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Investigation of genetic variability in populations*

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The paper describes the origin and the development of Russian population genetics and its main discoveries achieved in experiments with *Drosophila*. The conceptual contribution of two main centers or schools led by N. Koltzov and S. Chetverikov in Moscow and Yu. Filipchenko in St. Petersburg is briefly considered. The ideas and methodology of these schools were introduced into American and European genetics by Th. Dobzhansky and N.V. Timofeev-Ressovsky. The authors presented in general the results of their own long-term studies on genetic variability both in natural and laboratory populations. These investigations were conducted independently in two laboratories and appeared to be connected with action of the evolutionary forces due to mobile elements (ME). It is argued that the main source of the origin of hereditary variations in nature is an interaction of environment with the facultative genomic elements.

Keywords: population, genetics, mutation, *Drosophila*, lethals, mobile elements.

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Introduction

At the beginning of XX century the biology in Russia was flourishing. It is noteworthy to mention here that I.P. Pavlov in 1904 and I.I. Mechnikov in 1908 were Nobel prize winners. Leading Russian biologists traditionally were interested in evolutionary problems (Adams, 1980a). In his comprehensive review Vucinich (1985) correctly concludes that Russian scientists alone represented the full spectrum of attitudes and critical stances toward the scientific, sociological and general intellectual merits of the Darwinian theory of evolution. Even an idea as popular in modern cellular and evolutionary biology as symbiogenesis was conceptually developed firstly by Russian botanists but almost completely ignored in the West (Khakhina, 1992).

Russian evolutionary thought developed through dynamic discussion and often controversy. One group of evolutionists accepted and contributed widely to Darwinian theory. Among them were the eminent Russian zoologists — brothers Alexander and Vladimir Kovalevsky, M.A. Menzbir, A.N. Severtzov and his follower I.I. Schmalhausen, V.A. Dogel', A.A. Zavarzin, V.M. Shimkevitch, botanists V.L. Komarov, V.N. Sukachev, V.I. Taliev, A.V. Tsinger. At the same time there were eminent critics of the main concepts of Darwinian theory. The most illustrious embryologist of the pre-Darwinian period, Karl von Baer (1792–1876), a distinguished member of the St. Petersburg Academy of Sciences, was one such critic. We may also include here the famous botanists: C.I. Korzhinsky discovering simultaneously with Hugo de Vries mutations in plants, and also A.S. Famintsyn and I.P. Borodin. The great zoologist Lev S. Berg (1878–1950), the father of a famous population geneticist Raissa L. Berg, developed the impressive anti-Darwinian conception of Nomogenesis. His book was translated into English and issued in the 1960s as a second edition with a preface by Th. Dobzhansky. He characterized this book as marshalling an abundance of evidence comparable to Darwin (Dobzhansky, 1980).

With this intellectual background the appearance and flourishing of population and evolutionary genetics seems preadapted. Two main centers or schools of general and population genetics were set up in Moscow and Petersburg (Leningrad). In Moscow an eminent biologist N.K. Koltzov (1872–1940) organized the Institute of Experimental Biology. According to Dobzhansky (1980), Koltzov was a man of multifarious interests and knowledge, of imposing presence, and with the eloquence of a spellbinding orator. His public lectures were events memorable to his peers and to beginners alike. In 1921 he invited in his institute S.S. Chetverikov (1880–1959) and A.S. Serebrovsky (1892–1948) to develop genetical studies. Their disciples make up the famous Moscow school of evolutionary and population genetics [Adams, 1980b; Babkov, 1985; Kaidanov, 1989; Vorontsov, Golubovsky, 1989).

Chetverikov conducted regular evolutionary seminar series named «Droz-So-Or» literally translated by Adams (1980b) as «the combined cacophony of drosophilists» or more loosely «the drosophilist screeching society». The restricted membership of this informal seminar which was conducted at Chetverikov's home was mutual sympathetic (Chetverikov, 1983). Chetverikov's students were B.L. Astaurov, E.I. Balkashina, N.K. Belyaev, S.M. Gershenson, P.F. Rokitsky, D.D. Romashov, N.V. Timofeev-Ressovsky, Helene A. Fiedler (then Timofeev-Ressovsky's wife). Other biologists attended the seminar: Koltzov himself, A.S. Serebrovsky and his students V.V. Sacharov, N.P. Dubinin. Serebrovsky's own students included the eminent scientist Zoya S. Nikoro (she collaborated then with Chetverikov since middle 1930s up to 1948) and also N.I. Shapiro and R.B. Khesin, who combined in the 1970s molecular, general and population genetics.

