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USSR Report

LIFE SCIENCES

BIOMEDICAL AND BEHAVIORAL SCIENCES

(FOUO 7/81)

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CONTENTS

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EXPERIMENTAL STUDY OF DOLPHIN KINEMATICS

Moscow DOKLADY AKADEMII NAUK SSSR in Russian Vol 253, No 3, 1980 received 4 Apr 80 pp 741-743

/Article by Ye. V. Romanenko (presented by academician V. Ye. Sokolov 15 Jan 80), Institute of Evolutionary Morphology and Ecology of Animals imeni A. N. Severtsov of the USSR Academy of Sciences, Moscow/

/Text/ In this work an attempt was made to apply the theory of G. V. Logvinovich (2), academician of the Ukrainian SSR Academy of Sciences, to a case of fish and dolphin swimming by the "scombroid" method, when the law of their body deformation is taken in the form

$$(1)\quad \eta = \eta_0\left[k_r - 1 + \exp\left(\alpha\left(\frac{x_2 - x}{L_p}\right)^{\gamma}\right)\right]\sin\omega\left\{t - \frac{x_2 - x}{c_r[1 + b(x_2 - x)]}\right\}.$$

Here η_0 is the amplitude of tail oscillations, k_r, the ratio between the amplitudes of head and tail oscillations, x, the moving coordinate in the inertial coordinate system x, y, z moving together with the body in an unbounded medium in the direction of axis Ox, the coordinates of body extremities having designations x_2 (of the head) and x_1 (of the tail), $L_p = x_2 - x_1$, the body length, ω, the circular frequency of body oscillations, t, the time and c_r, the phase velocity of locomotor wave propagation through the body in point x_2, $\alpha = \ln(2 - k_r)$. Coefficients k_r, γ and b characterize the individual features of kinematics of various fish and dolphin species and should be determined experimentally.

This work presents the results of an experimental study of the bottle-nosed dolphin for the purpose of determining the above-mentioned coefficients.

The kinematics of this dolphin was studied by two methods, that is, the filming method and the method of three accelerometers.

The filming method consisted in filming the swimming movements of the dolphin, which swam along a straight line past the camera lens, with a subsequent reading of records and determination of coefficients. Coefficient

k_r was determined as the ratio between the amplitudes of head and tail oscillations. To determine the indicator of degree γ, the amplitude of dorsal fin oscillations, not only of head and tail oscillations, was measured. Then a value of the indicator of degree γ was selected so that the measured magnitudes of oscillation amplitudes at the indicated three points of the dolphin's body might comply with the law of deformation represented by formula (1). To determine coefficient b, the mean values of the phase velocity of the locomotor wave propagated through the dolphin's body on the sections from the head to the dorsal fin and from the dorsal fin to the tail ($c_{r.cp}$ and $c_{xв.cp}$ respectively) were measured. The ratio of the second magnitude to the first was calculated. Then, under the assumption of a linear dependence of the phase velocity on the coordinate, we turned to the ratio of the values of the phase velocity of the locomotor wave at the tip of the tail ($c_{xв}$) to its value in the head area (c_r). Finally, coefficient b was calculated according to the formula

$$b = \left(\frac{c_{xв}}{c_r} - 1\right)/L_p.$$

The method of three accelerometers consistsd in fixing accelerometers at three points of the dolphin's body (on the head, in the area of the dorsal fin and on the fluke), which recorded the magnitudes of fluctuating accelerations. Information from the accelerometers arrived through screened wires at the input of a small tape recorder attached to the dolphin's dorsal fin and was recorded.

This method, in contrast to the previous one, has one significant advantage. It makes it possible to study dolphin kinematics continuously in the process of swimming, whereas the filming method makes it possible to do this only when a dolphin is in a frame. The determination of magnitudes k_r, γ and b according to the record results does not differ fundamentally from that described in the previous method with the only difference that, first, the record is twice integrated in time in order to change over from fluctuating accelerations to the amplitudes of shift of the body points in which the accelerometers were.

As a result of measurements the following values of the parameters of dolphin swimming were obtained (see table 1).

Table 1

Parameter	Value	Parameter	Value
k_r	0,22 ± 0,02	$\frac{c_r}{V}$	1,05 ± 0,05
$k_{сп}$	0,29 ± 0,02		
γ	4,07 ± 0,25	ω, c^{-1}	14,00 ± 0,7
$b, м^{-1}$	0,23 ± 0,02	$V, м \cdot c^{-1}$	4,3 ± 0,07

It is necessary to stress once again that all the measurements were made with the same value of the velocity of dolphin swimming indicated in the table. The errors presented in all the cases are equal to one mean square error of measurement of the mean value. The measurements were made on one dolphin specimen, whose weight was about 150 kg and length, 2.24 m.

In study (1) the performed analysis of the physical mechanism of fish and dolphin swimming made it possible to assume that the correlation between parameters γ and b was in the form

$$\frac{V\alpha^2 e^{2\alpha}}{L_p^2}\gamma^2 = \frac{\omega^2}{V}\left[\frac{1}{1+L_p b}\right]\left[1-\frac{1}{1+L_p b}\right]$$

It is more convenient to write this formula as

$$\gamma = \omega L_p\sqrt{L_p b}/\alpha e^{\alpha} V(1+L_p b).$$

Substituting the value of parameter b and of the other necessary parameters from the table presented above into this formula, we will obtain the value 3.5 for γ, which correlates with the measured value 4.07 quite satisfactorily, differing only by 16 percent from it. It must be stressed that the values of parameters γ and b presented in the table were obtained in the experiment quite independently and by various methods.

The results presented make it possible to draw the following conclusions: 1. A previously unknown dependence of the phase velocity of the locomotor wave propagated through the dolphin's body from the head to the tail in the process of active swimming on the coordinate in the coordinate system connected with the animal's body was detected. The phase velocity of the wave in the area of the dolphin's tail exceeds by a factor of 1.5 the phase velocity in the head area in the regime of dolphin swimming with a constant velocity equal to 4.3 m/s. Thus, the assumption expressed in study (1) was confirmed. 2. The law of deformation of the dolphin's body in the process of active swimming is significantly nonlinear and is approximated satisfactorily by the exponential function represented by formula (1). 3. The satisfactory conformity of the measured and theoretically predicted values of parameters γ and b indicates that the dependence of the phase velocity of the locomotor wave on the coordinate, apparently, is close to the linear.

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MICROBIOLOGICAL PROTEIN SYNTHESIS. THE STATE OF THE ISSUE, AND THE DEVELOPMENTAL TRENDS

Moscow IZVESTIYA AKADEMII NAUK SSSR: SERIYA BIOLOGICHESKAYA in Russian No 4, 1980 pp 595-610

[Article by T. Ye. Popova, USSR Academy of Sciences Institute of History of Natural Sciences and Engineering, Moscow]

[Text] The proportion of protein from unicellular organisms in the total quantity of protein produced is not large for the moment, but microbiological methods of protein production are highly promising, and they have been developing swiftly in the last 10-15 years. This paper examines the production processes for obtaining protein from unicellular organisms, the problems of choosing the raw materials and producers for these processes, and the areas of application of the obtained product. The range of taxonomic groups of microorganisms and the types of raw materials used in these processes have recently been broadening. In particular, much attention is devoted to the use of renewable resources and industrial wastes (cellulose-containing, and so on). Their application for microbiological synthesis may compensate fully for the worldwide shortage of proteinaceous substances. The problems of improving, enlarging, and automating the apparatus used in these processes are examined.

The problem of supplying the planet's growing population with proteinaceous substances is recently becoming more and more pressing. The world shortage of dietary protein, which is now estimated at several million tons, and the unevenness of food distribution have resulted in the fact that the concentration of proteins in the food ration of the population of a number of countries, especially proteins having a balanced amino acid composition (animal protein for example) is much below normal, causing many serious diseases and raising mortality. For example more than 55 percent of the world's population and only 28 percent of food production are concentrated in the countries of Asia (not including USSR territory) (25).

While the food of people in the industrial countries contains 90 gm total protein and 44 gm animal protein, the figures for developing countries are only 58 and 9 gm respectively (8). Protein is also a pressing problem in the developed countries.

Because of further population growth, shrinking agricultural area due to urbanization, industrialization, pollution of the ocean, and other causes, the protein shortage will grow, and therefore finding ways to increase protein production is one of the most important worldwide problems.

The food problem is being solved mainly through intensification of agriculture by introduction of the achievements of chemistry, genetics, microbiology, and other sciences, by expansion of the agricultural area, and by mechanization and industrialization. As a rule there is little protein in plant products, and its amino acid composition is not balanced--it contains an insufficient amount of essential amino acids (leucine, lysine, etc.). Soy contains relatively more protein rich in lysine. The area devoted to this crop is growing today in many countries of the world, including the CEMA countries: Worldwide soy production was 21 million tons in 1955, 61 million tons in 1975, and 80 million tons per year in 1978-1979 (3, etc.). It should be noted that the potential of the "green", or agricultural, revolution is limited. As in prehistoric times, agriculture depends today on climate. Water shortages are already limiting the contribution the green revolution could make to solving the food problem in many regions of the world, and the growth in agricultural production will be lower than population growth in a number of countries (25).

Many of the world's countries have recently been conducting intense scientific and practical research aimed at acquiring protein from the most diverse plants, both ones that had previously served as feed, and ones being introduced into the feed ration for the first time. For example Hungary built a facility to obtain protein concentrate from green plants in 1972, and construction of two more similar enterprises was started in 1974. Methods for extracting proteinaceous substances from plant materials have been developed and are being introduced into production in the USSR and a number of foreign countries (USA, Japan, France, etc.).

Application of microbiological and chemical methods for processing coarse fodder with the goal of raising its nutritional value, particularly raising protein assimilability, is an interesting research direction.

Because plant food lacks essential amino acids, use of animal and fish protein has decisive significance to supplying man with food having a balanced amino acid composition.

It was believed earlier that the oceans are unlimited protein sources, but due to pollution of the water basins and overfishing, the amount of fish caught per capita is dropping (32).

Animal husbandry could be intensified only if an adequate feed base is created. Due to a shortage of a number of amino acids, animals receiving plant feeds consume more feed per unit product than normal. Animal protein balanced in amino acids (fish and meat-bone meal, milk, buttermilk, skim milk, and so on) is added to feed to raise its protein value. But this does not compensate for the protein imbalance of plant feeds. Moreover the animal feed resources are limited, and the price of fish meal is rising abroad.

On the whole, the productivity of food industry is now very low. In comparison with other sectors for example, it is the lowest in a developed country such as the USA (19).

The time has come to fundamentally modify the traditional methods of food production. Food production must be industrialized, and it should proceed on the basis of the scientific principles of engineering. Extremely promising in this regard are industrial methods for producing proteinaceous substances based on cultivation of lower organisms--yeasts, bacteria, fungi, and algae--in nondietary raw materials. These methods offer the greatest potential among all of the ways for solving the protein problem.

Acquisition of protein with the help of unicellular organisms is promising owing to the much faster doubling of biomass in comparison with plants or animals (there are bacteria capable of doubling their cell population every 5-8 minutes), and owing to the high concentration of protein in the biomass (up to 70 percent true protein). For comparison, here are FAO figures for the protein concentration of livestock products (percent): beef--16.5, pork--10.2, poultry--18.6, eggs--4.9, milk--3.5.

Microorganisms can be cultivated around the clock, and uniformly throughout all seasons; moreover these processes are not fearful of low-harvest years, epizootics, plant diseases, and so on. Microbiological production operations require little room, they use fertilizer better than agriculture, they consume water more effectively than irrigated land, and when properly organized they cause no harm to natural ecosystems and promote nature conservation, while agricultural expansion requires transformation of virgin land into fields and pastures, and extensive fisheries have an unfavorable effect upon oceanic fauna. Microorganisms adapt themselves easily to new environmental conditions, and the composition of their biomass yields readily to industrial control and selection. Another advantage of microbial biomass is its homogeneity, the possibility for processing it as a single whole. The reserves of raw materials required by microbiological processes are practically unlimited, since microorganisms are capable of utilizing most naturally occurring carbon compounds. Microbiological production yields readily to automation, and consequently it does not require considerable outlays of manual labor, which is especially important to technological development in the time of scientific-technical revolution. A shortcoming of microbiological production operations is their high energy consumption (23).

The idea of using unicellular microorganisms to feed both man and animals is not new. Brewing and distillation wastes have been used as feed since ancient times. Use of microorganisms to prepare dietary products and to improve the nutritional properties of food, or to preserve it, can be traced throughout the entire civilized period of human society. In this case microorganisms enter into the finished food products (bread, sour milk, fermented vegetables, and so on), and they are consumed by man).

The records of using molds for food production go back to the 1st century B.C. in China and about the 6th century A.D. in Japan (30). The alga *Spirulina* had been eaten for centuries in Africa and Mexico. Higher fungi were consumed as food in antiquity. The procedures for growing higher fungi in aseptic conditions were developed at the beginning of the present century. Use of yeasts for dietary and therapeutic purposes began. Yeast production enjoyed development in Europe during the world wars and in the postwar era. But microorganisms were grown in relatively small quantities prior to the middle of the present century.

Work on single-cell protein was stimulated not only by the growing demand for p[illegible] since the shortage of dietary products has been felt in all stages of mankind's history, but also by the need for answering the question as to how much pro[illegible] what amino acid composition there must be in the food and feed ration, and wh[illegible] insufficiency of these substances could lead to. Moreover it is only at the p[illegible] level of scientific and technological development that it has become possible to create large, automated, profitable enterprises engaged in microbiological protein production.

Skryabin and Yeroshin (11) feel that the main reason why attention toward this problem has been growing is that the logic of the scientific-technical revolution promotes production of proteins by microorganisms as one of the major pressing problems of modern times.

This problem has just recently started attracting increasingly more attention from the world's scientists. While in 1967 the technical feasibility of the processes was one of the main questions addressed by the first international conference devoted to this problem (34), by the time of the second conference in 1973 (35) the technical feasibility of the processes no longer raised any doubts, and the discussion centered on the processes for obtaining protein from unicellular organisms grown in hydrocarbons and other raw materials. Production of protein out of petroleum hydrocarbons was approved in October 1973 in Vienna at a meeting of a group of UNIDO [United Nations Industrial Development Organization] experts (28).

The Soviet Union was the first country in the world to organize large-scale production of feed protein from purified liquid paraffins distilled from petroleum. The output capacities of enterprises built in our country during the Ninth Five-Year Plan are 50,000, 60,000, 70,000, 120,000, and 240,000 tons per year (1).

Single-cell protein can be used as a basic protein source. In this case we would need to select cultures in which the essential amino acid composition of the protein would be close to the standard (milk and egg proteins). However, at the present time the USSR is using protein-containing biomass obtained by microbiological synthesis as an additive to plant feeds in an effort to reduce the acute lack of proteins and certain amino acids (10, 12, etc.). In this case it would be suitable to use cultures containing large quantities of the essential amino acids lacking in plant feeds, in order that after their addition, the mixture would have a composition close to the standard. For example cereal grasses contain little lysine, and thus it would be suitable to add protein-containing biomass rich in this essential amino acid to them. Microorganisms having a higher lysine concentration than all other naturally occurring food products were selected for this purpose. Yeast protein is assimilated more completely by animals than the protein of bran, cake, and grain products. Yeasts are richer in group B vitamins than foods of plant and animal origin. The effectiveness of adding protein-containing biomass to feeds may be raised by supplementing the latter with methionine, found in small quantities in yeast, vitamin B_{12}, and other biologically active compounds.

Research conducted in the Soviet Union demonstrated the high national economic effectiveness of using social labor to acquire single-cell protein in comparison with the traditional methods for obtaining proteinaceous substances. Mass use of

synthetic microbiological products will permit us to raise livestock productivity by 25-30 percent without additional feed expenditure (12). Single-cell proteins are now being used successfully as fish feed at fish farms as well.

The literature contains numerous reports indicating that the outlays on producing single-cell protein are about the same as those for producing plant protein, while in terms of biological value and composition, single-cell feed preparations are more complete. As an example Chepigo (17) notes that the corrected outlays per ton of digestible protein from microbial biomass do not exceed 900 rubles, for pulse crops they are 900 rubles, for fish meal they are 1,563 rubles, and for meat-bone meal they are 1,026 rubles. According to Kamenkovich and Kozlov (5), given the present wholesale price on protein-vitamin concentrate in the USSR (460 rubles per ton), the net income enjoyed by farms selling additional products per ton of feed yeast is about 240 rubles in pig raising, 1,180 rubles in poultry raising, and 260 rubles in egg production.

The transfer of energy in food chains from certain organisms to others is associated with high energy losses. The ecological coefficient (the ratio of the biomass of certain organisms to the quantity of organic matter they consume) does not exceed 10-20 percent as a rule. For example the yield of animal products in relation to the amount of feed consumed does not exceed 20-30 percent for fast-growing young animals, and 5-10 percent for adult animals; the rest is lost irretrievably in the course of vital activity. Today, man consumes about 0.2 percent of the primary production of the organic world; if we include feed for animals raised by man the figure would be more than 1 percent, while several millenia ago this figure was 0.01 percent (2). Enlargement of this figure is an extremely important problem. Replacement of the three-link food chain (primary proteins, animal, man) by a two-link chain--that is, direct consumption of single-cell protein by man--would increase the effectiveness of protein utilization by a factor of 5-10.

The possibility for using microorganisms not as a vitamin source (common even in earlier times) but rather as a source of calories and proteins has been discussed at many international symposiums (24, 29, 34, 35, etc.) and in a number of publications.

