a small hole is punched in a pail, all the water will soon run out of it. But if we have a scratch, or even a sizable cut, on the skin, we are not greatly worried. It never occurs to us that we may lose all our blood through it. But very rarely, perhaps once in several tens of thousands of cases, there are people with good reason to be fearful of any scratch. In them bleeding is very difficult to arrest, so even a small scratch may be fatal for them. The blood of all humans contains fibrinogen, a protein substance that in normal people is converted into fibrin, the clotting of which stops the bleeding of wounds. This happens from the presence of a number of 'blood coagulation factors'. In rare individuals one of these factors is missing. The defect is hereditary, a disease known as haemophilia.

This malady, as is known, afflicted Tsarevich Alexei, the son of Nicholas II, the last Russian tsar. The Spanish Princes Alfonso and Gonzalo died from this disease. So did Leopold, the brother of the King Edward VII of England, and Waldemar and Henry, brothers of the Prussian Prince Sigismund. Is it a 'royal disease'? A legitimate question for any one unfamiliar with genetics to ask.

A geneticist, however, will remember that according to

:oyal family laws a prince was obliged to marry only a)rincess. It will be recalled that not so long ago, in the :hirties, King Edward VIII of England was forced to ab-dicate because of his marriage to Mrs. Wallis Simpson. But princesses are few in number, all the reigning dynas-:ies of Europe were closely related by blood (which, in-:identally, did not prevent them from starting sanguinary wars and all sorts of intrigues against each other).

Indeed, kings and queens, princes and princesses would make a fairly good subject for genetic research. Human beings cannot be used for cross-breeding experiments to establish the laws of heredity; but European sovereigns entered into wedlock contrary to nature's laws and close to what could have been done by an experimenter. And then, the genealogies of kings are known much better than those of peasants.

I have before me the genealogy of the eight last generations of European monarchs. It clears the matter up immediately. Ten cases of haemophilia, and all in males only. In none of the cases did a son inherit the disease from his father. But the brothers of their mothers were often afflicted. From uncle to nephew! It was by 'the knight's move', to quote William Bateson's metaphor, that haemophilia is transmitted. It means that the son inherits the harmful gene from his mother who looks perfectly healthy; and that can take place only if the recessive mutation is in the X-chromosome.

A human cell contains two sex-chromosomes. In women these are two identical X-chromosomes, in men, one X and one Y. In women the presence of the gene of haemophilia is compensated by a normal gene (in the other X-chromosome), whereas in men it is absent, which explains the intricate 'knight's move'. Closer examination of the genealogy shows that the first carrier of haemophilia was Queen Victoria of England. None of her ancestors or relatives in the collateral lines had suffered from the disease. Apparently she herself, or one of her parents, developed the mutation at a very early stage of embryonal development.

The law of inheritance of haemophilia is fairly simple and was known long before Mendel's time. It was described in the scientific literature in the early years of the last century. But folk lore had noted it centuries earlier; and

the Talmud said that circumcision was dangerous for babies whose senior brothers or uncles on their mother's side were prone to bleeding.

The study of genealogies has brought to light the hereditary origin of many normal and pathological traits in man and their pattern of inheritance. A genealogy, in general, is a most important, though by no means the only, way of studying human genetics.

If the same character is observed in close relatives, say, in brothers, that fact still does not mean that it is hereditary. It may have arisen from identical conditions of life, upbringing, nurture, etc. As for diseases, they may simply be due to infection. But such characters as haemophilia, let alone symphalangia, cannot be ascribed either to upbringing or to infection. But what about mental abilities, character traits, and diseases like rheumatic fever, cancer, schizophrenia?

Nature itself has given geneticists a remarkable object for study. It is twins. Twins, of course, occur in one of two types. Sometimes they are as like as two peas so that it is hard to tell them apart, or they may be no more alike than most brothers and sisters. These types differ in origin. In the former twins develop from the same fertilized ovum; they are known as identical twins, and have quite identical gene complements, which is why they are so alike. In the latter case the twins develop from two different ova, and are known as fraternal twins.

Geneticists are interested to know just how often one and the same character occurs in each of identical and fraternal twins who live in identical and different conditions, as they can ascertain in that way the relative role of heredity and environment. If the number of coincidences in identical and fraternal twins is the same, the role of heredity is ruled out; but if their number is much larger among identical twins, the characters are definitely inherited.

The birth of twins is a rare phenomenon occurring in about ten out of a thousand births. In the total number of twins identical twins account for roughly one-third. To that it must be added that infant mortality is higher among twins. Their importance for science is so great that some investigators have concentrated on the problem of twins, and a special term has been coined for their study—gemelology.

The results obtained from the study of twins are so sp
ctacular that it is worth considering a few examples.