N.I. Vavilov (1887–1943) and Yu.A. Filipchenko (1882–1930) were leaders of the Leningrad (St. Petersburg) school of evolutionary and population genetics. In 1921 Vavilov headed the

Institute of Applied Botany (later the Institute of Plant Industry). He succeeded in collecting a cohort of an outstanding scientists. Among them were famous cytogeneticists G.A. Levitsky and G.D. Karpechenko, both of whom together with their leader Vavilov were killed during Stalin's reign of terror. Levitsky studied the structure of the chromosome from the point of view of systematics and evolution. He coined the term «karyotype». Curiously, namely Levitsky, originally the professor of botany in Kiev, accidentally met there the graduate student Dobzhansky (he rented the room at flat of Levitsky) and attracted him to genetics. In 1913 Filipchenko began teaching the first course in genetics in Russia at Petersburg University. He then formed the Department of Genetics and Experimental Zoology (1919) and later in 1921, the Laboratory of Genetics in the Russian Academy of Sciences. With the sudden death of Filipchenko in 1930, Vavilov became the director of this laboratory. In 1933 it was moved to Moscow and transformed into the Institute of Genetics. Vavilov headed the institute up to his arrest in 1940.

Filipchenko was a brilliant biologist combining both a profound knowledge of the general biology and the history of evolutionary thought with vast experimental skills. His interests in genetics range from plant genetics to eugenics. He wrote six textbooks (1923, 1926) and many reviews, which, according to Dobzhansky (1980), were used in institutions of higher learning until "Lysenko's pogrom". Filipchenko had great impact on the evolutionary and genetical thought in Russia. He was the first person who clearly distinguished between micro- and macroevolution. Dobzhansky was an assistant professor in Filipchenko's department between 1924–1927. Many famous Russian geneticists graduated from Filipchenko Department: Ju.Ya. Kerkis, A.A. Prokofieva-Belgovskaya, M.L. Belgovsky, N.N. Medvedev, I.A. Rapoport, M.E. Lobashov and R. L. Berg. The ideas and methodology of Koltzov's school were introduced into European genetics by Timofeev-Ressovsky. His dramatic biography and scientific life were recently reviewed (Paul, Krimbas, 1992). Certain traditions of Russian evolutionism were transferred to America by Dobzhansky. Both emigrants are renown in their fields and together helped to promote evolutionary and population genetics.

1. Major contributions before 1948

Let us to discriminate between two related fields. Evolutionary genetics embraces the analysis of the organization of genetic material, its comparison in different species and mechanisms of change, phenomenology of the expression of genetic factors, genetic aspects of speciation and events of intra- and interspecies hybridization. Population genetics includes first of all an analysis of genetic heterogeneity and the polymorphism of populations together with the mechanisms responsible for its maintenance, the study of the genetic consequences of selection and other evolutionary forces, gene geography and the phenetics of natural populations.

Hugo de Vries could be named the father of evolutionary genetics. He rediscovered Mendel's laws of inheritance of genetic variants. He established the principles of the spontaneous mutation process, He described polyploidy and chromosomal speciation in *Oenothera* and he described non-mendelian peculiarities in the progeny of interspecies hybrids. At the same time Chetverikov contributed to the foundation store of both theoretical and experimental population genetics. In his classical paper (Chetverikov, 1926, 1961) he presented important conceptual discoveries — the concepts of mutation pressure and genotypic milieu. He described material, methodology and tasks of population genetics. He linked the concepts and data of mendelian genetics with the theory of natural selection and ontogenesis. He also made important

theoretical predictions which were consequently confirmed by his students. From the point of theory of knowledge or epistemology it was a real conceptual discovery (Polanyi, 1962).

Using the inbreeding method, Chetverikov's students established the predicted existence of hidden recessive mutations in the progeny of wild flies of different *Drosophila* species (Gershenson, 1934; Romashov, Balkashina, 1929; Timofeeva-Ressovskaya, Timofejef-Ressovsky, 1927). Dubinin and his collaborators used the method of homozygotisation of autosomes of *D. melanogaster* with the help of dominant balanced markers, a modification of famous Muller's classical approach. They conducted a systematic comparative analysis of the concentration of lethal mutations in remote populations. During 11 years of study they described the lethal and visible mutation frequency in 14 populations. This study produced the first reliable data allowing a comparison of the genetic load of drastic mutations from distant populations (Dubinin et al., 1934; Dubinin, 1966). These results were confirmed by other geneticist from the Leningrad school (Olenov, Kharmatz, 1938; Olenov et al., 1939; Berg et al., 1941). Similar data were also obtained both on *D. melanogaster* and other *Drosophila* species in United States in the well known studies of Ph. Dobzhansky, M. Gordon, P. Ives and W. Spencer.

Gershenson (1934) succeeded in carrying out simultaneous «isogenization» of all autosomes of *D. melanogaster* in a sample of flies caught from a wild population. This approach revealed that practically every fly from nature carried some mutations. This fact permitted a more accurate evaluation of genetic heterogeneity in natural populations and gave a better insight into the mechanism of interaction between mutations located in different chromosomes. The description of minor or physiological mutations distributed in natural populations was made simultaneously by Dobzhansky and Queal (1938) and Muretov (1939). Regretfully this talented young geneticist was killed on the WWII.

The concepts of penetrance, expressivity, specificity of gene action and genetic constitution were developed by Timofeev-Ressovsky (1925, 1927; Babkov, 1985). In addition, Rokizky (1930) introduced the idea of a «field of gene action» or a stereotyped pattern of gene expression through studying inherited *Drosophila* bristle variations. All of these components or modules of a gene manifestation may be under the influence of genotypic and external factors. Timofeev-Ressovsky (1934) also conducted a series of obvious and simple experiments showing that the combination of two or three drastic mutations may increase variability. The similar methodology was used by Dobzhansky in his studies on the viability of lethal mutations heterozygotes isolated from nature.