The Protein Advisory Group held many discussions on the ways for processing single-cell protein into a safe product, and in 1970 it concluded that yeast, algae, and bacteria can in principle be useful sources of protein, vitamins, and minerals for a man, but the permissible quantity of nucleic acids introduced together with single-cell protein into the adult human diet must not exceed 2 gm per day. A higher quantity of these acids in food could increase the risk of gout in persons predisposed to this disease, and cause formation of urates in the urinary duct. Yeast may contain 6-18 percent nucleic acids; therefore its maximum quantity should not exceed 20 gm. Many ways for reducing the quantity of nucleic acids in biomass have now been described. They include thermal influences, processing the biomass with alkali and extracellular enzymes, activating intracellular nuclease to break nucleic acids down to readily removable products of low molecular weight, and so on.

Direct use of protein involves solution of other problems as well--sometimes cell walls, lipids, and substrate residues detrimental to human nutrition must be removed, natural texture, pleasant appearance, good taste qualities and odor must be imparted to the products, and so on.

A large number of papers generalize the results of experiments in which single-cell proteins are used directly as human food. Most publications note that introduction of this protein into the food ration does not cause negative consequences, but conflicting data are encountered as well: Some people consuming such food experienced allergic reactions, gastric diseases, and so on. Scrimshaw (32, page 38) wrote in this regard that the world contains many higher plants but that only a small quantity of them can be consumed as food in significant amounts. Many foods we eat today on a large scale would not have been approved, had they been suggested today as new foods. The usability of plant food depends on the growing and storage conditions, the way the food is cooked, and individual features of the consumers: There are people who suffer negative consequences from consuming some common dietary products. The higher plants have undergone selection and the methods of their preparation have been developed in the course of millenia, but man is now trying to reduce this term significantly in his search for single-cell proteins. One important factor hindering introduction of single-cell food products is the psychological barrier.

Today many countries of the world are using single-cell protein to enrich food products (sausage, cheese, bread, preserved foods). As an example Poland has developed the procedures for acquiring food products containing 3-5 percent dried nutrient yeast. Biochemists of Budapest have proposed a microbiological method for obtaining dietary protein close in value to chicken.

In Switzerland, microbial protein is processed into a meat substitute after imparting particular structure to it. Japan's process engineers are working on various food additives made from microorganismic biomass.

While in 1907 the German chemist E. Fisher criticized a newspaper article entitled "Food From Coal" accompanied by a picture of coal being transformed in a restaurant into gourmet dishes, and he concluded that a sober-minded chemist could not tolerate such pipe dreams, in 1974 Stewart (36) wrote in a commentary on this excerpt from Fisher's work that many of today's rational-thinking microbiologists would not hesitate to draw a picture of a coal mine or petroleum pipeline connected through fermentation units to a restaurant.

Use of single-cell protein for industrial needs is also a promising direction. Use of such proteins to manufacture fabrics not inferior to silk and wool, synthetic leather, plastics, and so on is now being studied.

The process of acquiring biomass from microorganisms consists of several stages--preparation of the raw material and inoculant, fermentation (the main stage), isolation, heat treatment, and drying of the finished product, purification of waste gases, and the waste water treatment stage, which may represent a second (additional) fermentation stage. Sometimes liquid wastes are used as fertilizer.

Growing the microorganisms (fermentation) is the main stage of the process, and it consumes the most energy. Cultivation usually proceeds in a chemostat in the presence of limited oxygen or carbon. In order to raise the profitability of the fermentation stage, it would be best for it to proceed in apparatus (fermenters) having high unit capacity (hundreds of cubic meters) and permitting intense mass exchange. Aeration and mixing of the medium in the fermenters of different enterprises and companies are based on different principles. There are fermenters employing both mechanical and pneumatic mixing, fermenters with self-feeding and jet aeration systems, cascade fermenters in which the liquid and gas moves in parallel and opposite directions, and so on. The large quantity of varying parameters are regulated and stabilized at a given level during fermentation automatically. Computers have been used in recent years to control the work of fermenters.

The productivity of microbiological processes increases tenfold with introduction of continuous cultivation, in which the entire process proceeds within fully controllable conditions, and in relation to which introduction of full automation is possible. Protein production by unicellular organisms is an industrial sector producing a single product--biomass, accumulation of which is associated with culture growth, and therefore it is relatively easier to introduce continuous processes than biphasal ones, in which accumulation of the end product is not associated with culture growth. Continuous cultivation of feed yeast was achieved prior to World War II, but use of this progressive method became possible on an extensive scale only after discovery of the basic metabolic pathways of microorganisms depending on cultivation conditions, and after development, in the middle of the current century, of the mathematical theory of this process (26, 27).

Modern equipment and automation are now being introduced into all stages of the production process for acquiring single-cell protein (from preparation of the raw material to the finished product).

A tendency toward cultivation of microorganisms producing protein in aseptic conditions can be observed in the world. This guarantees acquisition of a finished product not containing infectious microflora, but it does require higher capital investment in order to create sealedequipment, to sterilize raw materials, to support the sizable water and air consumption needed, and so on.

Biomass isolation in microbiological processes performed in a medium with a water phase of up to 99 percent plays a significant role in the economics of the entire process as a whole. To make this stage easier and cheaper, it would be desirable for the producer to exhibit a high capability for separation--that is, for the cells to be of large size and mass; or the cells should have a capability for forming agglomerates. Enlargement of cell density in the medium has important significance to reducing the amount of material entering the separation stage.

While there are some common, basic principles associated with the design of the process and the apparatus involved, there are a number of unique features associated with the use of different microorganisms and different substrates. For example substrates may differ in their solubility in water and their volatility, which influences the design of the fermentation equipment; they may also differ in their purity, which affects the finished product purification stage. The oxygen demand

depends on both the substrate and the strain of the microorganism. As an example the oxygen demand is 2.5-3 times greater in paraffin than in carbohydrates; therefore the supply of oxygen to cultures in fermenters using paraffin as the raw material must be higher.

Production scale has a great influence on the cost of single-cell protein. Specialists of some English and Japanese companies, for example, recommend units having a yield of more than 60,000 tons per year, since they believe units of lower capacity to be economically less advantageous.

Back in 1971 Vincent (37) wrote that in the absence of good equipment, highly skilled personnel, and good raw materials, it would not be profitable to develop microbiological production operations. The paradox here is that large production operations in which protein is obtained microbiologically are arising in developed countries in which the population enjoys a better food supply, since the necessary advanced technology and capital investments are within the means of these countries. There is also another way for developing single-cell protein industry--that of creating small production operations in those regions of the world having a high protein demand; these operations can use inexpensive locally available raw materials that are hard to transport elsewhere. However, these would suffer a significant disadvantage in comparison with large production operations in terms of product quality, production excellence, process automation, the proportionate outlays of energy and metals, labor productivity, and so on.

The choice of the producer also has a great influence upon production economics. In addition to the biomedical requirements (nonpathogenicity, absence of toxins in the obtained biomass, its wholesome composition, its digestibility, and so on), it is also important to consider the technical-economic and ecological indicators when selecting microorganisms for protein production. The producer must insure a high yield per unit substrate per unit time, and it must be capable of growth in simple mediums not containing expensive ingredients. In order to achieve fuller utilization of the raw material, sometimes it would be desirable for the producer to develop in a medium having a low carbon concentration. When the process does not call for complete sterility, the cultures must allow the selected strains to compete and to maintain dominance in the fermenter's ecosystem. The producer can enjoy selective conditions favoring its development if, in particular, it has a capability for developing at low medium pH (yeast for example) or at a high rate of flow (bacteria), and at high temperature (thermophils, heat-tolerant cultures). Use of thermophil cultures reduces energy consumption for cooling, but when the process is run at higher temperatures, solubility of oxygen in the fermentation liquid decreases, and more substrate may be lost together with waste gases, which would make the production operation more expensive. Therefore the question as to the economic and technological feasibility of using thermophils must be answered individually for each case. Depending on the substrate used, special requirements are imposed on the producer strains. As an example plant waste hydrolysates may contain microorganism growth inhibitors, and thus it would be suitable to use special strains resistant to these impurities. It would be important for the culture to tolerate industrial handling in the biomass isolation stage.

In order that the process would satisfy ecological requirements, wastes must be reduced to a minimum, or a transition should be made to a practically wasteless process using water recycling systems. This imposes special requirements on the producers--they must accumulate a minimum quantity of metabolites in the medium, and they must be sufficiently resistant to these metabolites as well as to unutilized ingredients in the medium, accumulating in response to repeated recirculation of the culture fluid. Processes promoting acquisition of high biomass concentrations in the culture medium are also promising from this standpoint.

Various species of yeasts are used most often in traditional microbiological production operations. Since time immemorial, bread and wine have been obtained with the help of these organisms in particular. Yeasts were also used in the first modern high-capacity plants producing single-cell protein in our country and abroad. The advantages of these microorganisms lie in their tolerance of industrial handling: their resistance to infections (by phages, bacteria, and so on), the ease with which they are separated from the medium owing to large cell size, their capability for assimilating different carbon and nitrogen sources, their capability for growing in relatively simple mediums, their cultivational and genetic resistance, their high nutritional properties, and the pleasant odor of the biomass.

A tendency toward broadening the assortment of taxonomic groups of microorganisms used in protein production is presently being observed. In particular, various species of bacteria are now being used. The advantage of bacterial strains is a high growth rate, and a higher biomass protein and methionine concentration than other organisms. The lipid concentration of bacteria intended for such use must be carefully analyzed, since the lipids of some of them (for example mycobacteria grown on paraffins) may contain toxic components. The relative biomass output of fermenters may be significantly higher with bacteria than with yeasts. With the same lot of petroleum distillate for example, the maximum relative biomass productivity of a fermenter was 7 gm/kg·hr, with *Candida guilliermondii* yeast, and 22 gm/kg·hr with *Mycococcus lactis* bateria (9). This is associated not only with the higher growth rate of bacteria, but also with their capability for oxidizing a broader spectrum of hydrocarbons. The shortcomings of bacteria are that their cell diameter is three to five times smaller than that of yeast, and their density is close to that of water, which complicates the isolation stage; this is why successful use of bacteria requires development of systems for their isolation. We have already developed ways to affect bacterial biomass in such a way that agglomerates that can be easily isolated by simple centrifugation are formed. Another shortcoming of bacteria is their lower resistance to phages in comparison with yeasts.

Protein biomass can also be acquired from industrially grown fungi, both lower (*Penicillium* etc.) and higher. The advantage of fungi is their low concentration of nucleic acids in biomass (1.5-2.8 percent), the ease with which biomass is isolated, the capability of some fungi for assimilating lignin, and so on. A shortcoming of fungi is their slower growth in comparison with yeasts, and especially bacterial cultures. Among the higher fungi, accumulation of fungal biomass proceeds faster than that of fruiting bodies, but they are about the same in relation to their taste qualities. The mycelia of higher fungi grown artifically may have a more complete amino acid composition, and they may contain more protein than fruiting bodies. Fungi have a fibrous structure that is suited to preparation of synthetic meat products. On the whole, there may be a great future for industrial acquisition of proteinaceous substances with the help of fungi.

Algae may also serve as protein producers. As with fungi, they are easily separated from the substrates, and they grow slower than yeasts, and therefore they contain fewer nucleic acids in their biomass. The total protein concentration of algae may reach 70 percent (20); moreover the amino acid composition of these proteins may be complete as well. Unicellular algae (*Chlorella*, *Spirulina*, etc.) are used as feed for agricultural animals and birds. When *Spirulina* is added to the ration of ruminants, conversion of algalprotein into beef protein attains 15 percent (33). Use of algae to prepare biological mediums has also been proposed. According to the data of Bulgarian scientists 1 kg of dry algae could replace 18.8 kg of meat for this purpose. Use of algae as a source of dietary protein also seems promising (16). *Chlorella* is attracting interest as an ingredient of artificial ecosystems to be used in life-support of the crews of space ships and stations on other planets. These algae could utilize carbon dioxide and other human excretory products to form biomass. Thus wastes are removed, food is obtained, and oxygen is regenerated at the same time. It should be noted that use of algae as a food ingredient is associated with a number of technological and physiological problems. As an example we would need to remove cell walls so as to reduce the quantity of undigestible components, and we would have to concentrate the products in order that enzymes in the intestinal tract would have access to the proteins contained. The product would have to be clarified and degreased, since when some components of the lipid fraction undergo oxidation, they impart an unpleasant taste. A survey of people who had consumedvarious prepared foods made from *Spirulina* revealed that hydrolysates, which have no taste or odor, are the most usable (31). Dietary algae are already being produced today. As an example a restaurant with a menu containing 200 dishes to which appropriately processed *Chlorella* biomass has been added was opened in Czechoslovakia.

As with higher plants, algae may be grown photosynthetically. Were we to produce algae in a continuous culturing system--one in which specially grown material is removed in order that the mass of photosynthesizing matter would remain optimum per unit area, the maximum yield of dry algae (22) would be about the same as the yield of higher plants at the peak of their growth.

Usually, algae produce two to ten times more dry matter than do higher plants. It should be noted that algae contain more protein in their biomass than do plants (usually up to 50 percent), and therefore from the standpoint of protein production algae have a 6-30-time advantage over higher plants (37).

Another advantage of algae is that their cultivation requires fewer labor outlays and less area than does cultivation of traditional food sources. The area required to provide enough protein for one person for 1 year (a norm of 29.2 kg/year) would be 4,870 m^2 for the meat of range cattle, 970 m^2 for wheat, 174 m^2 for clover leaf protein, and 17.5 and 12 m^2 for *Chlorella* and *Spirulina* respectively (37).

However, photosynthetic cultivation of algae requires carbon dioxide and light. The required mixing equipment and the need for adding carbon dioxide to the medium means significant capital investment, and sometimes it is economically more feasible to grow heterotrophic organisms on various carbon-containing substrates. In Japan, which is the main producer of algae, cultivation on carbohydrates is encountered more frequently than processes based on photosynthesis.

Protozoans may also be used in the future to produce single-cell protein.

In addition to using monocultures, researchers are now considering the use of associations of cultures. Some advantages of growing mixed cultures may be fuller utilization of all substrate ingredients, use of cultural mediums of simpler composition, since one culture may use the metabolic products of another as an additional source of nutrition, higher concentration of proteins and other valuable components in the biomass, and so on.

It should be noted that only a small fraction of the microorganisms existing in nature have been studied yet. Information on new cultures capable of synthesizing protein components and utilizing highly specific substrates is constantly appearing in the literature.

The next important problem is selecting the raw material in which microorganisms are to be industrially grown. The profitability of the production operation depends significantly on the choice of the substrate, since its cost is usually a third of the cost of the finished product, and since it defines the product's qualities in many ways.

We can get an impression of how great a part the raw material plays in the cost of the finished product from Lewis' work (23), which shows the cost of producing 1 ton of microbial proteins, in pounds Sterling, using different substrates for fermentation (1974 prices): molasses--233, paraffins--176, methanol--150, methane--118, solid agricultural wastes--72, liquid agricultural wastes--62.

In order that the process would be economical, the raw material must be cheap, abundant, and accessible. It would be best for the raw material to be close to the microbiological enterprise processing it, and for it to be deliverable year-round. The choice of raw material should account for the price of the substrate per unit of produced protein, and for the possibility of using sophisticated equipment and production processes and of introducing automation so as to guarantee economical production and a finished product of high quality.

At first, single-cell protein production was based on the wastes of a few production operations, mainly food processing plants, and due to resource limitations the yeast shops were small.

Microorganisms capable of developing in petroleum hydrocarbons became known at the end of the last century. Classical works in this area were published by the Soviet scientist V. O. Tauson back at the beginning of the present century. However, it was not until the early 1960's that the potential industrial significance of this raw material was demonstrated. Among the protein sources of nonagricultural origin, "protein from petroleum" was met by the greatest enthusiasm of the experts. By as early as October 1969 the UN Industrial Development Organization registered 46 companies and industrial enterprises in the world working on this problem. Hydrocarbon raw materials yield better to industrial production than do plant materials, since the former are stable in composition, they are accessible, they are easily transported, and they insure high biomass yields (practically 100-110 percent, as opposed to 50 percent in sugars). A small proportion (2 percent) of the world's oil production would be enough to produce 20-30 million tons of yeast protein, which would be enough to feed 2 billion people for a year (7).

As was noted earlier, the Soviet Union has the lead in production of proteins on hydrocarbon substrates. Successful solution of the interdisciplinary problem of obtaining protein from petroleum hydrocarbons became possible in the USSR owing to the efforts of specialists of different profiles--microbiologists, biochemists, chemists, process engineers, engineers, experts in nutrition and public health, and specialists in integrated petroleum and gas processing; this insured an abundant supply of raw materials for microbiological industry. Thorough studies were made of microorganisms capable of utilizing petroleum hydrocarbons (N. D. Iyerusalimskiy, G. K. Skryabin, A. B. Lozinov, A. P. Kryuchkova, Ye. I. Kvasnikov, B. Gradova, etc.) and of hydrocarbon penetration, movement, and accumulation in the cell (M. N. Meysel' and others), the theory of the material-energy balance of microorganism growth (I. G. Minkevich, V. K. Yeroshin) and efficient apparatus to support large-scale processes were developed (P. I. Nikolayev, I. D. Boyko, and others), biomedical and veterinary-zootechnical investigations were made of the resulting product (A. A. Pokrovskiy, N. I. Denisov, P. Ye. Ladan, and others), and many other important problems were solved.

Yeasts of species *Candida guilliermondii*, used in our country to obtain protein-vitamin concentrate from petroleum alkanes, use hydrocarbons with a long carbon chain, from C_{11} to C_{24}. A study of the kinetics of hydrocarbon consumption showed that strains usually utilize C_{11}-C_{14} petroleum alkanes easier, C_{15}-C_{18} alkanes occupy an intermediate position, and high molecular weight compounds are utilized with more difficulty (6). Using purified liquid paraffins, which are easily assimilated by yeasts, we can obtain a feed product without having to remove residual hydrocarbons from the biomass. To make this possible, the microorganisms must use up practically the entire carbon source in the medium as they grow, since the end product must contain a minimum quantity of unutilized raw material. The higher the concentration of paraffins in the culture medium, the greater may be the concentration of residual hydrocarbons in the end product. Therefore the process should proceed in a medium containing the highest concentration of paraffin, or we should add a second stage of utilization of hydrocarbon residues, concentrated both on the cell surface and in the membrane, and in the protoplasm.