Let us start with the most obvious cases. In identic
twins the same colour of eyes is observed in 99.5 per ce
of cases, of hair in 97 per cent, of skin colour in 100 p
cent. In fraternal twins the analogous figures are 27, 2
and 45 per cent. It is perfectly obvious that these are a
'good' hereditary characters; but that was known witho
gemelology.

It is more interesting to examine the data on diseas
in twins. For that account is taken of the incidence of tl
same disease in both siblings. For schizophrenia, for in
tance, the rate of coincidence in identical twins is 69 p
cent, in fraternal twins only 10 per cent; for epilepsy, tl
figures are 67 and 3 per cent respectively; for diabete
65 and 18 per cent. It can be inferred that hereditary pr
disposition is a major contributory factor in these disease

But the picture is by no means always so clear. Whe
we examine data on cancer, we do not see any essenti
difference between identical and fraternal twins; but whe
we compare only pairs suffering from cancer, we find th
the character of the disease is very close in identical twi
as regards localization, the age at which the tumour appe
red, and its course. There is no such similarity betwe
fraternal twins, which means that there is a predispositic
to certain forms of cancer dependent on heredity. Th
dangerous factor, however, is very seldom brought in
play.

A third method widely used in the study of human g
netics is to compare different population groups. The a
pects of interest here are the different conditions of li
(climate, diet, natural radiation levels) and long isolatio
for instance in mountain villages, where intermarriage
a common occurrence in the circumstances prevailing i
a small community.

The study of chromosomes contributed greatly to tl
advance of general genetics, and it has clearly been impo
tant for human genetics as well. Unfortunately, howeve
man's chromosomes are quite inconvenient for study. The
are fairly numerous, small, and generally indistinguishabl
from one another. It was so difficult to obtain good pr
parations that even quite recently the number of chrom
somes in human cells was debatable.

But where there is a will there is a way, and in recent years human genetics has made spectacular progress. The main thing is that several minor discoveries have given such an improvement in research methods that it is no longer difficult to obtain a good preparation for microscopy and analysis. Even more interesting is the fact that blood has now become the most common material for studying human chromosomes. Blood cells, of course, do not divide, but a remarkable substance has been found (produced from beans) that causes lymphocytes divide and makes chromosomes accessible to study.

The study of human chromosomes immediately revealed important facts. First, it was finally established that normal human cells contain 46 chromosomes, that female cells have two X-chromosomes, while male cells have one X- and one Y-chromosome. Sex determination is not quite the same in humans as in Drosophila. In the fruit fly sex is determined solely by the number of X-chromosomes. Two produce a female, one a male, and it does not matter whether a Y-chromosome is present at the same time. In man, however, male sex is determined by the Y-chromosome, and female sex by its absence.

Chromosomal diseases have then been discovered. It has been found, for example, that Down's disease, a severe form of congenital idiocy, is associated with a superfluous chromosome. The sufferer has 47 chromosomes instead of 46. More detailed examination showed that cells contained a third, small, chromosome No. 21.

Human chromosomes are being studied more and more often in clinics as well as in research laboratories. There have been reports of the development of computers capable of analysing them, and the time is possibly not far distant when every case history will contain a 'picture' of the patient's chromosome number.

Certain hereditary diseases can be diagnosed without detailed study of the chromosomes, while the analysis of microscopic preparations is so simple that even a not very skilled laboratory assistant can examine several dozens in a day.

Toward the end of the forties the Canadian scientist Murray Barr found that the nuclei of all female cells contain a readily stainable body that is not present in male cells. Later this body was identified as an X-chromosome.

When a cell has only one X-chromosome, the latter does not yield this body, but if it has two X-chromosomes, one of them does. There are rare individuals with two of these bodies (called Barr's bodies, or sex chromatin); they have three X-chromosomes. Thus study of sex chromatin permits the detection of anomalies in sex chromosomes. A swab of cells from the oral mucosa is stained for the purpose, and examined for the number of chromatin corpuscles.

Long before the discovery of sex chromatin certain congenital anomalies affecting several characters had been known. For example, approximately two in every thousand male births have Klinefelter's syndrome. They have underdeveloped sex glands (and are sterile), very long legs, sparse hair, and retarded mentality. Microscopic examination showed that the cells of individuals with this syndrome have sex chromatin, i.e. appear to be female. As might be expected they have been found to have three sex chromosomes, two X and one Y.

Incidentally, not only are boys with sex chromatin encountered but also girls without it, though this anomaly is observed much less often, in approximately one in 5,000 births. The cells of such patients contain only one X-chromosome. This genotype is responsible for the Turner-Shereshevsky syndrome, characterized by several severe anomalies. This disease was also first discovered in the clinic, and its chromosomal nature was only revealed many years later.

There are other anomalies due to an abnormal number of sex chromosomes, and many associated with other chromosomes.