One of the major problems studied in Filipchenko's Department was the genetics of speciation and interspecies hybridization. The possibility to investigate this problem arose when Sturtevant discovered the species *D. simulans* which is the sibling to *D. melanogaster*. After reviewing the long history of such studies, Provine (1991) concluded that, after Sturtevant, primary among these were the studies of Julius Kerkis of the Laboratory of Genetics, USSR Academy of Sciences in Leningrad. Kerkis (1907–1977) was involved in genetics with Dobzhansky after their curious accidental meeting in a forest near Kiev in 1920. Kerkis was then a boy collecting butterflies and Dobzhansky was a student collecting ladybirds. Later they met again in Filipchenko's Department in Leningrad. Kerkis became a student of Dobzhansky's and his friend until death. Kerkis (1933, 1936) conducted remarkable experiments on the influence of temperature on the hybrids and described the character of conjugation of polytene hybrid chromosomes.

Profound ideas in the fields of evolutionary and population genetics were developed by Serebrovsky. He proposed the concept of the gene pool and gene geography (Serebrovsky, 1928, 1930). In 1929 he was the first, together with his student Dubinin, to deduce the complex linear structure of the *scute-achaete* locus. Modern molecular data confirmed their principal conclu-

sion, mentioning «the pioneering work of the Russian genetic school in the 1930s» (Campuzano, Modolell, 1992). In 1938 Serebrovsky came to the profound conclusion that new genes arise in the process of evolution via the process of duplication and divergence. This idea was also ahead of its time.

The dramatic fate of the other original idea of Serebrovsky (1940) of induced translocations usage for insect pest control is also now well known. The original paper rested in obscurity till 1968. In 1968 Serebrovsky's paper was resurrected by C.F. Curtis and then an English translation was disseminated throughout western literature. In 1941 Serebrovsky prepared a more detailed version of his paper «Theoretical foundations of the translocation method of pest control» which was not published until 1971. The impact of these ideas for pest genetic control was thoroughly analyzed by Whitten (1985). One of the peculiar achievements of Chetverikov's school is the synthesis of data from population and developmental genetics (Babkov, 1985). Timofeev-Ressovsky established the main principles of the morphological manifestation of mutant genes. Outstanding biologist M.M. Kamshilov (1910–1979), working in the laboratory of I.I. Schmalhausen (Institute of Experimental Morphology, Moscow), had shown how the selection process can transform the norm of reaction. This term means the phenotypic variability produced by a given genotype under the range of environmental conditions, standard or experimental ones. Thus, wild or normal *Drosophila* flies have stabilized eye size that independent of developmental conditions. Mutation *eyeless* (small eyes) disturbs autonomous eye development and its size became dependent from temperature, humidity and feed pattern. By means of selection Kamshilov (1941a, 1941b) have got the lines with stabilized mutant expression under definite environmental conditions. Phenotypic change of norm of reaction resulted to change of multiple gene actions in the process of development. The selection of flies on cold resistance showed that adaptive norm of reaction could be also transformed under natural selection. These results demonstrated the dynamic character of developmental interactions between genotype/phenotype and environment. The similar results and conclusions were established later in the well known experiments of K. Waddington.

2. The direction of further studies

After Lysenko's pogrom in 1948 all genetical studies in the USSR were ceased. They were renewed only in the 1960's in three main centres: (1) The Institute of Developmental Genetics in Moscow headed by Astaurov, an eminent evolutionary geneticist from Chetverikov's group; (2) The Department of Genetics in St. Petersburg (Leningrad) University, headed by M.E. Lobashov and (3) The Institute of Cytology and Genetics organized in 1957 in Novosibirsk Academic City (Academgorodok). Dubinin, the first director of Novosibirsk Institute, invited there Ju. Kerkis and Zoia S. Nikoro who collaborated with Chetverikov. In 1963 R.L. Berg headed there the first laboratory of population genetics where she renewed her long term studies on mutation process in natural *Drosophila* populations.

We briefly summarize some of the main results obtained after the 1960's. The dependence of inversion polymorphisms on ecological factors discovered initially in *D. funebris* populations by Dubinin and his associates was confirmed by Borisov (1969) following his studies of *D. funebris* populations in the Moscow region. The existence of urban and rural races of *Drosophila* differing in karyotype structure was confirmed together with spreading of the rural race over a 20 year period from 25 to 800 sq. kms. A remarkable series of experiments on interspecific hybridisation