Another way to obtain biomass with liquid hydrocarbons is to grow microorganisms on unrefined crude petroleum products (for example petroleum distillate), followed by careful removal of hydrocarbon residues from the resulting biomass. Consumption of petroleum alkanes contained in the raw material results in the latter's deparaffination, yielding a raw material with a low freezing point which may be used as an ingredient of winter diesel fuel. Purification of biomass by extraction with organic solvents removes lipids, which are a valuable source of industrial fat.

A triphasal system (carbohydrates, aqueous medium, gas phase) is used to grow microorganisms in water-insoluble hydrocarbons (paraffins, petroleum distillates, and so on). The cells must come in direct contact with all phases, which requires additional outlays on mixing.

Production of single-cell protein from petroleum paraffins purified by molecular sieves or by other means, or with unpurified petroleum raw materials--gas oils--has been developed in many of the world's countries (Japan, USA, Great Britain, France, Italy, FRG, etc.), and a number of countries have built facilities for acquisition of this protein, but almost none of these production operations have

gone into operation. Only a few countries (Romania for example) are planning to initiate large-scale industrial production with this raw material. The first automated device producing a feed protein preparation from petroleum distillates, used as a feed additive for chicks, cows, pigs, and fur-bearing animals, has been placed into operation in the GDR (18). Environmental conservation experts in Italy and other countries have stated their opposition to production of microbial protein from paraffins and gas oil. But most foreign experts believe that the obstacles to such production operations are political, social, and economic in nature, and not scientific or technical. Due to the oil prices of the capitalist countries, the price of oil has risen, and this has made microbiological production using this raw material unprofitable. Moreover influential importers of soy meal are creating obstacles to expansion of microbial protein production in the capitalist countries, since this would undermine their monopoly in the protein feed market.

A process of microbiological synthesis employing gaseous hydrocarbons has been developed in the USSR, USA, Japan, Great Britain, FRG, Canada, and other countries. This process is interesting in that owing to its volatility, the gas is easily removed from the end product. The technological difficulties are associated with the poor solubility of methane in the culture fluid (up to 0.02 gm/liter), the higher oxygen demand of the cultures (2.5 times higher than in paraffins), and the relatively slow growth of the microorganisms. Judging from the publications and patent literature, the technological and economic problems associated with this process have been solved by scientists of a number of countries, but the process has not been practically implemented yet.

Recently many publications discussing acquisition of single-cell protein from alcohols (methanol, ethanol), organic acids, ketones, aldehydes, esters, and so on, arbitrarily grouped as oxidized carbohydrates", or oxidates, have appeared in the foreign and Soviet literature. In the opinion of a number of scientists, alcohols are the most acceptable raw material for acquisition of proteinaceous substances. One particular reason for the great interest in methanol is that in distinction from liquid hydrocarbons, it is completely soluble in water, the substrate has a lower oxygen demand, and unit heat production during fermentation is lower. Thus there are fewer relative costs associated with mixing, aeration, and heat removal with methanol cultivation. Residual methanol is easily washed from cells. The technology of acquiring single-cell protein from methanol is somewhat simpler than that associated with petroleum paraffins. Raw material preparation, recirculation of culture fluid, which contains practically no substrate at the fermenter's outlet, and purification of the end product are simpler. Methanol can be obtained from a broad range of crude hydrocarbons--liquid, gas, and solid fuel phases, including coal. The principal source of methanol today is methane. In distinction from petroleum alkanes, production of methanol is not limited by the productivity of petroleum refineries. The biomass yield per unit of methanol is lower than for petroleum alkanes--about 60 percent of the raw material, but in general, according to the figures of foreign companies, the cost of a facility producing protein from methanol may be 10-15 percent lower than a paraffin production operation. Methanol production is constantly growing abroad.

It was known since the beginning of this century that methanol can serve as a carbon source for bacteria, but it was not until 1967-1970 that this research assumed a

broad front, and practical developments aimed at utilizing methanol as a substrate for acquisition of single-cell protein were started. A process for obtaining fo proteins from this raw material was developed in Great Britain, Japan, Sweden Italy, FRG, and the USSR. An experimental industrial facility producing a nutrient product from methanol was put into operation in Frankfurt-am-Main. After process and removal of nucleic acids, this product contains up to 90 percent protein. It was demonstrated in recent years that not only bacteria but also yeast can develop in methanol. For example Poland has developed a procedure for obtaining yeast protein from methanol; in this case the biomass yield reaches 50 percent of the utilized methanol.

The attention of the world's scientists is turning more and more to ethanol as a substrate for obtaining single-cell protein intended for use as food. The quality of the product obtained with this raw material is high. There is no psychological barrier in the way of its use. The yield of yeast biomass grown in synthetic ethanol is 60-75 percent, and it can reach up to 90 percent. In 1975 the USA began producing a dietary product in a medium containing highly purified synthetic ethanol--an egg substitute used in the production of meat and confectionery articles. This substitute is added to food in a proportion of 3-10 percent. The main emphasis is now being placed on improving the taste, odor, and appearance of food products. Japan, Spain, FRG, Czechoslovakia, and the USSR have also developed ethanol-based processes. Skryabin (12) believes that the USSR should begin using this raw material to produce protein additives for human food.

Works raising doubt as to the profitability of making wide use of nonrenewable raw material resources have recently been appearing. As an example the Canadian scientists Dawson and Phillips (21) wrote that while until recently the problem of producing single-cell protein has been looked at from the standpoint of technical and economic feasibility, today the emphasis is more on the social and, probably, the political importance of this problem, since doubts as to whether we should use a nonrenewable mineral (petroleum) in irreversible processes have risen. Perhaps the greater interest in renewable resources, particularly plant materials, and in use of industrial wastes has risen in the world in connection with the petroleum crisis.

The world possesses practically unlimited sources of cellulose-containing substrates. The annual increment of plant biomass in the world is estimated at 155 billion tons. When a fraction of this biomass is processed, a very large quantity of wastes is produced, estimated at hundreds of millions of tons. For example when we process timber into pulp to be used in paper production, we use up only 50 percent of the raw material (13).

The total quantity of wood waste in the USSR is about 100 million m^3 per year (not counting low-quality wood used mainly as fuel). The waste of agricultural production (straw, cotton pods, corn stems, potato pulp, beet pulp, and so on) and of wood-working and timber industry (wood chips, bark, sawdust), and other plant raw materials usually contain up to 75 percent of water-insoluble polysaccharides such as cellulose and hemicellulose. Their hydrolysis proceeds through intermediate products down to the simplest sugars--monosaccharides. Hydrolysates usually contain volatile substances (organic acids, alcohols) and a solid residue--hydrolytic lignin.

Hydrolysate has been used for a long time in microbiological synthesis. Hydrolysis industry appeared in the USSR in 1935, but before 1943 its production was limited to ethyl alcohol, and nutrient yeast as a byproduct. Special enterprises producing nutrient yeasts were created beginning in 1943, and by 1968 the quantity of yeast produced was 97,100 tons. Similar plants have been operating in Bulgaria since 1965. Sulfite liquor was used in the GDR and Czechoslovakia to produce nutrient yeast. In 1953 A. A. Imshenetskiy noted the extreme significance of efforts aimed at clarifying the possibility for direct fermentation of wood without initial acid hydrolysis.

World interest in cellulose-containing raw materials increased dramatically in recent years, and intensive research is now being performed to reveal cellulolytic microorganisms capable of actively accumulating biomass in such materials. A number of the world's countries are planning or building facilities utilizing wood pulp. As an example the Finnish Scientific Research Institute of Pulp and Paper has developed and introduced, at a facility with a capacity of 10,000 tons per year, a method for growing *Pecilomyces* fungi in sulfite liquor. The USA has developed a method for obtaining bacterial biomass (genus *Cellulomonas*) from agricultural and timber wastes and from urban domestic sewage. Methods are being developed for growing microorganisms in ground and suspended cellulose substrates without initial hydrolysis.

The quantity of other wastes scientists of different countries are proposing for microbiological synthesis is expanding as well: wastes from animal husbandry (manure), milk processing, meat, fish, alcohol, brewing and winemaking industry, and production of caprolactam, plant and animal fats, and sugar; wastes containing starch, synthetic fatty acids, phenol water, and so on.

Thus in regard to the use of raw materials for microbiological synthesis, we can observe a trend toward using individual compounds with which to obtain a product of strictly constant quality, and toward using various wastes characterized by negative cost but whose processing is important in the ecological aspect. Before using multiple-ingredient, complex substrates and combined mediums, it is very important to study the kinetics of consumption of the individual ingredients, which are usually consumed at different rates. Development of systems for controlling the cultivation processes is complicated by the instability of the ingredients of different lots of carbohydrate substrates (especially wastes), by impurities in the raw material used as the source of micro- and macroelements necessary for culture development, and by the inconstancy of the composition of the industrial water employed. All of these factors influence the metabolic activity of the producer, and they yield poorly to regulation.

Because the reserves of organic compounds are not unlimited, theoretical research is presently being performed on the basic principles of obtaining protein with the help of autotrophic bacteria, which do not require ready-made organic compounds for their development. Photosynthesizing bacteria and algae are of great interest as potential sources of protein and other valuable components of feed and food. In regions of the world possessing few carbohydrate and hydrocarbon substrates, cultivation of photosynthesizing algae together with, for example, microorganisms that fix atmospheric nitrogen might be suitable.

Hydrogen-oxidizing bacteria may be promising nutrient protein producers; they also offer some promise in the creation of life-support ecosystems. The procedu[illegible] for growing these bacteria are being developed both in the USSR (14) and abroad.

Thus intense research is being performed today in an effort to expand the range of substrates used to acquire proteins by the methods of microbiological synthesis, to expand the assortment of organisms used in this process, and to improve the procedures and equipment involved in these processes.

It should be noted in conclusion that a large quantity of safe, complete proteinaceous substances intended as feed and food may be acquired with the help of microbiological synthesis in the future.

The world's scientists view acquisition of large quantities of microbial protein as the basis for creating a feed industry as a revolution in the history of food production.

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BIOTECHNOLOGY

DNA INDUSTRY: PROSPECTS, FIRMS, PATENTS

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[Article by Academician A. A. Bayev]

[Text] DNA industry--such is the name given to a sector of pharmaceutical industry which is just now arising on the basis of the achievements of gene engineering.

Gene engineering--a new and promising branch of molecular biology--is just barely 8 years old. It represents a system of experimental techniques for building artificial genetic structures in the laboratory. It must be stated that the idea of reproducing genetic processes in the laboratory has been around since long ago, but for a long time the creation of genetic structures was treated more as science fiction. However, a time came when physiological approaches were supplemented and deepened in biological laboratories with molecular concepts, and our understanding of the essence of life processes and of the experimenter's possibilities changed.

In essence a living cell is nothing more than a small chemical factory, the production of which is subordinated to a hereditary program written into one of its nucleic acids, namely deoxyribonucleic acid--DNA. Physically and functionally, this program consists of blocks--genes, each of which controls production of a certain product (usually a protein) and performance of a cell function depending on this product.

This concept was formulated relatively recently, but as soon as it came into being, the dream of obtaining genes in the laboratory and putting them to work became a reality. At first, however, no one had any idea as to how the needed genes could be isolated from the huge DNA molecules (even in the simplest forms of life), and then gathered together into a single working structure.

In the end, development of enzymology furnished the researcher with tools suited to such operations. These tools are enzymes, created by nature itself and contained within living cells. One group of them (the restrictases) split DNA molecules at strictly determined points into greater or smaller segments, while others (the ligases), on the other hand, link these segments into a single whole. After such enzymes were isolated from cells and purified, creation of artificial genetic structures became a technically possible task.

In principle, the basic procedures of gene engineering boil down to the following: A compact genetic structure--recombinant DNA--is assembled out of a set of DNA fragments created with restrictase and containing the needed gene, and then introduced into a cell, usually bacterial. The new genetic information causes a change

in the cell's metabolism, and as a result either a significant quantity of the introduced genes or the products which they program are obtained.

Thus began the era of gene engineering in biology, which now has a directing influence upon fundamental research, and which initiated many practical applications.

The mass media in the West, and even the scientific journals concerned with the organization of science, are anticipating the realities, and no one is concerned that there are no enterprises of DNA industry yet, there are no pr· arations, consumers, or advertising, and someone has yet to earn a profit--this mandatory component of all business ventures in the capitalist world. In a word, what we are dealing with for the moment is a unique sort of mirage. What we have instead of real phenomena is a confidence in the unlimited possibilities of gene engineering and the hope of quickly enjoying the first commercial results of utilizing the technology of recombinant DNA.

I. Johnson, vice president of Ely Lilly and Co., who feels that it is difficult to predict when industrial lots of human insulin will be obtained (it will apparently be the first product appearing on the market), and that the present prices on the product, based on the output volume that has been obtained for it, cannot be thought of as economically acceptable; does nevertheless assert that "the potential uses of recombinant DNA technology are limited only by the imagination of those who use it."

Major pharmaceutical companies are investing generous amounts into developing DNA industry, and for the moment they are not receiving any profits--that is all for the future. But the first millionaires have already appeared, though not entirely of the conventional sort. These are not the businessmen of the past, such as for example Morgan and Rockefeller, or the more-recent Hughes; moreover we do not even know for sure whether they are millionaires or not.[1] I am referring to scientists possessing shares in the newly created companies (see below for more detail on the companies). As an example when Genentech was founded, (G. Boyer) and (R. Svenson) kept half of the shares for themselves and a limited circle of key colleagues, paying not a single cent for them. (U. Gilbert), chairman of the scientific council of the "(Biogen)" company, and members of the council possess 15 percent of the company's shares. For the moment the shares are not producing income, but their price is gradually rising, and it will doubtlessly leap dramatically as soon as a competitive preparation hits the market. This is when the first millionaires will appear, for whom molecular biology will become a stepping stone to wealth.

The young DNA industry is being supported not only by university laboratories but also by lawyers, who have taken on the job, not without compensation of course, of patenting the methods and processes used in gene engineering. In this case, as anyone can see, patenting creates legal protection for future profits.

This article is not intended to be an exposé, unmasking and condemning the morals dominating in business and, alas, in the scientific world of capitalism. Its objective, being far from moralistic, is much more serious--to demonstrate the importance of measures being implemented abroad to develop applied and fundamental gene engineering. There is no need to draw any sort of parallel with the way things are here, or to make conclusions--the language of facts is sufficiently eloquent in this case.

We are now approaching a boom in DNA industry, since indications have appeared that commercial successes connected with the production of preparations having great medical significance with the help of the recombinant DNA method are close at hand.

Human insulin has already been obtained by Genentech on contract with Ely Lilly and Co. on a laboratory scale. Insulin is a polypeptide hormone consisting of two chains--A (21 amino acid residues) and B (30 amino acid residues)--linked together by disulfide bridges. It is synthesized in the body as preproinsulin which contains, in addition to chains A and B, a third chain--C (31 amino acid residues), and a "leader" sequence (24 amino acid residues). Peptide C facilitates correct linkage of chains A and B, and in the final stage it is split away. The "leader" is responsible for transport of proinsulin, for its transfer through the membrane of the secretory cell, at which time it is separated from the proinsulin part of the molecule by the action of a specific protease.

The genes for human insulin, namely for chains A and B, were synthesized in Genentech's laboratory by Crea et al.[2], and later Goeddel et al.[3] cloned synthetic genes for chains A and B separately in the same laboratory, using a method that had been employed by (G. Boyer) and his colleagues when they cloned the gene for somatostatin. The researchers joined chains A and B into a single molecule *in vitro*: Because of the absence of leader chain C, the yield was rather unpretentious--10 mg for every 24 gm of bacterial mass. This is 10 times greater than the somatostatin yield, but it is still not enough for commercial purposes.

According to a prediction by (N. Shneyder), an investment specialist, human insulin produced by Ely Lilly and Co. will appear on the market in a year, despite possible obstacles on the part of the FDA--the U.S. Food and Drug Administration, and it will be 30-50 percent cheaper than insulin obtained from the pancreas of pigs and cattle. It should be noted incidentally that it is not yet certain how the appropriate U.S. administrations will interpret this preparation--as a new one or as an old one obtained by different methods: In the first case clinical tests would be required, and this would postpone the preparation's appearance on market shelves.

The next candidate is human growth hormones obtained in Genentech's laboratory on the basis of a contract with Sweden's A. B. Kabi.[4]

Growth hormone is a peptide consisting of 191 amino acid residues. It stimulates human growth until the time of sexual maturation, and it is used for therapeutic purposes in the presence of bone fractures, skin burns, and other cases. The hormone is distinguished by high species specificity.

The gene for growth hormone was cloned in Genentech's laboratory. A synthetic fragment corresponding to the 23 starting amino acid residues and obtained by treatment of a longer fragment (from the 24th to the 191st amino acid residue) with reverse transcriptase was used for this purpose. The fragments were first cloned separately, isolated, and linked with ligase, after which the whole gene was cloned. The hormone yield was 2.4 mg per liter of medium.

And finally, we should mention two products of "Biogen". The first was reported on at a specially called press conference in Boston on 16 January 1980 by C. Weissmann (the project leader), a professor of Zurich University and director of the Institute

of Molecular Biology No 1 in Zurich, and W. Gilbert.[5] It was stated that an antiviral protein--human interferon--was obtained in a bacterial culture by the methods of gene engineering.[6]

Interferon is a glycoprotein with a molecular weight of 15,000-20,000, and its molecule consists of 150 amino acid residues. It is known mainly as an antiviral agent (an antiinfluenza agent in particular). It has recently been used to treat tumors as well: Favorable results were obtained in the presence of Hodgkin's disease, lymphoma, breast cancer, leukemia, and even melanoma. But the clinical use of interferon is limited for several reasons, mainly its high cost. As an example $2 million were allocated in one U.S. program to obtain a quantity of interferon sufficient to treat 150 cancer patients; this translates to more than $50,000 per patient. A second reason is the low concentration of interferon in the preparations--less than 0.1 percent in the best case; moreover impurities are not without ill effects. Finally, very little of this preparation is being produced.