Therefore, although genetic research on man is very difficult for a variety of reasons, scientists are searching for ways of doing it. The point is not simply that experiments cannot be made and that human chromosomes are difficult to study. There is also the difficulty of the long period between birth and the period of reproduction, plus the fact that each human couple has very few offspring. Man is the exact opposite of Drosophila in this respect. But man is the most important genetic subject, and that necessitates a search for new ways of exploring his heredity. We should also note that in addition to his shortcomings, man has certain advantages as an object of study. Indeed, the biology, physiology, and immunology of no other species has

been studied in greater detail and in no laboratory subject can we distinguish such delicate differences as in human beings.

Wiser Than Solomon

Two women fell asleep on a wide bed together with their newly-born babies. When they woke in the morning, they found one of the babies dead; the heavier mother, tossing in her sleep, had smothered it. But whose baby had died? Each insisted that it was her baby that remained alive. They went to King Solomon, renowned for his wisdom and argued the case before him. They disputed for a long time, but neither changed her mind. Then the wise King gave his verdict.

'Divide the living child in two, and give half to the one, and half to the other.

'Then spoke the woman whose the living child *was* unto the king, for her bowles yearned upon her son, and she said, O my lord, give her the living child, and in no wise slay it. But the other said, Let it be neither mine nor thine, *but* divide *it.*

'Then the king answered and said, Give her the living child, and in no wise slay it: she *is* the mother thereof' (The First Book of the Kings, Chapter 3).

So, they returned the baby to the real mother and drove the other woman away in disgrace, and again praised the wisdom of Solomon.

That is what the Bible story says. But was King Solomon really so wise? Perhaps the women did not know whose child it really was and one of them was simply more kind-hearted than the other. There is no reason for certainty in the fairness of Solomon's decision.

When such a dispute occurs in our day, it is not necessary to seek the judgement of a Solomon. It is settled more simply, by an accurate scientific method. In our day medico-genetic consultants would be called in; blood samples would then be taken from the child, and from both women and their husbands; and the child's parents can usually be named with 100 per cent certainty.

There are four blood groups differing in their immunological properties. These groups have been known for a long time; more recently the development of immunology and human genetics has led to the discovery of scores of

other immunological characteristics of human blood, and today at least 50 are known. Just imagine how many combinations they can give.

It is difficult to find two persons with absolutely identical antigenic blood properties, and it can be stated with certainty whether or not a child is born of particular parents. Geneticists are more and more often called as experts in court cases and their testimony is considered reliable.

There are now medico-genetic consultation centres in most big cities, though they are of quite recent origin. The very fact of their existence is evidence that human genetics has advanced to the point where it can yield practical results in addition to theoretical investigations. What do these consultation centres do?

Their tasks are varied and will increase with time. First, they are consulted by the parents of children with congenital defects seeking advice on the care of the child and its future development. Second, sober-minded couples having an abnormal child or a defective relative should think twice before having another baby. For them genetic advice is truly valuable; it can warn them against a risky step or, on the contrary, allay groundless fears, for not all congenital defects are hereditary—far from it. The same is true of possible contra-indications against marriage. In addition, these consultation centres are a great help to other specialists in identifying hereditary or non-hereditary diseases, in making forensic medical examinations, etc.

Consultation! Advice! Isn't it possible to cure hereditary diseases? Of course, we are still unable to 'repair' a defective gene; and if to be realistic about it, it won't be soon. But we can compensate for the harm done by a mutant gene. The mutation will remain, but the person will feel normal. We can also try to correct maldevelopment. All that is far from fantasy, and certain steps have already been taken in that direction.

One case is probably known to nearly everybody. Diabetes is a severe disorder of carbohydrate metabolism due to failure of the pancreas to secrete insulin. But insulin is now available from any chemist's, and sufferers can compensate the deficiency. It is still beyond our power to cure diabetes completely and to make the pancreas function normally, but insulin can help the patient to feel almost

healthy. What of it that many cases of diabetes (but not all) are inherited?

Similar measures are taken for haemophilia, the abnormal tendency to haemorrhages due to delayed clotting of the blood. Special tubes containing an antihaemophilic globulin and provided with a hypodermic needle are available. A haemophiliac should always carry one in a sterile pack. In case of injury he can then give himself an injection, and his blood will clot as in a normal person, so that he need no longer be in fear of bleeding to death. In Sweden, with its small population, almost every haemophiliac carries this saving remedy.

There have been cases of full recovery from hereditary diseases. Certain forms of imbecility, for example, are inheritable. One of them has the queer name of phenylketonuria; its main symptom is the presence of a specific chemical substance in the patient's urine, from which it takes its name. The disease is not very frequent, occurring in approximately four cases in 100,000. But the world's population is so great that the total number of sufferers is quite large. More than a thousand cases have been reported in the medical literature.