among the *D. virilis* group was conducted by N.N. Sokolov and his followers. Sokolov (1959) developed an exact cytogenetical method of chromosome substitution for the study of nucleocytoplasm incompatibility for interspecies hybrids. He showed that in the hybrids of *D. virilis* x *D. lummei* somatic heteroploidy regularly occurs due to the elimination of one chromosome in the first mitotic cleavage division. Then M.B. Evgeniev showed that the elimination of this chromosome from one species results of AT-rich region and its retarded replication (Evgeniev, Sidorova, 1976). Mitrofanov (1969, 1974) continued the phenogenetic tradition of the Moscow school of evolutionary genetics. He found that penetrance of dominant *Puffed* mutation greatly varied in intraspecies hybrids, depending on the origin of the wild strain and the presence and concentration of modifier genes. In interspecies hybrids the *Pf* mutation expression was influenced by cytoplasmic factors. M.B. Evgeniev and E.S. Zelentzova (1984) described a new family of mobile elements in *D. virilis* group called pDv. In *D. virilis* individual copies of pDv are scattered over approximately 200 sites on all chromosomes. In other related species *D. texana* and *D. novamexicana*, the number of pDv sites is markedly lower. The pDv copies are completely absent in *D. littoralis*. Localisation of pDv coincides with the sites of concentration of satellite DNA. In interspecific hybrids of *D. virilis* x *D. littoralis* and *D. virilis* x *D. lummei* transposition of pDv from *D. virilis* chromosomes to foreign ones was demonstrated. These data can be used to explain the drastic reshuffling of stDNA in *D. virilis* and other related species. MEs may well be functioning as a shuttle system. Afterwards Evgeniev and co-authors (1990) discovered a hybrid dysgenesis syndrome in *D. virilis*. The dysgenic traits (male and female sterility, chromosomal abnormalities and numerous visible mutations) occurred in F1 hybrids between wild flies females and males from laboratory inbred strain. This syndrome appeared similar with other dysgenesis systems in *D. melanogaster* and resulted from activation of the species-specific MEs.

Korochkin and his associates (1990) conducted comprehensive comparative genetic and biochemical analysis of the expression of a clusters of esterase genes in different *Drosophila* species. They found the species-specific differences in the expression and developmental regulation of esterase genes connected with the action of regulatory mutations. They discovered and localized different types of trans-acting regulators or modifiers which are selected during evolution. These include (i) regulators controlling isozyme activity and the amount of mRNA, (ii) temporal regulators which control the exact time of tissue-specific expression and (iii) «architectural» genes controlling the ratio of free and membrane bound fractions. These results may be presented as the molecular incarnation of phenogenetic concepts of Timofeev-Ressovsky and Rokitsky. An important original set of data were obtained on the problem of the origin of spontaneous mutations. As early as 1939, Gershenson (1940) discovered the mutagenic action of foreign DNA in *Drosophila*. These promising studies were interrupted firstly by war and then by the collapse of Russian genetics in 1948. Since the 1960s Gershenson together with his follower Yu.N. Alexandrov undertook a systematic study of the peculiar mutagenic action of this natural source of variation. It was established (Gershenson et al., 1975; Gershenson, 1986) that foreign DNA extracts, including DNA and RNA viruses added to *Drosophila* food or injected in haemolymph, raised the mutation rate and produced an unstable state of some host genes. The action of foreign viral DNA and RNA differed in their chromosome and locus specificity. Autosomal lethal mutations and unstable visible ones occurred preferentially in a definite group of loci characteristic for each agent tested. Multilocus damages, which resulted in so called multi-lethal chromosomes, have been observed regularly. On the other hand multi-lethal chromosomes were isolated in distant natural populations (Golubovsky, 1970). Genetic analysis showed definite allelism of multilethal chromosomes from nature with sets of lethals induced by different viral DNA (Alexandrov, Golubovsky, 1983). Together with other relevant data (Golubovsky, Plus, 1983; Gazaryan et al.,

1984) it presented undirect evidencies that (a) viruses may be a specific source of spontaneous mutations and (b) virus-induced multiloci lesions can occur repeatedly in natural populations as a result of a single mutation events. In 1980s the occurrence of multiple chromosomal lesions due to activation of MEs was found in the various systems of hybrid dysgenesis (Berg, Engels, Krever, 1980; Lim, 1988). The main conclusions from these original studies are very important. Gershenzon and his students (1975) stressed that if we bear in mind how universally distributed viruses are, how often human beings come into contact with them after various prophylactic virus inoculations and when virus preparations are applied in the struggle against harmful insects, etc. then we have to recognize that the mutagenicity of viruses is a very serious problem. The search for the source of genetic variability in nature leads to the study of the interaction between different DNA and RNA and to symbiogenetic and biocenotic genetics. One of this interesting aspects was developed by Luchnikova et al. (1981, 1987). In the ecological system *D. melanogaster* — *Saccharomyces cerevisiae* fly is a consuming species and the yeast is a producing species. Flies and yeasts are linked through the food chain in nature: *Drosophila* shows an obligate dependence on sterol biosynthesis of yeast. Sterols are required by insects as the building blocks of membranes and as precursors of ecdysone. The steroid hormones control larval moults and metamorphosis. E.M. Luchnikova and S.G. Inge-Vechtomov decided to study the effect of a genetic block in the synthetic pathway of the producing organisms on the genetic variation of the consuming one. Mutant yeasts deficient in sterol biosynthesis were used. The feeding of *Drosophila* larvae on the mutant yeast blocked larval development. Starving adult flies of sterols shortens their lifespan and decreases fertility. The genetic consequences of the abnormal yeast-*Drosophila* food chain are an increased rate of induced mutations in flies (aneuploidy, dominant lethals) and a decreased frequency of crossingover.