For the moment, lymphocytes from donated blood are the main source of interferon. Another possible source is leukocyte cultures induced by Epstein-Barr virus, which is oncogenic in relation to man (cells begin to reproduce only in its presence); removing the viral particles is the critical point in the procedure. Human fibroblast cultures are also used.

"Biogen" is developing a method for obtaining interferon by molecular cloning of genes in the conventional scheme: acquisition of leukocyte information RNA → synthesis of double-stranded DNA copies with reverse transcriptase → acquisition of recombinant DNA consisting of a fragment of copy DNA and vector pBR 322 → replication of recombinant DNA in *E. coli* and selection of clones containing the sought gene. Many clones were obtained, and only a few containing the interferon gene were selected from them. Interferon synthesis was demonstrated by microinjection of DNA into oocytes from the frog *Xenopus laevis*. For the moment the amount being formed is small, only one one-thousandth of its concentration in leukocytes of equal volume. Nor is it known whether or not interferon's carbohydrate component, which is missing with this method of acquisition, has significance to its biological activity. This is what was communicated by C. Weissmann in the press conference cited above. Somewhat later, an article on this subject appeared in NATURE. Weissmann complained to reporters that despite all of the successes, Genentech's shares were selling poorly in Europe, and established firms in France and the FRG were reluctant to purchase them.

The largest shareholders of "Biogen" are the International Nickel Company (Canada) and the patent-holder for interferon production, Schering-Plough (USA). Therefore all profits will be collected in the USA and Canada, which angers Weissmann considerably.

Production of interferon in cell cultures is competitive. Thus Welkham Research Laboratory is setting up production of interferon in lymphoblastoid cell cultures infected with Epstein-Barr virus. Work is also being done in this area by the Searle Research Laboratory (England) and by du Pont Chemicals jointly with the Massachusetts Institute of Technology (USA).

Next in line is hepatitis virus vaccine. "Biogen" is also working on this preparation; research is being conducted by (K. Mari), (P. Tiolle), (P. Khofshnayder), (G. Shaller), and other scientists working in different European countries. They reported their work with hepatitis B virus at the Third West German-Soviet Symposium on Molecular Biology (Munich, 1980),[7] at which time it became clear that several

laboratories were coordinating their efforts. Viral hepatitis is a very serious and widespread disease, especially on the African continent, where virus carriers and, consequently, hepatic cirrhosis and cancer are frequently encountered. Acquisition of vaccines against viral hepatitis would make it possible to conduct a broad preventive program against this malady, and who knows, perhaps to conquer it.

Hybritech proposes (in an advertisement published in SCIENCE, Vol 206, No 4423, 1979), for research purposes, monoclonic antibodies to the surface antigen of hepatitis B virus, obtained with the help of hybridomas--cellular chimeras formed by fusing lymphocytes with cells from a plasmacytoma.

Influenza prevention is epidemiologically especially important because of the tremendous economic and social harm done by the regularly recurring pandemic outbreaks of this disease. Thus pharmaceutical companies are naturally interested in influenza virus hemagglutinin--a protein located in the capsule of the virus particle and serving as the main immunity factor.

Hemagglutinin is a glycoprotein, its molecule has a mass of about 250,000 daltons, and it consists of four subunits of 60,000 daltons each.

The Searle Research Laboratory has obtained a recombinant DNA molecule containing the hemagglutinin gene from fowl plague virus. It used vector pBR 322 with a built-in regulator area represented by the tryptophan operon of *E. coli*, a segment for attachment to a ribosome, and the first seven amino acids of the gene trp E (anthranilate synthetase). This system as a whole is far from perfect; nevertheless, synthesis of a protein immunologically similar to hemagglutinin was discovered in *E. coli* into which a hybrid molecule containing the hemagglutinin gene was introduced. This is an indication that in the very near future, influenza virus hemagglutinin will apparently be synthesized by the method of gene engineering.[8]

In April 1980 the U.S. National Institute of Health granted Genentech permission to produce five preparations on a major scale: human growth hormone, somatostatin, chains A and B of human insulin, human proinsulin, and α-thymosin-1.

Thus the hopes for using the methods of gene engineering to obtain various preparations having significant medical and commercial value are becoming increasingly more realistic. Of course, there are still many obstacles to transforming laboratory procedures into production processes advantageous in engineering and economic respects, but the experience of the past attests categorically that these obstacles are surmountable.

These facts demonstrate, with unquestionable obviousness, the likelihood of the predictions major capital has responded to under the influence of researchers in its assimilation of an area of capital investments new to it.

The creative foundation at the basis of DNA industry is associated, of course, with university and institute laboratories, with the enormous amount of facts and ideas that have been accumulated by molecular genetics, biochemistry, nucleic acid chemistry, microbiology, and virology. This is mainly where we should seek the roots and prospects of the industrial use of the methods of gene engineering.

Research on recombinant DNA has achieved extremely broad scope abroad in the last 3 years. This pertains mainly to the USA. It would be difficult to say anything about the number of laboratories and researchers employed in this area; judging from journal articles and symposium programs, it is large. A certain impression could be obtained from information on the grants for gene engineering in 1979, published in BUSINESS WEEK (22 October 1979): The National Institute of Public Health awarded 717 grants totaling $91.5 million ($50 million in 1978), and the National Science Foundation awarded 194 grants for $15 million.

By as early as 1975 some laboratories, for example at the University of California, began receiving grants totaling hundreds of thousands and millions of dollars extending over different periods of time--from 1 to 5 years. In any case gene engineering had assumed an "elite" position by that time. Before 1977, and even a little after that, its position was rather uncertain due to the excessive strictness of the rules of working with recombinant DNA. But all of the data show that U.S. federal agencies planning expenditures on science had recognized the significance of work with recombinant DNA molecules long ago. It should also be noted that at least since 1977, pharmaceutical companies have been financing research in this area.

Europe, of course, is behind the USA, especially England and France. Research on recombinant DNA is developing successfully in the FRG, on a sound financial basis. Some researchers in this country are associated with particular firms (for example P. Khofshnayder and G. Shaller). A new institute has been organized in Braunschweig (the Society of Bio-Engineering Research). It is financed by the Ministry for Research and Technology and by the government of Lower Saxony at a ratio of 90:10. This is a large institute with 330 colleagues; its 1979 budget was 20 million FRG marks. ($11 million). The institute's program is applied in nature, but gene engineering occupies a significant place within it. In particular J. Collins, the creator of cosmids, works there.

Work on recombinant DNA has not yet been started at the European Molecular Biology Laboratory, though everything has been prepared for this.

In addition to research, much work is being done to organize symposiums, lecture courses, and schools. The 12th Winter Symposium in Miami in 1980 (7-11 January) was very informative; we should also note the schools and courses created by the European Molecular Biology Organization in Europe.

Industrial DNA companies came into being on this academic soil and in connection with academic institutions. There is now a complex structure, a sort of layer cake, in which we can distinguish several "layers": university laboratories, industrial companies, newly organized pharmaceutical firms, and financial and industrial giants.

Companies organized for practical application of the methods of gene engineering with the goal of obtaining commercial products cannot be said to be large on an international scale. Nevertheless, the capital of such companies is now valued at about $5 million, having doubled in the last 6 months and continuing to grow. The activities of five companies are the most noticeable: (Sites) Corporation and Genentech Incorporated, "Biogen", Genex Corporation, and Hybritech Incorporated.[9]

Sites Corporation (Berkeley, USA) is the oldest company, founded by its present director (R. Keyp), and by (D. Glezer) and (P. Farli). J. Lederberg is the chairman of the company's expert council. The company employs 200 persons, 35 of them with doctorate degrees. The company's capital, which was initially valued at $5 million, is now estimated at $100 million, and it will be increased to $155 million. The founders hold 20 percent of the shares, the (Sokal) Company holds 25 percent, Standard Oil of Indiana holds 22 percent, National Distilleries holds 16 percent, and the remaining shares are distributed among 200 small shareholders. The initial goals of the company were to obtain genetically improved industrial strains of microorganisms by conventional methods, and gene engineering became a result of a natural course of development. According to published data the company is working on 15 projects having a relationship to petroleum, energy, and production of medicinal preparations and unicellular protein. One such project financed by Sokal is transformation of ethylene and propylene into their oxides and glycols with the help of immobilized enzymes and cells, which under ordinary conditions requires high temperatures and pressures. Another project (financed by National Distilleries) is associated with saccharifying the cellular tissue of a special race of yeast.

Genentech (San Francisco, USA) was founded by (G. Boyer) and (R. Svenson) in 1976. It employed 50 persons, 25 of whom are doctors. Its initial capital was $1 million, and now it exceeds $100 million. As was noted earlier, about half of the shares belong to G. Boyer, R. Svenson, and other colleagues of the company. The initial capital was provided by the International Nickel Company, which also invested into Sites and Biogen. However, Nickel's shares were recently bought out for $15 million by (Labrizol) Enterprise--a daughter company of Labrizol, which acquired 15 percent of Genentech's shares in September 1979 for $10 million; as a result it became the owner of 25 percent of Genentech's shares. Shares are also possessed by Kleiner and Perkins, Monsanto, Hillman-Pittsburg Company, Mayfield Fund of San Francisco, (Soffinova) (France), and the New Jersey Company.

The two best known projects of Genentech are the one mentioned above--acquisition of human insulin by cloning chains A and B in *E. coli* (this project is being financed by Ely Lilly), and acquisition of human growth hormones (on contract with Sweden's A. B. Kabi) by cloning a semisynthetic gene.

Biogen is registered in Luxembourg, but its actual residence is in Geneva. Its president is (R. Kousorn). It employs 16 scientists. W. Gilbert believes that its staff will climb to hundreds and even thousands of persons in the future. The initiative for organizing it belongs to D. Adams, who heads the exploratory investments department of International Nickel, which possesses 23 percent of the shares. Schering-Plough possesses 16 percent of the shares, which it bought for $8 million. The company's capital is presently valued at $100 million. The scientific council includes the Europeans (K. Mari) (England), C. Weissmann (Switzerland) and, apparently, (P. Khofshnayder) (FRG), and the Americans W. Gilbert (Harvard) and P. Sharp (Cambridge). As was mentioned above, W. Gilbert and eight members of the council now hold 15 percent of the shares, and in the future this proportion will rise to 30 percent. Two of the company's projects should be noted: acquisition of interferon and vaccines against viral B hepatitis. Genex (Bethesda, USA) was founded in 1977 by (R. Dzhonston) and (L. Glik). (D. Dzhekson) is chairman of the scientific council. The company employs 12 scientists. Its capital has risen from $9 million

to $75 million. A third of its shares are held by the founders and scientists, another third are held by (Innoven) (a daughter company of Monsanto) and Emerson Electric, while the rest are owned by the Coppers Company. The work of Genex is directed mainly at acquiring expensive amino acids microbiologically.

Hybritech (La Jolla, USA) was founded in 1978. Its initial capital was $2 million; it employs 52 persons (there will be 100 by the end of this year). It has specialized in the use of hybridomas--cells capable of unrestricted reproduction in culture, and formation of antibodies. A special method permits selection of cells producing only one particular antibody. The company is now producing antibodies to the following proteins, intended for research purposes: the surface antigen to hepatitis B virus, prostate acid phosphatase, creatine kinase isoenzymes, lymphocyte surface antigen, alpha-fetoprotein, immunoglobulins G and E, and chorionic gonadotropin.

Mention should be made of the fact that a small company, (Kabigen), a daughter enterprise of the state-owned (Kabi vitrum) pharmaceutical company, was founded in Sweden in 1968.[10] It intended to acquire growth hormone with the help of recombinant DNA methods, but it encountered problems associated with safety restrictions.

Pharmaceutical companies have been investing money predominantly in specialized firms, but they themselves are now gradually beginning to assimilate the technology of recombinant DNA. Such firms include Ely Lilly and Upjohn, each of which possesses $1 billion in capital, Pfizer and Abbott, Searle, Merck, Sharp, and Dohme, and Hoffman-Laroche.

Oil and chemical corporations are also investing money into DNA industry. Moreover they are also organizing their own research. An example of this is du Pont. But in general, the large corporations are exhibiting a certain amount of caution, and they are tending to approach DNA industry slowly, believing that the profits are not dependably assured yet. Their main effort continues to be to finance small companies. Thus in 1976 D. Adams purchased $500,000 worth of Sites shares, in 1977 he bought 10 percent of Genentech's shares, and in 1978, following the advice of P. Sharp and W. Gilbert, he founded Biogen, of which he has been the president for some time.

One shareholder in Sites and Genentech is Kleiner and Perkins, which provides financial support to electronics industry. The New Jersey Company receives funds from Aetna Life Insurance, Emerson Electric, and Monsanto, and in turn it finances Genentech and Genex. Labrizol controls 25 percent of Genentech's shares.

It should be noted that a competitive struggle is gradually taking shape between companies involved in recombinant DNA technology. An example of this is the rivalry in interferon and insulin production. But this is a special topic unto itself.

The influx of researchers and, most importantly, assets into gene engineering brought with it the almost instantaneous development of the manufacture of preparations and materials intended to satisfy the new experimental needs.

New companies have appeared, and they are apparently flourishing and developing quickly.[11] Their initial goal was to service the needs of research laboratories, but now their field of activity has broadened significantly; they began using the methods of recombinant DNA from the very beginning.

Thus (S. Terner), with only $30,000 in his pocket and one laboratory assistant, founded the Bethesda Research Laboratory (USA), which now employs 150 persons, 35 of which have degrees, and it sells $2.5 million worth of preparations per year from a catalog containing hundreds of names. It utilizes hybridoma technology, and it was announced in March 1980 that the laboratory cloned one of the genes responsible for proline synthesis.

New England Bio Labs (Massachusetts, USA) was founded in 1976 by (D. Komb), and it is owned by him and his wife. Possessing a small staff (22 workers), the firm sells various biochemical preparations, mainly restrictases, with a total volume of $3 million per year. It was the first to use the recombinant DNA method to obtain ligases (1974).

And, finally, we should mention the firm Collaborative Research (Waltham, USA), founded in 1962; its president is (O. Fridman). The firm produces synthetic linkers and other deoxynucleotides. It is now specializing in yeasts, with genetic research and production concentrated in a specialized branch of the firm, Collaborative Genetics, which employs the methods of gene engineering. The supervisory council contains prominent specialists, (Dzh. Fink) in particular.

Old firms, Boehringer (FRG) for example, have expanded and increased their production with an eye on gene engineering. Seapy Laboratories Ltd., which markets the products of Biolabs Inc. (USA), offers a highly rich assortment of enzymes: 40(!) restrictases (their total number is now up at 150), DNA-ligases, polynucleotide kinases, polymerases, exonucleases, and so on.

Microbiological Research Establishments, founded in Porton (England), offers not only several conventional *E. coli* strains, but also *E. coli* strain W3110 Lambda c1857ts-S_7-am (1.5 gm lambda phage can be isolated from 100 gm of the latter) as well as the bacteria *Stearothermophilus*, *Thermus aquaticus*, and *Haemophilus influenzae*.

The company Life Science (Florida, USA) is producing reverse transcriptase, obtained from fowl myeloblastosis virus.

The rules of working with recombinant DNA have a direct bearing on DNA industry, but they should be mentioned in only one respect. In its time, a savage campaign against gene engineering, having the goal of demonstrating its extreme danger to mankind, was initiated in the USA. This campaign did not enjoy support in European countries, and it did not spread there. Now the pendulum has swung in the other direction in the USA--the violent attacks on gene engineering have abated, and a powerful movement in favor of dramatically relaxing the rules of working with recombinant DNA has arisen.[12] The situation today is such that about 80-90 percent of all work done in the USA with recombinant DNA will not have to be registered, and it will not be subjected to any sort of limitations.

The reason behind this astounding change is clear: One one hand the restrictions that had been enforced were in fact unjustified and excessive, while on the other hand they inhibited development of fundamental research on recombinant DNA and gave an advantage to the USA's European competitors. Industrial organizations in the USA accepted these rules voluntarily; formally, the mandatory registration of research and production processes was not extended to them. Now they enjoy complete freedom in the use of recombinant DNA technology at their enterprises.

Patent law is most intimately associated with commercial production in capitalist countries as a means for protecting profits; DNA industry is not an exception in this regard.

It should be stated first of all that no patents have apparently been issued on recombinant DNA yet. However, the patent departments of different countries have received numerous claims, in relation to which decisions have not yet been made, and in many cases (most?) the claims have not even been subjected to expert examination for their novelty and their qualifications as objects of patents.

The patent campaign has become most active in the USA, where most of the gene engineering firms are. Strange as it may seem, however, the Bureau of Patents and Trademarks has not issued a single patent yet, and all claims that have been submitted are lying on the desks of this bureau without action, and not because it usually takes 2 or 3 years for expert examination of patent claims in the USA: The bureau is waiting for a decision from the U.S. Supreme Court, which must establish whether or not "life" or, more simply, living beings can be patented.[13]

This question arose in 1972 when the Upjohn Company submitted a claim for a bacterial strain producing lincomycin, and in 1973 General Electric attempted to patent a strain of *Pseudomonas* bacteria that decomposes petroleum hydrocarbons (inventor--(A. Chakrabarti)). The part of the claim concerning living bacteria was rejected. The decision was based on the fact that U.S. patent law does not specifically foresee patents on living beings, having in mind only "...any new and useful processes, machines, articles, and materials." Exceptions have been made in relation to some plants on the basis of laws adopted by Congress in 1930 and 1970, but the patent laws do not extend to fungi and bacteria.