When the disease was suspected of being hereditary, studies were made on patients' genealogies. It was found that phenylketonuria behaved as a recessive character. It was traced to mutation of a single gene.

The mutation results in the metabolic disorders responsible for the symptoms of the disease, the most formidable of which is an irreversible affection of the central nervous system. All the pathological changes are based on a disturbance in the metabolism of phenylalanine, one of the amino acids. In healthy persons an excess of phenylalanine is excreted from the organism, but in the sick it turns into a toxic substance. Since that is so, a child will grow up perfectly normal if it is put on a low-phenylalanine diet a few weeks after birth.

But how can we establish that a newly born baby may become an imbecile? Even Einstein did not know his multiplication tables when he was a baby. Early diagnosis of phenylketonuria, however, proved fairly simple, for the patient's urine is already abnormal at birth. So, for an accurate diagnosis, it is enough to take some wet napkins and a few drops of ferrous chloride.

The rapid development of human genetics and medical genetics is quite recent, but they have already made much progress. Suffice it to say that over 1,500 different hereditary diseases are now known. Society rightly expects even greater progress. For its part medical genetics is entitled to expect the attention to its needs that it is getting. As I complete this chapter it has been decided, for example, to found a research institute in the USSR for medical genetics.

Genes and Man

In our day the most important sciences are taken to be those leading to outstanding technical achievements in the field of atomic energy, semiconductor electronics, cybernetics, and space exploration. But that is not quite just, and soon will be even less so, because all technical devices are intended to benefit man, it is necessary, indeed, to take good care of man of the future, of the human race.

Human heredity is governed by laws that are valid for the organic world as a whole. But human society develops according to its own laws, which are quite unlike those governing animal and plant communities. The latter develop through natural selection but in human societies that long ago ceased to be significant.

Even in the distant times when men first began to unite in primitive hordes, individual characters ceased to be decisive factors in survival. What is more, it was quite often the strongest and healthiest who died first as warriors and hunters, while the weak and sick sheltered at home in caves and transmitted their 'bad' genes to posterity. As human society developed, more and more factors appeared that impaired heredity; of late their role has grown immensely.

Destructive wars took a huge toll of lives, and Nazi death camps have eliminated some of the strongest and most valuable members of the human race. Thanks to the progress of medicine individuals with hereditary diseases, which were lethal until recently, survive and produce offspring. Birth control is practised above all by talented people, by people actively engaged in production, while the feeble-minded do not bother about it.

Hereditary diseases are now a heavy burden on human society. Let us consider a couple of examples.

About half the total bed-days in hospitals are spent on neurological and psychiatric patients, who remain in hospital for long periods and often return for further treatment. A half of neuro-psychic disorders are hereditary in nature. The patients require constant attendance; it has been calculated that six out of every thousand able-bodied persons spend their whole working time looking after them.

Another example is Down's disease mentioned above. It is infrequent, occurring in about two births in a thousand. But the disease causes almost as much economic harm as influenza. Everybody loses an average of one day a year through influenza; but Down's disease is chronic, so that one healthy person has to spend his whole time looking after one idiot.

A dismal picture, isn't it? And if we don't try to remedy it things will go from bad to worse. But can we do anything about it?

Long ago, soon after the birth of modern genetics, scientists coined the strange word 'eugenics', the science of improving the qualities of the human race. The word really puts one on the alert, and sometimes causes revulsion. The reason is that back in the twenties, when human genetics was in its infancy, enthusiasts of eugenics put forward fantastic and ill-considered proposals, such as the institution of marriage control (love is a private affair, while 'childbirth' is a social one), the use of the most talented people as human sires, etc. And eugenics was exploited as a cover by the Nazi butchers who exterminated whole nations for the glory of Aryan 'supermen'.

The word became badly compromised and acquired an ominous ring. But what is it, that medical-genetic consultation centres are engaged in, if not eugenics? Is the ban on incest not a eugenic law? The basic idea of eugenics has nothing objectionable about it, but for practical measures to be based on real knowledge it is necessary to know their character and what their aim is.

Today we still do not know nearly enough about human heredity to take steps to improve it radically. What is more, ill-considered interference with nature is extremely hazardous, and that must always be kept in mind. When crocodiles were almost completely wiped out in the Amazon, the more destructive piranhas greatly multiplied. Then the problem arose of restoring the crocodile population,

since all other measures proved futile. When the fate of the human race is at stake we must be infinitely more cautious.

There is no doubt, however, that we shall learn enough about our own nature in the foreseeable future not to be uneasy about the fate of the human race. In countries like the USSR, where the health services and medical statistics are centralized and great attention is paid to the health of the people and of the rising generation, particularly great progress can be expected in human genetics.

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