Long-term population studies on *Drosophila*

Now we are starting on our own series of long-term experiments with *Drosophila* connected with the genetic analysis of natural populations and the analysis of the genetic consequences of selection. As noted by Dobzhansky (1971), there are only a handful of cases in which genetic changes in populations were actually observed. The need for such studies on *Drosophila* became more necessary after recent the discovery of global changes in the genetic structure and distribution of movable elements and after evidence of their recent horizontal transfer (Anxolabehere, Kidwell, Perique, 1988; Kidwell, 1992). Long-term systematic population studies yielded an unpredictable results.

3. Long-term selection and ordered ME-mediated variability

3.1. Survival strategies of inbred long-selected lines: genetic mechanisms

During long-term experiments we analyzed the spectrum of genetic changes resulting from inbreeding on male sexual activity. To approach this problem, a long term experiment was conducted in 1965 (Kaidanov, 1980, 1990). The establishment of low-activity (LA) strains by means of close inbreeding was started in 1965 from a sample of flies that originated from a natural population in Yessentuki (Crimea). Up to 1993 the LA stock had been inbred for 650 generations.

Three main phenomena have to be identified: (i) a highly increased level of mutability in inbred stocks, the accumulation of supervital mutations capable of suppressing lethals and semi-lethals, and the maintenance of a high potential for variability; (ii) the nonrandomly ordered transpositions of some *copia*-like MEs accompanied with increased viability; (iii) a considerable increase in genome instability of lines selected in the minus-direction. The manifestation of the first mechanism was demonstrated by successful reverse selection of flies from the inbred LA stock in the plus direction. The possibility of successful selection in the plus and minus direction after many dozens or even hundreds of inbred generations demonstrated the high potential for hereditary variation in the strains studied. Using the standart *CyL/Pm* procedure we found in second chromosomes of inbred LA flies the whole spectrum of mutations from lethal to supervital. The proportion of various classes of mutations was repeatedly estimated during the selection protocol (Kaidanov, Genova, Gorbunova, 1979). In the high-activity (HA) strain selected for a high male mating activity, the genetic load was minimal, whereas in the LA strain nearly 50% of the second chromosomes carried deleterious mutations. A considerable proportion of chromosomes in the highly active strain carried supervital mutations. By recombination analysis we have demonstrated the presence of suppressor mutations in the HA inbred stock. Owing to the presence of suppressor chromosomal segments, lethals become vitals and even supervitals in homozygous condition. Our data showed that so called “synthetic lethals” described first by Dobzhansky in 1946 are not curiosities but usual component of genetic variability. The half-dominant and dominant suppressor mutations can be viewed as elements of a compensation complex (Strunnikov, 1974).

3.2. The study of behavior of different MEs in inbred stocks

The behavior of different MEs in selected inbred stocks was studied in collaboration with V.A. Gvozdev and his colleagues in the Institute of Molecular Genetics of the Russian Academy of Science. The distribution of MEs *mdg1*, *mdg3*, *mdg4* and *copia* was analyzed in the original inbred stocks and its derivatives selected in both plus and minus directions. The original strains were quite stable over many years. Transposition frequencies of *mdg* elements according to rough estimates were close to 1:10 000. The directed selection for increased adaptive properties resulted in the segregation of certain rare families with an increased adaptive capacity. It turns out that in these families the genomes are reconstructed: *mdg* elements appear at new sites and their number generally increases. Copies usually vanished from old sites but in some cases a proportion of them may remain at their previous locations. It has been demonstrated for the first time that this type of genome reconstruction involves a large number of MEs operating synchronously. The copies of MEs in new sites often appear together. The genome presumably contains «hot spots» that are targets for highly effective transposition of MEs during selection for increased fitness. In the LA strain the number of *mdg1* was minimal. But in the LA sub-strains with increased viability from one to seven new sites of *mdg1* appeared. At least two MEs, *mdg3* and *copia* have an affinity for similar chromosomal regions. This leads to the conclusion that their transposition is coordinated. Such trends have not been observed for other *mdg* families. Copies of the *mdg4* or “*gypsy*” never change their localization in response to selection.

Some LA chromosomes with an apparent lethal mutation were maintained as *CyL/lethal* heterozygotes in a balanced condition for nearly three years. Then they were screened for their disposition of MEs and for the presence of rearrangements. The result was striking. A consid-

erable number (13 of 33 or 39,4%) of chromosomes containing lethal mutations in balanced condition carried also chromosomal rearrangements, predominantly paracentric and pericentric inversions. Most of the rearranged chromosomes (nine of thirteen) carried a combination of several inversions, and among them two also had transpositions and one a translocation. Apparently in crosses of *CyL/Pm* strains to LA, the induction of complex multisite rearrangements had taken place. They strongly resemble those appearing in crosses which induce hybrid dysgenesis due to the transposition of *Hobo*-elements (Lim, 1988).