The claimants appealed to the U.S. Court of Customs and Patent Appeals, which decided that there were no obstacles to issuing patents for the claims submitted by Upjohn and General Electric. Then the issue of awarding patents on bacteria and on living beings in general were submitted to the U.S. Supreme Court, where it has been awaiting its resolution since 1976 (or approximately since that time). If the Supreme Court returns a favorable decision, which is expected in mid-June 1981, patents will be granted almost automatically to claims having to do with genetic manipulations.

We do not have complete material for an exhaustive analysis of patent practice in gene engineering, but the general pattern can be seen rather definitely.

As far as we know, one of the early claims was submitted by the American scientists (S. Koen) (Stanford University) and G. Boyer (University of California). For practical purposes it covered most of the methods and processes in gene engineering; however, according to the claimants, it did not extend to research, pertaining only to commercial uses. The claim submitted by S. Koen and G. Boyer will hardly make it through in this form, since the broad area of patent protection it calls for will probably raise objections.

Knowledge of this claim comes only from literary sources. But some claims have been publicized, and this has permitted tentative analysis of patent law in gene engineering. The documents employed in such analysis are claims published by the

appropriate patent offices raising the question of so-called conventional priority. We do not have access to the initial claims submitted to the patent offices of the USA, the FRG, and Japan and serving as the basis for establishing priority, but one way or another they reflect the content of documents that have been submitted to European patent offices. Incidentally a claim by Genentech submitted to the patent office of the FRG combines seven claims of this industrial company in the USA. Legal protection is obtained immediately in the patent offices of numerous countries as well as in the European Patent Service and in the Organization for Protection of Intellectual Property. Tests for novelty and other criteria of patent law have not apparently been conducted in relation to these claims. Thus the fate of patents in Europe remains unclear.

As far as the content of the claims is concerned, we should make mention of their scientific and legal qualities--well-informed people have worked on them (or at least this is the impression that is created).

Each document consists of two parts, the patent claim itself, and a description. In the first section, the content of the claim is worded in short and dry phrases--lawyers had obviously edited this part. The description was written up by the scientists--the essence of the claim is presented in extremely great detail in laymen's terms, and sources, quotations, graphics, and photographs are presented. As an example in the claim submitted by the University of California to the patent office of the FRG on 24 May 1978, No 2822568, entitled "A Microorganism Containing a DNA-Vector and Gene of a Higher Organism", the object of the claim is presented in the description as follows: "This invention deals with isolation of a specific nucleotide sequence containing the genetic code of a specific protein; synthesis of DNA by means of this sequence; transfer of this DNA into a host-microorganism, in which this DNA undergoes replication. In particular the invention has to do with isolating the genes for insulin and growth hormone, their purification, transfer, and replication in the microbial host, and their final characterization. Owing to this invention, new products have been obtained. They include a plasmid into which a specific nucleotide sequence originating in a higher organism were built in, and a new microorganism having genetic information containing a specific nucleotide sequence belonging to a higher organism."

In the claim, the details of the description given above are elaborated in 75 (!) paragraphs following in what might be called concentric circles--from the general premises to increasingly more-particular ones to very concrete premises. The latter, however, do not make up the full content of the claim and, in the opinion of the claimants, they should be interpreted only as examples, and nothing more. Thus as far as we can understand, the claim embraces all genetic manipulations used to obtain information RNA from appropriate cells (tissues, organs) and to obtain, from the latter, DNA copies and recombinant plasmids containing the intended gene; the selected recombinant plasmid transforms the bacterial host, thus producing the microorganism serving as the object of the claim. In the USA, this claim is represented by seven or eight more-particular claims; in the claims submitted to the patent office of the FRG, they are combined in a single document.

This claim requests patent protection for a produced substance--that is, copy DNA for example, processes--for example a means for isolating information RNA from cells, and an article--that is, a microorganism altered as described in the claim, and containing a recombinant plasmid obtained in previous stages (assuming that a living organism can be called an article).

The form of the claim itself indicates that the claimants are attempting to gain legal protection for the genetic manipulations they developed on the broadest possibl base.

All of the claims originating in the USA, of which we are aware, are of the same type. It might be that claims from the USA acquire this nature in certain cases because they are summary claims, and their initial variants have more particular, restricted nature (for example the claim cited above). But, for example, Genentech's European claim, No 0284805, 1978, is based on just a single initial American claim--No 0849691.

This does not change the situation in principle: There is doubtlessly a desire to achieve legal protection for the most diverse manipulations of gene engineering having the maximum possible breadth, extending not only to present but also future uses, results, processes, and methods. Whether this is done in the form of a single claim or many is of no fundamental consequence.

We need not doubt that patent law, especially in the event of a favorable decision by the U.S. Supreme Court, will become a field of fierce legal and scientific battles motivated not by a search for the truth or by assurance of scientific priority, but by bare material calculation.

Submission of an application for a patent on hybridomas may be said to be the episode which began this detective chapter of modern bioengineering.[14] Hybridomas--artificial products resulting from the merger of lymphocyte cells and mouse plasmocytoma tumors--were discovered by (Ts. Milsteyn) and (Dzh. Keler) in 1975 at the Laboratory of Molecular Biology in Cambridge (England). The authors and the Council for Medical Research, to which the laboratory is subordinated, did not sumit patent claims on hybridomas, and Milsteyn provided cell cultures to anyone who wanted them. In this case he requested the recipient to submit a written promise not to make hybridomas a subject of patent claims.

On 23 October 1979 (Kh. Koprovski) and (K. Kroche) from the Wistar Institute (Philadelphia, USA) obtained a patent for monoclonic antibodies against cancer cells, and on 1 April 1980 Kh. Koprovski, K. Kroche, and (V. Gerkhartdt) of the same institute obtained a second patent on the antiviral antibody. The claims were apparently worded in such a way that patent protection for the hybrid cells themselves was not sought. But Kh. Koprovski did obtain a hybridoma culture from Ts. Milsteyn; hybridomas and the general method developed by the Cambridge researchers were the foundation of the patented procedure. Milsteyn has not been able to find a written promise from Kh. Koprovski in his files, and he has no formal recourse against him. Now it is clear why Koprovski did not send the letter of promise to Milsteyn when he received the culture of hybrid cells from him!

Hybridomas have a great practical future, at least in the creation of monoclonic (pure) antibodies. The existing method produces only mouse antibodies, but methods for obtaining human antibodies with the help of human hybridomas or similar artificially formed cells are taking form.

Many firms are already using hybridoma technology: Hybritech, Bethesda Research Laboratory, later the firm (Sentokor) (Philadelphia, USA), founded in 1979 by

(E. Allen) and financed by the Bank of Paris and (Venrok)--one of the firms of Rockefeller empire. (Incidentally, Kh. Koprovski is the chairman of the council of scientific experts for Sentokor.) In addition, new firms were created in 1979: In the USA--Clonal Research of Newport and Monoclonal Antibodies of Palo Alto, and in Europe--Searle Research Laboratory (England). For the moment the products of these firms are intended for research purposes, and not for diagnosis and therapy.

The uncertainties surrounding the possibility itself for patenting microorganisms and cell lines in the USA are forcing industrial companies to review their commercial policy. The long duration of the patenting procedure, even if it does turn out to be legally possible, and the need for describing the object of the patent in detail (information which competitors may use for their own purposes) makes this means of insuring profits not very effective. Alternative means are being debated today. The opinion has been suggested that patents can and should be done away with, on the condition that the example of electronic firms is followed--keeping the research secret on one hand, and accelerating industrial assimilation of the process and commercial advance of the product to the market on the other. (During the writing of this article, Upjohn withdrew its patent claim on lincomycin. Apparently its executives decided to follow the alternative route. This created a true sensation!)

The general impression of the course of events in patent law pertaining to gene engineering may be summarized as follows:

The activity of firms and scientific organizations in this direction is exceptionally high; perhaps nothing similar has ever been observed in the past; all actions bear the imprint of feverish haste;

patent claims embrace an unusually broad range of methods, manipulations, and applications; once again, nothing similar has ever been observed in the past; attempts are being made to patent not only the methods for obtaining certain pharmaceutical preparations, for example polypeptide hormones, but also the methods representing the very essence of gene engineering as a fundamental science.

In the final analysis, all efforts are directed at achieving a complete monopoly over the applied possibilities of gene engineering.

This article will conclude with an assessment of the prospects of DNA industry. The successes enjoyed by firms exploiting gene engineering--in any case ones such as Genentech and Biogen--are undebatable and impressive. For the moment these firms have not enjoyed a commercial gain, and their achievements are of greater interest to science itself. In the near future, however, commercial success could hardly be doubted.

Despite the voices of the skeptics, business executives have been caught up by a rush likened by some observers to the gold fever of Jack London's time, or to the events occurring in the growth phase of microelectronics industry in the USA. Of course, the zeal of the businessmen does not emanate from their compentency in the complex and confused technology of recombinant DNA; it is fed by the frame of mind and opinions created by the press, television, and an entire army of scientific writers and commentators, and not in last place by the scientists themselves, even

though, they assert, they "are not seeking publicity for the sake of money." The risk associated with investing capital into DNA industry is not ignored, but the apprehensions of "being left out of the game", which promises piles of money, dominate. Businessmen may be likened to a cat before a dish of milk it knows to be hot, but which it decides to taste anyway. In any case, on 16 January 1980 (the date of C. Weissman's press conference in Boston) is referred to as the day when molecular biology became "big business".

There is a threat of many complications arising in this situation within the academic system of the Western countries. Up until now, molecular biology and molecular genetics have been typical profitless sciences, but now a dramatic turn has occurred in the direction of industry and commerce, and the picture has changed in a single bound. The scientist-businessman with a potentially large backing, unusual to this area of knowledge, has appeared. What sort of relationship will be established between such people and their less-successful colleagues in the universities and institutes? How will their example influence the psychology and behavior of young scientists who are just beginning to travel the road to academic recognition and material well-being? Will compatibility be achieved between the free traditions of the universities having to do with the publishing of research and with academic ties on one hand, and the stiff and mercenary restrictions imposed by industrial companies? It is difficult to answer these and other questions confidently at the moment. But we cannot doubt the fact that the invasion of business into the brittle system of science will not be uneventful to the academic institutions of the West.

There is a useful lesson to be learned from all of the above; namely, we must understand what it was that made such significant advances possible in an area which has not even celebrated its 10th anniversary yet.

All of the components of success in this area are in fact present in our country, and they must be effectively utilized.

FOOTNOTES

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PRINCIPLES OF BIOLOGICAL SUPERSYNTHESIS WITH INTRODUCED GENETIC MATERIAL

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[Text] Producers of various biologically active and other economically valuable substances are the foundation of modern microbiological industry. Research on these producers has shown that they include forms that produce at different intensities. Only those which provide a markedly higher yield of the given product have practical significance. The terms "marked overproduction", "effective fermentation", "hypersynthesis", "supersynthesis", and others have entirely definite biological meaning. In all of the cases above, the processes are quantitatively uneconomical to the cell, and they are actually nonbiological according to the yardsticks of natural populations (1). As a rule this situation is achieved through certain disruptions of regulatory mechanisms, as a result of which we observe more or less uncontrolled expression of a particular operon (2); as a consequence the quantity of protein produced by a single gene may make up several percent of the total protein biomass. But while this does have advantage to industry, it is inseparably associated with shortcomings that cannot be eliminated in the traditional methods for acquiring biosynthetic products. And in fact, the more intensively a given product is accumulated, the fewer structural and energy components remain for all of the cell's other needs, and cell growth decreases. Moreover when the quantity of the resulting product is commensurate with that of all other cell components taken together, such a mass of overproduced substance has a negative specific, nonspecific, or simply purely mechanical influence that hinders metabolism. A biphasal product in which biomass is first accumulated, and then it begins fermentation or biosynthesis, could be a certain improvement in the organization of biosynthesis. Biphasal processes enjoy broad application in the acquisition of secondary metabolites. As far as biosynthesis of a concrete protein is concerned, this principle has been found to be practically useless. But qualitatively new possibilities are opened up when exogenous genetic material is introduced into the process. When such material is introduced, on one hand the gene (or genes) responsible for synthesis of the given substance experiences amplification, and on the other hand a possibility arises in some systems for simple solution of the biphasality problem. We can subdivide, arbitrarily to a certain extent, biosynthesis with exogenous genetic material into several types depending on the unique features of gene amplification and expression.

Plasmid Amplification

The possibility of gene amplification with plasmidsis based on the fact that a number of plasmids exhibit relaxed control over replication--that is, their number in cells may vary from several copies to several thousand.

As an example colicinogenic factor E_1 (col E_1) and its derivatives number about 24 copies in the normally growing cell. If chloramphenicol is added to the nutrient medium, the bacterial chromosome ceases its replication, while col E_1 continues to synthesize DNA, and after 12-16 hours 1,000-3,000 copies of this plasmid can be detected in the cell. This capability for amplification as well as presence of one site for restrictase R, Eco R_1, made this plasmid and its derivatives a broadly employed vector for both molecular cloning and for DNA amplification.

Hershfield et al. (3) obtained the recombinant plasmid col E_1-trp, which under normal growing conditions produced 25-30 copies per cell but in the presence of chloramphenicol produced several hundred copies per cell; in this case the synthesis products of the tryptophan operon were subsequently 20-25 percent of total cellular protein.

Supersynthesis of the products of dna-genes with the hybrid plasmid col E_1 was described (the quantity of dna-gene product increased by a factor of 3-10) (4).

Using plasmid col E_1, Boyer obtained a number of vectors (pmB9, pBR 313, pBR 322), in which the capability for amplification was retained from col E_1 but additional sites for other restrictases were introduced (5, 6).

Vectors pBR 313 and pBR 322 were used to amplify the gene in the lac-operon of *E. coli* responsible for synthesis of galactoside permease (7), and pBR 322 was used to amplify the somatostatin gene (8).

A vector molecule pOP2 containing a lac-operon promoter was obtained with plasmid pmB 9. The ara C gene was placed under its control. The quantity of protein produced by the ara C gene in cells within which the plasmid was functioning was 50 times greater than in cells not containing the plasmid (9).

The possibility for using plasmids as gene amplifiers is reduced by a number of factors, the most serious being the instability of hybrid plasmids. On one hand hybrid plasmids may split to form miniplasmids, while on the other hand they may be eliminated from the cell, which creates difficulties in the use of plasmid strains of bacteria in the biosynthesis of products controlled by genes built into a plasmid.

As was noted earlier, chloramphenicol is used to amplify hybrid plasmids obtained with col E_1. Use of this procedure on an industrial scale is hindered by an insurmountable obstacle, since following processing of the producer with the antibiotic and amplification of the plasmids, it must be removed from the culture medium. This procedure is fully justified for small volumes, but it is absolutely inacceptable on a major industrial scale. The possibility of other approaches, particularly the use of temperature-induced plasmid mutants, should be noted here. The indications are that when the temperature is increased to 42°C, the number of copies of a mutant plasmid increases from 40 to 750 (per chromosome) (10).

Reports are appearing that the gene dose--that is, the number of plasmid copies--does not always correspond to the amount of the products formed on the basis of their information; in particular, an increase in the number of plasmid copies does not always result in a proportionate increase in the quantity of proteins they encode.

Phage Amplification

Besides plasmids, phages--rarely virulent and for the most part moderated--may be used to amplify a gene (or genes) and, consequently, to obtain an enlarged quantity of products synthesized by the amplified genes.

An investigation of virulent phages (T_4 in particular) has been described in relation to overproduction of DNA- and RNA-ligase in the cell. Following infection of *E. coli* cells with phage T_4, the ligase activity of the cells increases by a factor of 20. Maximum activity is observed 20 minutes after infection (11). It was demonstrated that gene 30 of phage T_4 is responsible for synthesis of DNA-ligase (12).

Thus normal phage T_4 can be used for ligase overproduction. The difficulty in this case lies with the fact that a slight delay in collection of the infected cells would result in their lysis, escape of the enzyme into the lysate, and breakdown of the enzyme. This difficulty can be avoided by causing amber-mutation in the area of genes responsible for lysis of the bacterial cell.

Moderated stages appear more promising. They have now been used as the basis for creation of a number of vectors serving the purposes of not only cloning but also amplification.

Moderated phages have the capacity for introducing themselves into the bacterial chromosome, and engulfing part of the bacterial genome at the time of breakage. Moreover, particular DNA fragments can also be inserted into phages by the methods of gene engineering. This was the starting point for using moderated phages in supersynthesis of bacterial products controlled by genes built into phages.

Thus by as early as 1967 Matsuda and Barksdale (13) described a system in which a virulent mutant of moderated phage β was used to effect a significant increase in the product of a bacterial gene carried by phage β. This product was diphtherial toxin. Cells synthesizing extremely small quantities of diphtherial toxin were infected by phage β containing, within its chromosome, a tox-gene responsible for synthesis of diphtherial toxin, and toxin production increased by a factor of $1 \cdot 10^6$ within a single cycle of phage development.

Moir and Brammer (14) suggested using a number of mutations of phage λ that would promote intensified formation of enzymes by bacterial genes built into phage λ. Mutations in Q- or S-genes create a situation in which expression of the late genes of phage λ is blocked, owing to which basically the early phage products accumulate; the latter include the product of the bacterial gene built into the early gene region of phage λ. This work was conducted on phage λ carrying a tryptophan operon consisting of five structural genes, as a result of which five trp-operon enzymes were

synthesized. Use of Q- and QS-mutations of phage λ in bacterial cells resulted in accumulation of up to 50 percent trp-operon proteins, in relation to the total quantity of soluble cell proteins. The same result was obtained with N-gene mutants of phage λ. The product of gene N is one of the first phage-dependent substances in the bacterial cell. It is necessary for the function of early genes O and P, the products of which participate in replication of phage DNA. In the absence of products of gene N, genes O and P express themselves extremely weakly. Therefore replication of phage DNA is retarded, and Q-dependent genes--that is, all late genes--do not express themselves at all. Moir and Brammer (14) emphasize that construction of a phage containing a mutation in the N-gene is much easier than introducing Q- and QS-mutations.