It appears that one of the LA substocks contained about 30–35 copies of the *Hobo*-element on all of its major polytene chromosome arms. In addition to rearrangements the lethal chromosomes maintained in balancers (*CyL/lethal*) showed an enormous level of mass transpositions. In lethal chromosomes of LA strains less than 30% of the original sites of *copia* -like MEs maintained original disposition (Kaidanov et al., 1991)! Such reshuffling of the genome is presumably the result of the activation of *Hobo*-elements capable of inducing hybrid dysgenesis. Gvozdev and Kaidanov (1986) have put forward the hypothesis concerning the existence of a system of adaptive transpositions of MEs. It is based on the regulatory effect of MEs on the array of structural genes. The long terminal repeats of *copia* -like MEs contain both termination sites and enhancers. This gives them the capacity to regulate the gene. Lethal mutations occurred in LA stocks at a high frequency.

The discovery of ordered or concerted transposition of MEs observed in this and other studies (Gerasimova et al. 1984) made it necessary to reevaluate earlier conventional views about the nondirectional nature of hereditary variation. We probably have to recognize that selection can control the pattern of migration of MEs in the genome. Genome hot spots are targets that quickly become occupied by MEs when selection is directed towards vital functions (Kaidanov, 1989; Kaidanov et al., 1991).

4. Gene pool dynamics, mutation bursts, and ME-mediate gene instability

4.1. Gene pool of lethal mutation in space and time

Long term studies conducted since 1963 by Golubovsky and his colleagues resulted in a number of important conclusions: (1) an existence of parallel and synchronous changes in the gene pool in adjacent and distant natural populations of *D. melanogaster*; (2) the discovery of ubiquitous stable polymorphism on the oncogenic lethal mutation; (3) evidence that mutation bursts in nature are connected with the appearance of unstable mutations resulting from activation of MEs, their insertions and transpositions; (4) a new understanding of the eukaryotic genome organisation and genetic variability occurrence. Dobzhansky and his colleagues have described synchronous fluctuations in the frequency of definite inversions in distinct populations of *D. pseudoobscura* (Dobzhansky, Queal, 1938; Anderson et al., 1975). Parallel results were found during long-term studies on mutability and the population of lethal and visible mutations (Berg, 1966, 1968, 1972; Golubovsky et al., 1974; Golubovsky, 1980). Up to beginning of the 1960s certain general features of distributions of heterozygous recessive lethal mutations and their allelic content were established. But what was needed was a detailed description of the population dynamics of the lethal pool and an evaluation the influence of the major microevolutionary factors. Thus it was decided to analyze the dynamics of gene pool of lethals (concentration, allelism and localization) in two to three adjacent populations together

with simultaneous genetic analysis of the geographically distant ones. Populations from Uman (Ukraine) were chosen for they were initially studied in the 1930s. About 40 000 diallelic crosses were carried out and the fate in space and time of more than hundred of lethal genes containing in second chromosome was investigated. Gene pool comparisons were made between the different seasons of fly reproduction (spring, summer and the end of autumn) and in successive years. We found two peculiar features: (a) a quasistationary gene pool state, (b) parallelism in dynamics and allelic content of lethal mutations in adjacent populations. The lethal heterozygous concentration was stably maintained in each population studied at a defined level. Allelism tests of intrapopulation samples showed that nearly half of the mutations occurred singly, while other lethals were repeated, being represented by two, three or more alleles. Each year there was a considerable turnover of the gene pool accompanied by the transition of rare (unique) lethals to the category of repeated ones and vice versa... hence the term quasistationary state. Meanwhile a systematic comparison of lethal sets in adjacent populations revealed remarkable parallelism despite the constant allelic turnover. Allelic sets of lethals from different populations studied in the same season usually showed greater similarity than sets of lethals extracted in successive periods from the same population. No mutation process or genetic drift can explain such parallelism. It has been suggested that the quasistationary state and parallel changes in allelic lethal content is a consequence of possible host/parasite selection with resulting tolerance of flies carrying some lethals in heterozygous condition to definite infectious microorganisms (Golubovsky et al., 1974). The lethal alleles giving relative tolerance to their carrier provide a selective advantage as long as they are relatively rare. But after spreading in populations flies carrying such repeated lethals lose their advantage when new mutations of virulence appear in the infectious agent. The similar ordered flow of lethal alleles is thereby ensured in different host fly populations. This picture of permanent turnover of the lethal gene pool is complemented by the remarkable ubiquitous stable polymorphism of lethal alleles of the *lgl* (*lethal giant larvae*) gene. The ubiquitous distribution of *lgl* alleles in natural populations of Ukraine, Crimea, Middle Asia and Far East was demonstrated in two periods: 1963–1978 (Golubovsky, 1978a, 1980), and then in 1979–1989. Hundreds of genes are capable to mutate to the lethal condition on the second chromosome of *D. melanogaster*. But it is namely *lgl* alleles that mutate most frequently. We observed that about one fly out of 20–50 flies from wild populations is $+/lgl$ in genotype. What is the reason for *lgl* ubiquitous distribution? It was found that $+/lgl$ animals had an advantage in stressful conditions: cold or high temperature during development and infection of virulent picornavirus *DCV* (Sokolova, Golubovsky, 1979; Plus, Golubovsky, 1980). In the middle of 1960s Elisabeth Gateff made a fascinating discovery that blockage of metamorphosis in *lgl* homozygotes is due to invasive neoplastic growth of brain tissue cells. The *lgl* gene appears the first example of a monogenically controlled neoplasm in *Drosophila* and the first case of a tumor suppressor gene found in animals (Gateff, 1974). Phenogenetic analysis of *lgl* alleles extracted from different populations showed their multiple allelism. So we are dealing with a continuous mutation process at a given locus following selection of newly arisen lethal alleles. This genetic conclusion was confirmed by the direct molecular analysis of natural *lgl* alleles. Surprisingly, most of them appeared intragenic deletions and mobile element insertions (Mechler, McGinnis, Gehring, 1983). At the same time Green and Shepherd (1979) found that *lgl* mutations are also frequent in a California populations and that the *lgl* gene is the target of the action of a powerful MR (Male Recombination) mutator factor. In the presence of factor MRh-12 microdeletions in the telomeric region of the left arm of second chromosome, where *lgl* is located, originated with a frequency of 1:1000. Thus it turns out that the selective gene is capable to regulate the level of its mutability, maintaining in population its specific mutator.