Steffen and Schleif (15) describe the use of S-mutations of phage λ, which prevents lysis of the bacterial cells, for overproduction of protein by Ara C. Ara C was built into the left part of the phage, but in the inverted form in relation to the P_L-promoter; therefore it could be read sensibly only beginning with the right promoter. But the S-mutation alone could increase synthesis of Ara C protein by only 10 times in comparison with uninfected cells. Inasmuch as the Ara C gene expressed itself beginning with the phage promoter Pr, it was subjected to phage regulation. Then the authors decided to use a bacterial mutation--tob (16), in the presence of which synthesis of early proteins by the phage does not turn off. As a consequence of this mutation, gene Ara C did not turn off, instead continuing to operate even while the late genes were being read. By this technique, synthesis of Ara C protein increased by 30 times in comparison with that in uninfected cells. A 100-fold increase in Ara C protein in comparison with infected cells was obtained by deletion of the transcription terminator for the late genes of the phage, located in region b_2 of the phage's DNA. Thus additional transcription of the Ara C-gene from the late phage promoter Pr' was achieved.

A 500-fold increase in production of another protein--DNA-ligase--was also achieved by introducing an S-mutation in phage λ (17). In this case this was a recombinant DNA molecule obtained *in vitro* with vector λgt and ligase genes. The third Eco R_1 site was removed by mutation from vector λgt, owing to which the att-site and the int- and xis-genes were preserved. This vector can integrate itself into the host chromosome and consequently exist in the form of a lysogen (prophage), which is a more-stable form for preserving and maintaining the recombinant molecule, and a more-convenient form for practical purposes.

An important question in the construction of a recombinant molecule with phage λ, involving inclusion of the genes whose expression is to be amplified, is that of what promoter will control transcription of the included genes. Genes included into the composition of the DNA of the transducing phage may express themselves as both their own promoter and as promoters of the phage genome. In order that transcription would be effective, the promoter must be strong. Strong promoters include the promoter of left-sided transcription in phage λ (P_L) and the promoters of the trp-operon and lac-operon. But strong promoters are not all the same. Thus Davison et al. (18) demonstrated that promoter P_L is 10 times stronger than the trp-operon promoter.

The life span of trp-operon m-RNA transcribed under the control of P_L in phage λ increases in comparison with the life span of trp m-RNA transcribed under the control of its own promoter (19). The authors showed that the products of gene cro (tof) play a role in the attainment of the stability.

Nevertheless Moir and Brammer (14) showed that expression of the trp-operon was more effective if it expressed itself through its own promoter, and that it was 3 times weaker if promoter P_L of phage λ was involved. The authors note that despite the fact that promoter P_L is stronger than the trp-operon promoter, it was much more difficult to use promoter P_L for effective expression of the trp-operon. Attempts at inducing mutation in the cro gene, the product of which represses transcription with the P_L-promoter, did not improve expression of trp-genes with the P_L promoter, since in this case replication of phage DNA was retarded significantly, having an effect on the number of copies of trp-genes and, consequently, the quantity of enzyme produced.

Murray (20) suggests another detour by which to achieve expression of bacterial genes with the P_L-promoter of phage λ, using so-called "hybrid immunity". Gene cro is within the immune region of phage λ; the product of this gene is immunospecific, and it will not influence the promoter of the heteroimmune phage λ imm^{434}. It follows from this that a hybrid phage with P_L from phage λ and P_R and the cro-gene from phage 434 (or vice versa) should be phenotypically cro^- for left-sided transcription, while preserving normal regulation of right-sided transcription with P_R. In order to intensify expression with the P_L-promoter, an amber-mutation was introduced into the N-gene of a phage with a hybrid region of immunity, and terminator t_{R_2} was deleted (nin-mutation), which creates a situation of uncontrolled expression of N-dependent genes in an N-suppressible host.

Helinski et al. (21) constructed a successful vector using phage λ's promoter P_L. The vector was obtained from plasmids col E_1 and Eco R_1--a phage λ fragment with a trp-operon (molecular weight $5.8 \cdot 10^6$), and genes N, C_1857, cro, P_L-, and P_R-promoters. Gene cro was mutated in order to depress transcription with P_L- and P_R- promoters. Following initiation of transcription with the P_L-promoter, synthesis of the product of gene N, which is necessary to surmount the plasmid terminators and synthesis of the entire vector's m-RNA, attained its maximum level. Were we to introduce any additional genes next to the trp-genes, they would also express themselves as trp-genes. Such a vector, using P_L-promoter from phage λ, was constructed out of plasmid pBR 322 and phage λ C_1857 cro^- (22).

In the absence of an intrinsic promoter in a gene (or genes) to be amplified and subsequently expressed, more than just the strong phage promoter P_L is used. In order to achieve overproduction of repressor by phage λ, the intrinsic promoter of which is very weak, Gronenborn used a lac-operon promoter, fusing it by deletion with gene C_1, responsible for synthesis of the repressor. A chemically synthesized gene for somatostatin also expressed itself through the lac-operon promoter (8). The lac-operon promoter was responsible for effective synthesis of the product for gene Z (β-galactosidase) following infection of *E. coli* cells by phage λ p lac, in which gene Z and the lac-promoter were all that remained of the lac-operon (24).

The Basis, in Genetics and Molecular Biology, for Introducing Particular Genes Into Supersynthesis Systems

It might be expected that supersynthesis systems would be sufficiently effective within a broad range of introduced genetic material. Therefore a gene or group of genes whose expression is responsible for production of a given product must be introduced into a vector ready for supersynthesis, one that is universal in its

interaction with the host cell. This can be achieved both *in vitro* and *in vivo*. *In vitro* systems used for these purposes must insure acquisition of the required recombinant molecules. They presently exist for both plasmids and phages, and they represent the most highly developed techniques of gene engineering (25). There are certain difficulties in choosing a vector capable of completing the task posed. In the case of plasmids, there should be a determinant that is technically simple to amplify. But technically simple amplification is precisely the main factor retarding the industrial use of plasmids. The possibilities are limited today basically to natural amplification, and amplification resulting from chloramphenicol blockage of synthesis of plasmid replication repressor, coupled with simultaneous inhibition of synthesis of other cell proteins, followed by removal of the antibiotic from the biomass and recovery of normal cell functions. This technique is useable only in the laboratory. However, promising plasmids with a ts-mutation in the repressor genes have recently appeared; because of this mutation, thermal induction of these plasmids by simple change in growing temperature is possible (10). We can expect that these are precisely the plasmids that will be promising as vectors in industrial supersynthesis. Today, the main difficulties lie not in how to introduce the information from without, but rather in the technical feasibility of realizing the process.

Tao and Rogers (26) suggest amplifying genes with a thermoinducible chimera consisting of phage λ and plasmid pBR 322, in which plasmid DNA replication occurs not as a result of chloramphenicol blockage but rather as a result of thermal inactivation of phage λ repressor. A 125-fold increase in production by gene xth (*E. coli*'s exonuclease III) was achieved in such a chimeric vector.

The same sort of chimeras, obtained by Helinski (21) and Bayev (22), also make it possible to avoid chloramphenicol blockage by the use of temperature inactivation of phage λ repressor.

Use of moderated phages for the purposes analyzed here was made possible owing to the presence of ts-mutations in the C_1-gene, responsible for repressor synthesis. However, certain difficulties, associated specifically with introducing economically valuable genes, stand in the way of applied use of moderated phages. Moderated phages are cut into several fragments by the overwhelming majority of the restrictases. After they are subsequently linked with the required gene or group of genes, the most diverse combinations arise, as a result of which the yield of viable recombinant molecules is below that with which we can realistically operate. Therefore mutants (basically of phage λ) with a reduced quantity of sites sensitive to restriction (mainly by Eco R_1 restrictase) were obtained (27). However, processes most convenient to supersynthesis involve work not with the phage as such but rather with lysogenic bacteria, from which the needed phage could be obtained in a certain amount of time with simple heating at 43°C. Most obtained derivatives of phage λ used to clone recombinant molecules following introduction of a foreign frament were capable only of the lytic process. This is graphically illustrated by one of the most widespread vectors, λgt (28). In order that the DNA molecule of the phage could be packed into the protein shell, the DNA molecule must be of particular size, namely 30 million daltons, +5 -20 percent (29). For practical purposes 5 percent of 30 million daltons is a tiny amount--it is usually desirable to introduce larger DNA fragments. Moreover as we approach the 5 percent limit, the phage yield drops dramatically, as a result of which we are forced to work with even smaller fragments. In order to avoid such complications the region not significant to development of

the phage is limited by restriction sites, but in this case development following replacement of this region by foreign DNA proceeds only by the lytic pathway, since genes int and xis are discarded.

But vectors from phage λ which are capable of lysogenesis following insertion of a foreign fragment already exist as well (17, 27). In this case the restriction sites are located between regions that are not only not significant to reproduction of the phage, but also have no influence upon integration. When combined with ts mutations in gene C_1, such derivatives are convenient both for cloning foreign DNA and for the purposes of supersynthesis.

However, in addition to *in vitro* introduction, *in vivo* acquisition of recombinant molecules, required for supersynthesis, on the basis of moderated phages is highly promising. This possibility is based on imparting, to these phages, the capability for generalized transduction following by selection of the required clones.

It has been demonstrated that in cases where as a result of deletion, lambdoid phages lose their att-sites, which are responsible for recombination with homologous segments of the bacterial chromosome, they acquire the capability for introducing themselves into other segments, though now the probability of this process becomes much lower.

The capability for breaking the host's chromosomes and capturing the adjacent chromosome segments is retained by such phages. As a result we can obtain a set of phages bearing different bacterial genes--that is, almost ready-made supersynthesis systems.

It is possible to obtain various recombinant molecules *in vivo* not only on the basis of the DNA of moderated phages, but also plasmids and episomes. For this purpose we can employ phage μ, which is capable of not only generalized transduction but also transposition of bacterial chromosome fragments in plasmids (30). The discovery of insertion elements and transposons, and swift development of the methods for working with them have demonstrated the possibility for using them to carry particular labels from literally any genetic element of a bacterial cell (chromosome, phage, episome, plasmid) to any other element. There is no doubt that as the methods of working with transposons improve, they will acquire increasingly greater significance in construction of recombinant molecules *in vivo* in general, and of molecules suitable for supersynthesis in particular. Special mention should be made of recently created vectors capable of integration in the bacterial genome. Work done by A. A. Bayev's school resulted in acquisition of a vector molecule consisting of plasmid col E_1 and a fragment of phage λ containing the att-site and the int- and xis-genes. The obtained hybrid molecule was found capable of integration with an *E. coli* gene (31). If a ts-mutation were to be introduced into the C_1-gene, an integrating system capable of release and operation as a plasmid at (nepermessivnaya) temperature would be obtained. It could be expected that such a system would be just as convenient to supersynthesis as are moderated phages, and that at the same time it would have a significant advantage over the latter in connection with its practically unlimited information capacity.

Thus use of the methods and possibilities of gene engineering has led to broad possibilities for technically acceptable amplification of genes responsible for

encoding economically valuable enzymes and other proteins and peptides, and for developing, on their basis, the theory and practice of supersynthesis of biologically active substances with exogenous genetic material. The promise of industrial use of this phenomenon is so great that the first gene engineering company has already been created abroad--Genentech, Inc; such laboratories are being created by chemical and pharmaceutical companies, and numerous patents are being sought for new methods and strains. It has already been announced that the commercial cost of gene engineering products will be hundreds (!) of times less than those obtained by traditional production processes. All of this attests to initiation of qualitatively new possibilities in the acquisition of the most diverse biological products for various areas of medicine, agriculture, and industry.

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CLONING THE INSULIN GENE OF FISH (ONCORHYNCHUS KETA) IN ESCHERICHIA COLI

Moscow DOKLADY AKADEMII NAUK SSSR in Russian Vol 256, No 4, 1981 pp 999-1003

[Article by N. G. Dem'yanova, M. L. Zlochevskiy, V. M. Kavsan, Yu. I. Kozlov, A. I. Petrenko, N. Ye. Polyakova, I. V. Prokopenko, B. A. Rebentish, A. V. Ryndich, Yu. S. Skoblov, V. V. Sova, V. L. Yurin, N. K. Yankovskiy, V. G. Debabov, the All-Union Scientific Research Institute of Genetics and Selection of Industrial Microorganisms, Moscow; the Institute of Molecular Biology and Genetics, UkSSR Academy of Sciences, Kiev; Moscow State University imeni M. V. Lomonosov; the Institute of Marine Biology, Far Eastern Scientific Center of the USSR Academy of Sciences, Vladivostok; Institute of Human Morphology, USSR Academy of Medical Science, Moscow]

[Text] Cloning of recombinant DNA molecules which include genes of eukaryotes is of considerable theoretical, and often practical, interest. This method made it possible for the first time to isolate individual fragments of DNA eukaryotes in large quantities[1-3]; this opened new vistas in the study of the structure and function of the genes of higher organisms. In practical respects the use of bacterial strains bearing desired genes of eukaryotes to synthesize a number of valuable proteins essential to medicine is apparently close to becoming a reality.

The general approach in such studies consists of isolation of messenger RNA (mRNA) and synthesis on the mRNA matrix using reverse transcription of double strand DNA fragments, which are then incorporated into vector molecules and inserted into bacterial cells.

The present study deals with cloning of the preproinsulin gene (of the Dog Salmon) in Escherichia coli cells. Selection of the subject was due to a number of factors, not the least of which was the relative simplicity of the task. In fish, in distinction from most other vertebrates, insulin is produced by a specialized organ (Brokman's bodies) consisting basically of beta-cells responsible for insulin production. Consequently, it could be anticipated that the content of insulin mRNA in the total RNA isolated from the Brokman's bodies would be high[4].

From the theoretical point of view, cloning the preproinsulin gene of the fish is of definite interest, since insulin is, at present, the most studied model for investigating the evolution of genes.

Brokman's bodies were obtained from Dog salmon (10,000 fish) during the period of spawning migration and preserved in liquid nitrogen. RNA was isolated using phenol extraction and purified by two cycles of chromatography in a column with oligo-(dT)-cellulose. The yield of total RNA per 1 g tissue (Brokman's bodies) was 4-5 mg, and the poly(A)-containing fraction was 40-50 ug.

The poly(A)-RNA was translated in an cell-free system of wheat germ[5], using S-methionine as the labeled amino acid. The translate was analyzed using disk-electrophoresis in a 17.5-percent polyacrylamide gel with subsequent autoradiography (fig 1c). Identification of the preproinsulin production of poly(A)-RNA translation was performed using indirect immunoprecipitation. The immunoglobulin fraction (Ig) of rat serum obtained after immunization of the animals with Dog salmon insulin was used as the first antibody component in immunoprecipitation. Rabbit anti-rat Ig serum was used as the second antibody reagent. The specificity of the antibodies, as well as the necessary immunoprecipitation parameters were established in reactions with labeled ^{125}J Dog salmon insulin. As the electrophoregram shows (fig 1b), the anti-insulin antibodies precipitate protein which corresponds to the zone with a molecular mass of 11,000 daltons.

Fig. 1. Identification of preproinsulin in translate of poly (A)-RNA translate from Brokman's bodies of the Dog Salmon. Disk electrophoresis in 17.5-percent PAAG with SDS of the following types: a. immunoprecipitate of translate with normal immuniglobulins; b. immunoprecipitate of translate with anti-insulin immunoglobulin; c. translate. Arrow indicates the position of the S cytochrome (molecular mass 12,000). [Figure not reproduced.]

The precipitation of this zone was not observed (fig 1a) in a control experiment using rat immunoglobulin fraction isolated from unimmunized animals. Thus, the protein with a molecular mass of $(10\text{-}11)\cdot10^4$ daltons which was synthesized in the cell-free system is apparently Dog salmon preproinsulin. The amount of radioactivity in the zone which corresponds to this protein is 30-40 percent of the total nonacidsoluble label. Sedimentation and electrophoretic analysis of total poly(A)- containing RNA demonstated that insulin RNA has a sedimentation constant of 9S and the proportion of RNA to the 9S-fraction is approximately 30 percent.

In order to synthesize cDNA, the total poly(A) containing the mRNA fraction, was used as the matrix. The DNA and the complementary total poly(A)-RNA of the Brokman's bodies of th Dog salmon were synthesized in a system containing 50 mmole tris-HCL pH 8.3; 7 mmole MgCl ; 20 mmole DDT; 40 mmole KCl; 0.5 mmole dATF; 0.5 mmole dGTF; 0.5 mmole dTTF; 0.5 mmole H-dCTF (100 imp/min·pmole); 60 µg/ml mRNA; 20 µg/ml oligo-$(dT)_{10}$ and 250 units/ml reverse transcriptase of bird myeloblastosis virus. The reaction continued for 1 h at 37 degrees Centigrade. The yield of the product was 0.1 µg cDNA per 1 µg of matrix added. Purification of the cDNA was performed as described in study[6] . The second DNA chain was synthesized without innoculation using reverse transcriptase. The yield of the second chain was 20 percent of the added cDNA. In order to remove the spindle, double strand DNA was treated with S_1 nuclease in a system containing 0.3 mole NaAc pH 4.5; 0.3 mole NaCl;

4.5 mmole $ZnSO_4$. The protein was removed by phenol extraction; DNA was precipitated using alcohol and dissolved in 10 mmole NaCl. Restriction analysis of synthesized double-strand DNA (dsDNA) demonstrated that the major fraction of this DNA contains splitting sites for BamHI and PvuII restriptase. Preparation of dsDNA using these two enzymes results in the formation of a fragment with a molecular mass of approximately 70·103 daltons.