This phenomenon is known as “genetic hitchhiking” — the term coined in 1974 by Maynard Smith. Paradoxically, the oncogenic mutation, that in homozygotes lead to tumors and lethality may provide in heterozygous condition a selective advantage. Can we expect a similar situation in humans?

4.2. Mutation bursts and mutation fashion in natural populations

A third aspect concerns the monitoring of the mutation process. The concept of specific periods during which the mutation rate sharply rises was first developed by Hugo de Vries but subsequently rejected. However, long-term population studies definitely support this old idea. Particularly demonstrative are outbursts of mutability at the same loci in distant populations. In 1930s Russian population geneticists found high mutability in the sex-linked genes *yellow* and *white* (Gershenson, 1940; Berg, 1945; Duseeva, 1948). After the 1940s the mutability of *yellow* and *white* loci returned to a normal level (Berg, 1966). From the beginning of 1980s the mutability of the *yellow* gene in the Uman population once more sharply increased. But this time the «fashionable» alleles were not *yellow1* but *yellow2* (Zakharov, Golubovsky, 1985; Golubovsky, Zakharov, Sokolova, 1987).

In summary, the authors, up to 1973, have accumulated much experimental evidence for the phenomenon of «mode of mutations». They predicted that one definite genetic mode will pass giving way to other (Golubovsky et al., 1974). This proved to be the case. Namely in 1973 in two geographically isolated populations (Caucasus and Middle Asia region) an outburst of mutability of the sex-linked *singed bristle* locus was discovered (Berg, 1973; Ivanov, Golubovsky, 1977). The *sn* mutability increased a hundred fold to $(0,3-0,9) \times 10^{-3}$. The peculiar thing that not only the *sn*-mutant alleles but their normal derivatives were also quite unstable. The detailed genetic analysis lead to the conclusion that instability of the *sn* gene is the result of MEs insertions (Golubovsky, Ivanov, Green, 1977).

We found allele-specific character of mutation of series of *sn*-unstable alleles concerning the phenotype expression, direction and rate of mutations both in germinal and somatic cells. We observed also the complex control of instability: its dependence from cytotype, modifier genes and presence of other unstable allele in the genome. We found also that phenotypic expression of some unstable mutations may depend both on temperature and the Y-chromosome being similar to position effect.

At Stadler's Symposium in 1978, M. Green concluded that the discovery of worldwide appearance and the distribution of unstable *sn*-alleles «represented the first systematic recovery of mutable genes in *Drosophila* and posed the novel question: what is the origin of unstable *sn* mutants?» (Green, 1978, p. 102). Our genetic analysis had showed that the B. McClintock hypothesis of mobile elements insertion appeared to be valid for explanation of instability of mutations found in *Drosophila* populations. As it is well known, in the beginning of 1980s ME were discovered in *Drosophila* independently by two groups of molecular geneticists in USA and Russia. It was shown that namely ME insertions induce genetic instability. The *sn* locus appeared to be the target for the now famous P-element. More than 50% of unstable *sn* alleles from different natural populations appeared to be connected with P-insertion (Golubovsky, Belyaeva, 1985). However, unstable *sn* alleles isolated simultaneously at the same population appeared to be connected with the insertion of different MEs (not only P). Thus the conclusion is inevitable that the mutation burst is the result of simultaneous activation in wild population of different MEs.

4.3. Natural genetic engineering

Of special interest is the first described case of natural genetic engineering. Two separate genes «*singed bristle*» and «*club wing*» on the X-chromosome isolated from a Russian Far East population appeared to be joined under the control of one ME capable of transposition. As a result of such natural engineering bimutant unstable construction occurred. This insertional bimutant construction was unstable and produced normal derivatives which once more reversed to the bimutant condition. Many of the genetic aspects of this new genetic construction mediated presumably ME insertion were clarified. The ordered changes of this natural engineering construction was observed (Golubovsky, Zakharov, 1979; Yurchenko, Zakharov, Golubovsky, 1984).