Enrichment of the cDNA by the individual sequence was performed using fractioning of ^{32}P-cDNA by hybridization using mRNA to a value of $C_0t_{1/2}2 \cdot 10^{-2}$ mole·s/l, at which only the class of molecules represented by a large number of copies in the total preparation (approximately 20 percent) is hybridized. Hybridization was performed in a solution containing 0.5 M Na Cl, 10 mmole GEPES pH 7.0, 1 mmole EDTA, 2 µg mRNA, 0.1-0.2 µg cDNA and 5 µg tRNA . Single-strand DNA was destroyed by treatment with S_1 nuclease. The cDNA obtained in this manner is hybridized with its matrix at values of $C_0t=10^{-5}-10^{-1}/C_0t_{1/2}$ 3:10^{-4} mole.s/l up to 80 percent saturation, which indicates at least 4-fold enrichment with the dominant DNA. All these data indicate that the major fraction which contains the insulin sequence is approximately 30 percent of the cDNA. The synthesized double-strand DNA was cloned by the connector method in E. coli bacteria C600. We used pBR322 plasmids which determine resistance to ampicillin and tetracycline as the vector. DNA of the pBR322 plasmids was split by BamHI or PstI endonucleases. The split pBR322 DNA was incorporated into the 3'-end of H-dGTF using terminal desoxynucleotidyltransferase using the previously described method[8]. In an analogous manner poly(dS)-connectors were synthesized on the 3'-ends of cDNA. The size of the connectors was from 12 to 25 nucleotides.

Figure 2. Inhibition of translation of preproinsulin mRNA by pND77 plasmid. Disk electrophoresis in 17.5-percent PAAG with SDS and 8M carbamide translates of the following types: a. fused hybrid of poly(A)-RNA with pND77; b. hybrid of poly(A)-RNA with pND77; c. poly(A)-RNA without DNA. [Figure not reproduced]

After completion the cDNA and pBR322 termini were centrifuged, as previously described[4], and the mixture was used for transformation. The effectiveness of the transformation was 10 clones per 1 ng cDNA. Transformation was performed according to method[9]. Incorporation of heterologous DNA into the BamHI splitting site of the pBR322 plasmid resulted in loss of the plasmidic ability to determine resistance to tetracycline, and incorporation of a heterologous fragment in the PstI splitting site results in loss of resistance to ampicillin. This made it possible to perform initial selection of clones by selection on media with the appropriate antibodies. As the result of this selection 300 clones were obtained.

The characteristics of the poly(A)-RNA and cDNA preparations give a basis for conjecturing that the desired fraction is as much as 30 percent of their composition. Hence we expect that the small sample of the transformants obtained contains clones bearing the preproinsulin sequence.

At the first stage, of 50 randomly selected clones 20 containing plasmids with fragments of heterologous DNA, 150,000 to 300,000 daltons in size were selected.

In the next series of experiments, methods which made it possible to select clones

b) CAC CTG TGT GGC TCT CAC CTT GTG GAC GCC CTC TAT CTG GTG TGT GGA GAG AAA GGA TTC TTT TAC ACC CCA AAG
c) his leu cis gly cer gis leu val asp ala leu tyr leu val cis gly glu liz gly phen phen tyr thre pro liz
d) his leu cis gly cer gis leu val gly ala leu tyr leu val cis gly glu arg gly phen phen tyr thre pro liz

Figure 3. a. Restriction map of cloned fragment of pND77 plasmid; figures indicate the distance in nucleotide pairs from the beginning of the fragment; b. nucleotide sequence of site 133-207 of cloned DNA; c. amino acid sequence of B-chain site of Dog Salmon insulin; d. amino acid sequence of B-chain site of human insulin.

containing the major fraction of cDNA were used. As the result of the experiment on hybridization of colonies in situ[10] with ^{125}J 9S RNA and hybridization of plasmid DNA with the fraction of cDNA enriched by individual sequence[11], out of 20 verified clones 4 were selected. Restriction analysis of the DNA plasmids isolated from these clones demonstrated that one of them (pND77) has an incorporated fragment which contains identification for BamHI and PvuII restrictases at one site.

In order to identify definitively clones bearing preproinsulin DNA, several of the selected plasmids were investigated for the ability to stop the synthesis of preproinsulin in a protein-synthesizing system. As is well known, RNA in association with complementary DNA is not capable of participating in translation (the method of "stopping translation" is based on precisely this fact). Plasmid DNA was denatured and centrifuged from the poly(A)-RNA, as previously described[12]. Next the mixture was divided into two portions, one of which (the control) was heated to 80 degrees Centigrade (in order to fuse the hybrid), and both preparations were used as matrices in an cell-free system for protein synthesis. The translates were fractioned by electrophoresis. As figure 2 shows, hybridization of RNA with pND77 plasmid results in the disappearance of the preproinsulin zone. Hence, this plasmid contains the insulin gene fragment. The molecular mass of the pND77-fragment of fish DNA incorporated into the plasmid is 340,000 daltons. The restriction map of this plasmid is presented in fig 3.

The 134-209 nucleotide sequence of the cloned DNA fragment was determined using A.M. Maxam and W. Gilbert's method[13] (fig 3a). This sequence corresponds to the B-peptide site of fish insulin and is homologous to the B-peptide of human insulin. As figure 3b,c shows, the amino acid sequences of the fragments of the B-chains of human and fish insulin have only 2 conservative amino acid substitutions: liz-arg, asp-glu. The homology of the corresponding DNA sites is 78 percent.

Preliminary analysis of the results of one experiment to determine the initial sequence demonstrated that pND77 plasmids are also contained in the A-chain of insulin, which begins at 302 nucleotides (fig 3a).

Considering the high homology between DNA of the corresponding sites of the B-chain of fish and human insulin, the cloned fragment may be used as a molecular probe for identifying clones containing the human insulin gene.

The study was performed in RZ [expansion unknown] conditions in conformance with the rules for working with recombinant DNA molecules (USSR).

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THE POSSIBILITIES OF USING GAS SELECTIVE MEMBRANES TO ENSURE LIFE ACTIVITY OF BIOLOGICAL OBJECTS IN A WATER ENVIRONMENT

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[Article by V.V. Petrash, A.R. Os'mak, N.A. Belyakov, S.A. Simbirtsev, All-Union Scientific Research Institute of Pulmonology, Leningrad]

[Text] The prolonged residence of man under water has been limited by the nature of the technical agents which ensure his life activity. Current rapid development of techniques for under water immersion has led to a search for new ways for its implementation. One of the basic factors of survival for the aquanaut is support by artificial gas agents and maintenance of a microclimate. Of interest is the possibility of producing direct gas exchange with the surrounding water environment, through poly-permeable membranes.

At the present time, two areas of research have been formulated for the implementation of membraneous gas exchange--a method of exchange directly with the blood and a method for exchange of exhaled air with the water environment. The first method is promising in medicine for conducting extra-pulmonary oxygenation of the blood (1,2). However, there are definite technical and medical complications in applying this method to aquanautics. A more productive approach for aquanautics is use of auxillary systems of life support involving a gas chamber which communicates with the water environment through a gas-permeable membrane. Specific aspects of this problem are elucidated in a review (3). Several theoretical positions on gas exchange in a water environment are examined in an article (4). In 1966, a system (5) was constructed which allowed a man to breathe under water in conditions of normal baric pressure by gas exchange through a millipore membrane. Progress in polymer chemistry has resulted in production of a variety of new gas-permeable membranes. Of particular relevance for gas exchange in a water environment

is the use of gas selective diffusion membranes which possess various degress of permeability for oxygen, hydrogen and nitrogen gases. Examples of membranes produced in this country are those based on polyvinyltrimethylsilicone (PVTMS), polydietylsilicone (Sigma) and others.

Of significance for construction of apparatus which fulfill the gas exchange function in a water environment are such factors as the properties of the membrane itself, the rate of flow of the gas mixture and water relative to the membrane and the degree of their mixing.

The purpose of this study is to define the potential of gas exchange function of selective diffusion membranes for various flows of gas mixtures and water in normal baric pressure conditions.

Studies were conducted using diffusion membranes of the PVTMS type produced in this country. The test membrane was placed in a special cassette, developed at the All-Union Scientific Research Institute of Pulmonology. Water was introduced from one side of the membrane using a feeder pump (P_{O_2} = 250 mm Hg; P_{CO_2} = 0-1 mm Hg) and a gas mixture containing 17.3 percent O_2, 5.3 percent CO_2 and 77.4 percent N_2 (a composition analogous to that of alveolar air) was introduced from the other side by the same type of pump. The functioning area of the membrane measured 0.05 m^2. The construction of the cassette allowed mixing either the flow of water or the flow of gas. Control of the gas content of the mixture was accomplished in the air from the cassette with the aid of a mass spectrometer of the MKh 6202 type (USSR). The rate of output of gas and water was preset by the pumps.

The second group of experiments was conducted according to the diagram shown in figure 1. In this instance, animals (rats) were included in a system for gas exchange. The rat was given ethyl carbamate anesthesia (1 mg/kg of weight) and placed in a special air-tight chamber and immobilized in a specific position--on the abdomen. To monitor the state of hemodynamics and external respiration during the course of the experiment, EKG and rheoplethysmograms (RPG) of the thoracic cells were recorded. With the aid of a feeder pump air was recirculated through the chamber (1) and gas exchange device (3) which had an exchange area of 0.2 m^2 (constructure of the exchange device was developed at the All-Union Scientific Research Institute of Pulmonology). The water was pumped through the exchange device at a rate of 0.6 1/min by the pump (2). The system was not connected to atmospheric air. Gas analysis was conducted through a meter (5) on a mass spectrometer without disturbing the air-tight nature of the system.

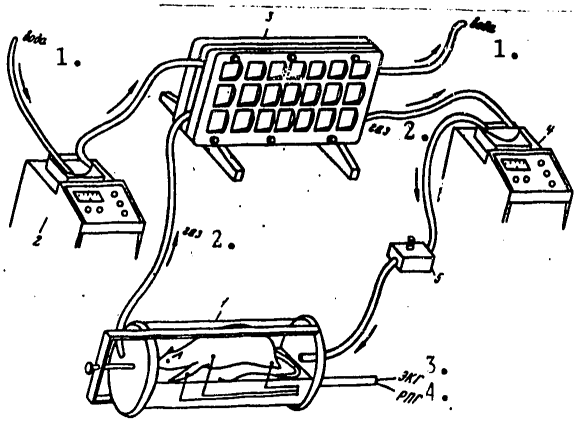

Рис. 1. Схема опыта с системой газообмена (пояснения в тексте)

Figure 1. Diagram of experiment for systematic gas exchange (explained in the text)

Key:
1. Water
2. Gas
3. EKG
4. RPG

In the control group of experiments, the gas exchange device was excluded from the system.

The results of the first series helped to define the relationship of gas transfer through the membrane to the rate of flow of gas and water. This relationship is shown in figure 2. Given a constant output of water at a rate of 40 ml/min and an output of gas at a rate of 10 ml/min, the gas composition of the mixture was restored to 21 percent O_2 and 0.03 percent CO_2; that is, the composition of the mixture, for all practical purposes, was no different from the composition of the surrounding air. With an increase in the output of gas, the gas exchange through the membrane was reduced and given a rate of gas transfer of 70 ml/min, the gas mixture contained 17.9 percent O_2 and 2.4 percent CO_2.

Increasing the output of water, given a constant output of gas, increased to a lesser extent the transfer of oxygen while at the same time, the elimination of CO_2 increased to a significant degree.

Given a laminar flow of water through the cassette, all indices for gas exchange were lower than those monitored during conditions of mixing. In this case, the percentage content of O_2 was

lowered by 2 percent and the content of CO_2 was increased by 0.3 percent. An essential change in gas exchange was not demonstrated when the gas was mixed.

In the second series of experiments, the control group of animals, placed in an air-tight system without gas exchange in a water environment, died after 90 minutes. It appears that from the first minutes of residence in the system, the composition of the air was altered to a significant degree. (figure 3). Significant changes in breathing and hemodynamics were observed in animals after 60 minutes.

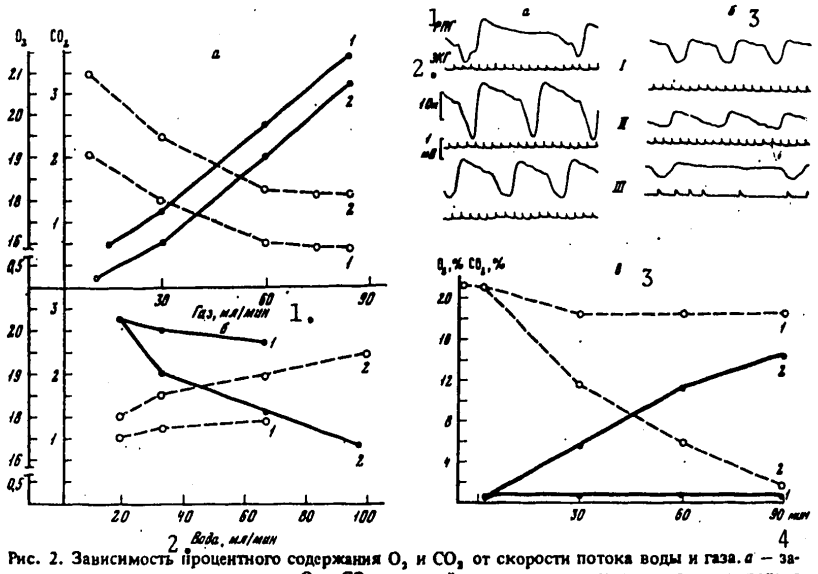

Рис. 2. Зависимость процентного содержания O_2 и CO_2 от скорости потока воды и газа. *а* – зависимость процентного содержания O_2 и CO_2 в газовой смеси при различных скоростях ее потока относительно мембраны и при постоянном потоке воды 40 мл/мин; *б* – зависимость процентного содержания O_2 и CO_2 от скорости потока воды относительно мембраны при постоянном расходе газа 40 мл/мин. *1* – ламинарный поток воды, *2* – турбулентный поток воды; сплошная линия – % CO_2, штриховая – % O_2

Рис. 3. Характер изменения реоплетизмограммы груди, ЭКГ и газового состава воздушной смеси в камере с животным при включении газообменного устройства (*а*) и без него (*б*). *I, II, III* – этапы эксперимента (*I* – исходные показатели, *II* – через 30 и *III* – через 90 мин пребывания животного в замкнутой камере). *в* – характер изменения процентного содержания O_2 и CO_2 (штриховая и сплошная линия соответственно) при подключении газообменного устройства (*1*) и без него (*2*)

Figure 2. The relationship of percentage content of O_2 and CO_2 to the rate of flow of water and gas. a--relationship of percentage content of O_2 and CO_2 in a gas mixture given different rates of its flow in relation to the membrane and given a constant flow of water at a rate of 40 ml/min; b--relationship of percentage content

of O_2 and CO_2 to the rate of flow of water in relation to the membrane given a constant output of gas at a rate of 40 ml/min. 1--laminar flow of water, 2--turbulent flow of water; solid line--percent CO_2, hatched line--percent O_2.

Key:
1. Gas ml/min
2. Water ml/min

Figure 3. Character of changes in EKG and rheoplethysmogram recordings of the thoracic cells and the gas content of the air mixutre in the chamber containing the animal given connection of the gas exchange device (a) and without it (b). I, II, III--stages of the experiment (I--initial indices, II--after 30 minutes and III--after 90 minutes of residence of the animal in the air-tight chamber. b--character of the changes in percentage content of O_2 and CO_2 (hatched and solid lines respectively) with connection of the gas exchange device (1) and without it (2).

Key:
1. RPG
2. EKG
3. b
4. minutes

Activation of the gas exchange device after the animal was in the chamber for 90 minutes did not result in any observable essential changes in physiologic indices (EKG, RPG). The gas content was found to be within the limits, acceptable for respiration. The increase in content of CO_2 in the gas composition was not observed but the content of O_2 was reduced to a constant value of 18.5 percent (figure 3).

The results of our investigation confirm that the use of a gas exchange membrane of the PVTMS type with a 1 m^2 area, given a flow of air at a rate of 0.25 l/min, is adequate to produce a flow of liquid volume of 0.5 l/min. In these conditions, recovery of a level of O_2 and CO_2 which corresponds to the content of alveolar air and to the level found in atmospheric air occurs in the gas mixture.

These established principles point to the fact that for an object placed in a state of rest, design of the surface of the membrane must be based on the required respiratory volume and the corresponding flow of water and gas relative to the membrane. For example, in order to ensure normal life activity of rats weighing 200 g and with a volume of respiration of 80-100 ml/min, it is necessary to have a gas exchange device with a surface area of

of 0.4 m^2 for a flow of water at a rate of 0.2 1/min. The relationship of the content of air in the chamber should not differ essentially from the atmospheric air.

In the second group of experiments, the area of the exchange surface of the gas exchange device was 0.2 m^2; that is, less than necessary for complete restoration of gas content. However, the flow of water was increased simultaneously to 0.6 1/min, which ensured complete elimination of CO_2.

Extrapolated data obtained in testing unit experiments were used to calculate the following: to completely restore the content of alveolar air to that of atmospheric air in aquanauts weighing 70 kg with a volume of ventilation of 6 1/min it is necessary to have an area of exchange surface of 24 m^2 for a flow of water of 12 1/min and for transfer of water. However, considering that the relationships are defined on the bases of tests to restore the content of the gas mixture to that of alveolar air and not exhaled air, then, in order to ensure the life activity, indices of O_2 content, lower than those used to designate atmospheric air, are adequate. One can assume that the exchange area in a concrete apparatus can be lowered to 8-12 m^2.

Thus, given an optimal selection of the proportions of the surface area of the membrane and the rate and character of the flow of liquid and gas, gas selective membranes can produce a volume of oxygen and hydrogen gas between the air and water media adquate for ensuring the life activity of biologic objects.