5. Two parts of a genome and two parts of genetic variability

We can now describe a new approach to the understanding of sources and factors inducing genetic variability. Classical mutations evidently make up only part of the genetic variability in natural populations. It was suggested to discriminate in the eukaryotic genome between two subsystems: the *obligate* and the *facultative* (Golubovsky, 1985). This subdivision is a natural one.

The obligate part includes the set of genetic loci (and their clusters) located in chromosomes and in DNA of cellular organelles. In classical genetics each gene has a definite position on a genetic map. It is the skeleton of the genome, its structural or conservative memory. But the genome also includes different kinds of facultative elements, varying in number and topography from cell to cell and from individual to individual. The facultative part of the genome includes the hierarchy of elements from highly repeated and satellite (st) DNA, plasmids, B-chromosomes and certain (relatively stable) cytobionts present both in the nucleus and the cytoplasm. This natural structural subdivision allows a discrimination between changes within obligate elements (changes of their structure, number and position) and changes within the facultative elements.

Only the first class of changes corresponds to classical mutations. Various changes of different facultative elements may be called *variations*. Variations are the most frequent class of hereditary changes, because facultative elements are susceptible to a wide spectrum of environmental alterations. Mutations or direct damage of genetic loci occur mainly following the strong action of environmental factors (e. g., radiation, chemical mutagenesis, defects of repair system). The sets of facultative elements respond initially to the weak action of environmental factors (in a broad sense: physical, biotic and genetic). The interaction between the components of the system *environment-facultative-obligate elements* is the major source of the most genetic changes occurring de novo in nature.

Thus, there exists the two-step mechanism of natural hereditary changes occurrence. The facultative elements are the first ones that react to various environmental fluctuations. Many variations (changes in the number of high repeated DNA, changes in number and topography of amplified segments and MEs, and the presence or absence of cytobionts) may have no visible or physiological effects detectable by usual genetic methods. At the same time such variations as transpositions of MEs may induce insertional mutations and rearrangements of chromosomes with definite physiological consequences such as longevity or fertility. Changes in number or cell topography of cytobionts (the usual kind of facultative elements in the eukary-

otic cells), for instance, the number of RNA-containing *sigma* virus in the cytoplasm of different *Drosophila* species, may have important physiological consequences as lethality in presence of carbon dioxide.

The relationship between the obligate and the facultative elements of the genome has to be studied in the terms of molecular population genetics. Changes in the frequency of specific facultative elements may occur in stem cells during ontogenesis, for example, a blockage of *sigma* virus replication by heat stress. On the phenotype level these changes may look like the inheritance of developmentally acquired (induced) traits (Golubovsky, 1985; Landman, 1991). There is a constant flux between obligate and facultative elements. For instance, insertion mutations can be presented as a transition of facultative MEs into the obligate parts of a genome. On the other hand, the amplification phenomena, which may result in additional micro-chromosomes, may be taken as a transition of obligate elements to facultative ones. Roman B. Khesin (1922–1985) put forth the concept that the eukaryotic genome must be viewed as a population of self-reproducing DNA and RNA molecules. Moreover, having in mind the regular horizontal transfer of transposons and plasmids in microorganisms, the increasing number of similar facts in *Drosophila* species, and the wide distribution of the same retroviral sequences among remote animal species, we may agree with Khesin's paradoxical conclusion that it is possible to conceive of a gene pool encompassing in its potential all living organisms (Khesin, 1984).

General conclusion

In conclusion we would note that the directions of Russian *Drosophila* population genetics and Dobzhansky's studies were often synchronous and parallel. This fact is rooted both in the inner logic of science and the «foundation principles», originated from the same scientific school. Dobzhansky regularly exchanged letters with his Leningrad University student and friend Ju.Ya. Kerkis. At the same time he was keenly interested in population studies in Russia. In one of his last letters to one of the authors Dobzhansky discussed the puzzling phenomenon of synchronous fluctuations of mutability and the appearance of multiple series of unstable *sn* alleles in distant populations. He remarked how incorrectly many molecular geneticists saw population genetics in the 1970s. They thought of it as an exhausted field, something like a “squeezed lemon”. Now, almost twenty years later, we see the beginning of a promising synthesis of population and molecular genetics.

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Исследование генетической изменчивости в популяциях

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Впервые полностью публикуется написанная в 1995 г. статья, в которой описано возникновение и развитие российской популяционной генетики и её основные открытия, сделанные в экспериментах на дрозофиле. Кратко рассмотрен концептуальный вклад двух главных научных школ, возглавляемых Н.К. Кольцовым и С.С. Четвериковым в Москве и Ю.А. Филипченко в Санкт-Петербурге. Идеи этих школ были внедрены в европейскую и американскую генетику Ф.Г. Добржанским и Н.В. Тимофеевым-Ресовским. Авторы статьи в общих чертах представили результаты своих собственных исследований генетической изменчивости как в естественных, так и в лабораторных популяциях. Исследования были проведены независимо друг от друга в двух лабораториях. Авторы доказывают, что главный источник наследственной изменчивости в природе — это взаимодействие окружающей среды с факультативными элементами генома.

Ключевые слова: популяция, генетика, мутация, *Drosophila*, летальный ген, мобильные элементы.