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MEDICINE

SOME PROBLEMS OF SPACE MEDICINE AND SPORTS

Moscow TEORIYA I PRAKTIKA FIZICHESKOY KUL'TURY in Russian No 12, Dec 1980 pp 49-52

[Article by Al. V. Sedov, doctor of medical sciences, Institute of Biophysics, USSR Ministry of Health]

[Text] Barely 20 years have passed since mankind made its first step in space. But in this short time, the intensive development of cosmonautics has already influenced the solutions to a number of theoretical and practical problems in various branches of science and technology. At present, it is even difficult to mention an area of human knowledge that was not beneficially affected by the conquest of space. More recently, there has been particularly intensive development of such an area of natural sciences as space medicine. This field, which emerged because of the needs of cosmonautics, has accumulated the advances in physiology, biochemistry, pharmacology, hygiene, clinical medicine and other biomedical disciplines. Space medicine deals with a rather wide range of problems, many of which are of definite interest to specialists in sports medicine. Since there are many aspects to the question of interrelation between space medicine and sports, they cannot, of course, be exhaustively discussed in a single article. For this reason, we deemed it useful to illustrate with several examples the feasibility of using the achievements of space medicine to train highly skilled athletes.

It is known that monitoring the heart rate, which is an integral indicator of neurohumoral regulation of the body, is among the mandatory and traditional methods of studying the condition of an athlete in the course of a medical examination. However, it is only in recent years, in connection with development of cybernetic conceptions in physiology of circulation, that it was established that the time organization of heart rate is closely linked with the state of neurohumoral regulation of the heart and adaptive activity of the integral organism [2]. Mathematical analysis of series of cardiointervals was used by Soviet researchers in experimental physiology, clinical practice, physiology of sports and space medicine [1, 9].

The possibility of determining the nature of neurohumoral regulation of circulation and deriving conclusions about the state of the entire body on the basis of the heart rate is particularly important to space medicine, where the volume of physiological information relayed from a spacecraft to earth is limited. In view of the fact that extraction of maximum information about a cosmonaut's functional condition with a minimal number of parameters is an important practical task of space biology and medicine, studies were conducted to find criteria for assessing the regulatory systems of the organism and degree of tension thereof on the basis

of analysis of the statistical characteristics of heart rate [22]. Studies were conducted on pilot-cosmonauts and athletes attending training meets. As a result of these studies, some rather distinct changes were demonstrated in the structure of the heart rate when changing from one state to another, which justifies discussion of the feasibility of using the rate of cardiac contractions as an integral indicator of functional activity of the body. In particular, in the course of these studies it was established that engaging in sports causes specific changes in the human body, which are directed toward optimum adaptation, chiefly to physical loads. The individual values of the statistical indicators of heart rate are of some practical interest in medical monitoring during training. Analysis of dynamic series of electrocardiograms revealed that the most appreciable differences in heart rate are observed in athletes, as compared to cosmonauts and individuals with average physical training. These differences consist of a higher daily variational scatter and lower mean daily amplitude of mode, higher parameters of 24-h adaptability and higher reciprocal correlation between the parameters in the circadian rhythm. On the basis of studies of regulation of function of cardiac automatism, some important information was obtained about the tonus of the sympathetic and parasympathetic branches of the autonomic nervous system, as well as functional state of subcortical centers and cerebral cortex.

Thus, evaluation of the degree of strain on the basis of analysis of heart rate, which has been refined for the purposes of space biology and medicine, is of definite importance to sports medicine, not only with respect to theory, but particularly practice.

There has been rather extensive introduction to space medicine of methods that permit determination of the degree of strain on regulatory mechanisms and functional reserve of physiological systems. In particular, functional tests are used for this purpose. For example, a physical load test is one of the most important ones in studies of the human cardiorespiratory system [3, 17, 27]. It has been proposed that the following method be used for complex evaluation of reactions to exercise of the cardiovascular and respiratory systems [4]. The subjects perform exercises corresponding to 600 kg-m/min for 7 min, pedalying on a bicycle veloergometer at the rate of 60±5 r/min. After this there is a 1-min recovery period. There are provisions for continuous recording of the heart rate on the ECG, oxygen uptake and carbon dioxide output on a Spirolit automatic gas analyzer. During the exercise tests, there is discrete determination of duration of phases of the left ventricular systole by the polycardiographic method, bioelectrical activity of the heart in the three leads of Neb, arterial pressure by the tachooscillographic method. Stroke and cardiac indexes are calculated by the indirect Fick method [8, 23] before the test, as well as in the 6th min of exercise and 10th min of the recovery period.

Studies conducted with the use of this test made it possible to demonstrate the distinctions of reactions of the cardiorespiratory system to a physical load. Some signs of poorer cardiorespiratory reactions in individuals who are and are not engaged in sports to exercise are largely related to fatigue and emotional stress [10, 12, 13, 15, 16, 21].

Prevention of disorders referable to circadian rhythms, as well as the possibility of predicting them, constitute a pressing problem of space biology and medicine. A change in biological rhythms is an essential and inevitable element of the process of adaptation of the body to altered living conditions, including the conditions of space flights. At the same time, questions of biorhythmology are becoming

increasingly important as well in sports activities [19]. Numerous experimental studies have shown that the circadian periodicity is characterized by a gradual rise in level of physiological reactions of the body in the daytime (to about 1600-1800 hours) and decline at night. The lowest level is observed at 0200-0500 hours. Special studies also demonstrated that the nocturnal decline of physiological reactions is observed not only during normal sleep, but during periods of intensive work at night. All this must, of course, be taken into consideration when scheduling performances by athletes, especially when far from home. However, studies dealing with the phenomenology of alteration of circadian rhythms on the theoretical basis of the conception of H. Selye [24] about stress were started relatively recently.

In this regard, studies of human circadian rhythms in the presence of stress factors, which were conducted with the problems of practical cosmonautics in mind, are quite interesting [20]. On the basis of experimental studies, the author concluded that desynchronosis of circadian rhythms is the biorhythmological correlate of the alarm reaction in the general adaptation syndrome. Exercise for 1 h, constituting up to 1200 kg-m/min, was the most intesive stress factor, with which there were appreciable changes in heart rate, arterial pressure and maximum changes in acrophases of circadian rhythms. Studies of heart rate, arterial pressure and body temperature were found to be informative enough for analysis of man's conditions in stress situations.

The obtained experimental data can be used not only in the practical support of long-term space flights, but for wise organization of schedules and evaluation of the condition of athletes.

Space flight conditions can lead to changes in functional state of the cardiovascular system, impairment of biochemical parameters and reduction of immunobiological reactivity; for this reason, specialists in space medicine and biology make rather wide use of pharmacological agents. A considerable amount of research was conducted in the Soviet Union and abroad to solve the special problems of space pharmacology.

Much attention was devoted to development of efficiency stimulators [7, 11, 25].

Products of the phenamine type are among the most widespread and potent stimulators of efficiency. These products can be recommended for intake on a one-time basis in critical situations that occur during space flights [26]. However, it must be borne in mind that phenamine can induce the opposite effect in 10-15% of the cases. Moreover, long-term intake of phenamine could deplete the nervous system and cause habituation [14].

However, with reference to methods of enhancing efficiency, one must take into consideration the basic difference in this matter as it relates to space and sports medicine. For example, an increase in dosage or repeated intake of products of the phenamine type in the case of considerable physical loads, against the background of depletion of catecholamine resources, could lead to acute cardiac insufficiency and even myocardial infarction. This explains the deaths among athletes who took phenamine and its analogues for doping purposes.

There is justification for experimental studies of stimulating properties of strychnine, ephedrine and caffeine. These general tonic agents are sufficiently

physiological, and their principal action is directed at stimulating metabolism and increasing efficiency [fitness] of the body.

In recent years, there has been a trend toward the study and use for intensive exercise of tonics of plant origin, or adaptogens. These substances elicit a state of increased nonspecific resistance of the body to the most varied factors, including physical loads. Numerous studies have confirmed that adaptogens (ginseng, eleuterococcus, "levzeya," "rodozina," acanthopanox root) enhance efficiency without having an appreciable stimulating effect, and they did not elicit any adverse changes in the function of viscera and metabolism [5].

Drugs used to improve nervous and mental stability also became the subject of in-depth medical research. It is known that emotional tension is associated, in particular, with excessive production of catecholamines by the adrenals. At present, drugs have been tested that actively intervene in the process of catecholamine synthesis. In this respect, the most promising are aminazin, trioxazin, meprotan, levopromazine and chlordiazepoxide [18]. In therapeutic doses, these products have a beneficial effect on neurotic states related to the feeling of internal anxiety, impatient anticipation, fear, restlessness and insomnia.

An important task for space medicine is to find the means of preserving health and maintaining high efficiency of cosmonauts. For this purpose, numerous studies were conducted over the last 20 years, as a result of which a rather large amount of information was accumulated about the reactions of various physiological systems and the body as a whole to the effects of the most diverse extreme factors, including physical loads. These studies broadened appreciably the conception of reserve capabilities of the organism.

The joint efforts of scientists of fraternal socialist countries in experiments conducted in the area of space biology and medicine, within the framework of the Intercosmos Program, were instrumental in solving such a complex problem as the reserve capabilities of the human body. A number of instruments, which were needed for experimental research on the functional state of cosmonauts, were developed by specialists in scientific institutions of the People's Republic of Bulgaria, Hungarian People's Republic, GDR, Socialist Republic of Rumania, Polish People's Republic and CSSR.

For example, one of the important biomedical problems is oxygenation of tissues when man is exposed to extreme conditions. The importance of knowing how tissues are supplied with oxygen in cosmonauts and people engaged in sports is obvious. For there are oxidative and reduction processes, as well as release of energy required for work, in tissues. The amount of oxygen required by the body depends on the specifics of his activities (physical work or rest), environment (air temperature, humidity, barometric pressure, etc.) and his state (calm, excited). For expressly this reason, the Oxymeter instrument, developed by Czech specialists, is of considerable value to this research; it permits examination of the dynamics of tissular oxygenation in man, both in space and on the ground.

Gathering diagnostic information needed to assure the safety of space flights is an important task for space medicine. Biological radiotelemetry serves as the principal investigative and monitoring method for this purpose. Space medicine has gained sufficient experience with miniaturized medical instrumentation, resistant to exogenous factors, for continuous remote monitoring of a man's condition, tested by the use of biotelemetry systems during space flights. At

present, some reliable methods have been developed for recording and transmitting via telemetry systems such physiological parameters as the ECG, EEG, blood pressure, seismocardiogram, kinetocardiogram, sphygomogram, electrooculogram, galvanic skin reflex and many others. These parameters have been recorded and relayed over telemetry channels both at rest and with graded loads [6].

Specialists in the field of space medicine developed methods for operational medical monitoring. Thus, for dynamic medical monitoring of a cosmonaut's pulse rate, a special device was used (cardiophone) which transforms the electrocardiogram into audio signals. Transmission of pulse signals by means of the cardiophone is the most elementary example of coding physiological information. In this case, the pulse rate is used as the integral indicator of intensity of the load on the body. The objectives of current programs include not only provisions for the minimum number of required readings, but obtaining an extensive range of information, which makes it possible to analyze the mechanism of the effects of space flight factors on man by means of radioelectrocardiography, radioelectroencephalography, radioelectromyography, radionystagmography, etc. The obtained biological data are processed on computers, with the use of effective diagnostic algorithms. At the present time, rather wide use is made of short-radius telemetry devices for transmission of physiological data from the body cavities (endoradiosonde measurements).

The problems related to the use of bioradiotelemetry in space medicine required many years of studies, conducted by physicians and engineers. The objective was to develop miniaturized and economical radio transmitters, small, multichannel radiotelemetry equipment impervious to interference, that would be able to transmit the maximum volume of information about man's condition over long distances. The advances of space medicine are closely linked with continued development of biological radiotelemetry, development of reliable systems for medical monitoring and medical examination. It will become possible to make broader use of this method in medicine when the main technical problems are solved, with respect to transmission of biological information in space physiology, aimed at reducing the weight and size of sensors, increasing economy and reliability of instrument operation.

Thus, the idea of continuous remote medical monitoring, which was brought to life for the first time during space flights, also had practical application to a number of branches of medicine, including sports medicine.

Use of miniaturized biotelemetry sensors to monitor athletes during training and competitions increases the capabilities of a trainer and hands to the sports physician a method for objective evaluation of the condition of an athlete who is at a considerable distance from the researcher.

In conclusion, it should be stated that the studies that are being conducted to solve such pressing problems of space medicine as the reserve capabilities of the human body, on-going medical monitoring of cosmonauts and predicting their health status on the basis of a minimal number of parameters, the search for adequate biostimulators to enhance efficiency and development of small-sized biotelemetry equipment capable of transmitting extensive information about man's reactions over long distances will, undoubtedly, have a beneficial effect on the continued development of medical science as a whole and sports medicine in particular.

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CARCINOGENIC ACTIVITY OF SYNTHETIC ASBESTOS

Moscow GIGIYENA TRUDA I PROFESSIONAL'NYYE ZABOLEVANIYA in Russian No 10, 1975 pp 31-35

[Article by L. N. Pylev, G. D. Koval'skaya, and G. N. Yakovenko, USSR Academy of Medical Sciences Institute of Experimental and Clinical Oncology, Moscow, submitted 13 Feb 75]

[Text] In recent years, both in our country and in the United States, Britain, Japan and the GDR, much attention has been given to the industrial fabrication of synthetic fiber materials of the asbestos type.

Synthetic asbestos is used for operation in superhigh temperature, high pressure and vacuum conditions, and also in certain sectors of the chemical industry.

The fibrogenic activity of synthetic asbestos has been studied by A. G. Valagov et al. It was found that Na, Mg-amphibole, manganese-fluorine-amphibole and synthetic chrysotile all display fibrogenic activity; in the last-named it was lower than in natural chrysotile asbestos.

No research at all has been done on the blastomogenic properties of synthetic asbestos.

Materials and Methods

We studied synthetic chrysotile and Na, Mg-hydroxyamphibole, which can be regarded as an analog of natural magnesium arfvedsonite, obtained using the hydrothermal method. Samples were synthetized at the USSR Academy of Sciences Institute of Silicate Chemistry imeni I. V. Grebenshchikov.

Making synthetic asbestos by the hydrothermal method eliminates the possibility of contamination with combustion products from the fillers. They do not even contain the traces of such metals as Ni, Cr, Al and others that are found in natural asbestos as the result of ore impurities (N. I. Nesteruk et al; D. P. Sinovskiy et al; M. V. Soboleva, A. D. Fedoseyev et al).

Asbestos materials were pulverized for 6 hours in an agate mortar; this was done at the Sverdlovsk Scientific Research Institute of Labor Hygiene and Occupational Diseases. The degree of fineness of the sample was determined under an optical microscope at 15 x 90 magnification (see table 1).

Table 1. Particle Fineness of Synthetic Asbestos Studied

Type of asbestos	Size of particles (μm) up to 1	1 - 5	6 - 10	above 10
Synthetic chrysotile asbestos	37.3	53.3	1.7	7.7
Synthetic Na,Mg-hydroxyamphibole	44.7	53.3	2.0	-

The size of the particles of the pulverized synthetic chrysotile was very close to a sample of commercial chrysotile asbestos that we (L. N. Pylev) had studied. More than 90 percent of the particles were smaller than 5 microns. The degree of fineness for the pulverized Na,Mg-hydroxyamphibole was somewhat greater than for commercial magnesium arfvedsonite. Whereas in the former, 98 percent of particles were smaller than 5 microns, the number of particles of this size in the natural asbestos was about 50 percent; in both samples, however, most particles were smaller than 10 microns.

Some 125 mongrel rats (63 females and 62 males) weighing about 100 grams were used in the experiments. A total of 64 animals (33 females and 31 males) was administered 3 intrapleural 20-mg doses of synthetic chrysotile asbestos in the form of a suspension of physiologic solution. The interval between administration of the doses was 1 month. Using the same method, synthetic Na,Mg-hydroxyamphibole was administered to 61 rats (30 females and 31 males).

Only animals that died were studied, and the histologic processing of material was the same as that used in the study of natural asbestos.

Experimental Results and Discussion

Pretumor changes and tumors found in the rats that received the synthetic asbestos materials are shown in table 2.

When 60 mg of synthetic chrysotile were adminstered, premesothelioma changes were found in the animals and diffuse, uneven hyperplasia of the pleural mesothelium was found more often.

A single, dense node was found in the pleural cavity in only one case, in a male that had died 24 months and 25 days later. Histologic studies showed that it was a benign fibrous mesothelioma.

In the experiment with Na,Mg-hydroxyamphibole, when 60 mg of the substance were administered premesothelioma changes were found at a level several percentage points higher than in the experiment with chrysotile (see table 2). Moreover, in a number of animals, pleural tumors were found. The first pleural mesothelioma was found in a rat that had died after 330 days of observation. As the time period of the experiment was prolonged, the percentage of tumors increased. Of the 24 animals that died 200 to 400 days after the start of the experiment, pleural mesothelioma was found in 6 (25 percent), while of the 22 rats that died after 400 to 600 days pleural mesothelioma was found in 14 (63.64 percent). Mesotheliomas were found in a total of 54.5 percent of cases and there was no difference between males and females in the frequency of tumors.

Table 2. Morphologic Changes Found in Rats After 3 20-mg Doses of Synthetic Asbestos Administered Intrapleurally at 1-Month Intervals

Changes	Period of death (in months) when synthetic chrysotile was administered			Period of death (in months) when synthetic Na,Mg-hydroxy-amphibole was administered	
	up to 1 (n=6)	1 - 9 (n=17)	10 - 29 (n=41)	1 - 9 (n=17)	11 - 21.5 (n=44)
Localized hyperplasia and epithelial proliferation in the bronchi without flat-cell metaplasia			1		
Diffuse uneven hyperplasia of the pleural mesothelium		6	12	6	17
Localized hyperplasia of the pleural mesothelium		5	9	1	16
Fibrous pleural mesothelioma			1		
Adenomatous pleural mesothelioma					2
Sarcoma-like pleural mesothelioma					11
Carcinoma-like pleural mesothelioma					5
Mixed-structure pleural mesothelioma					6
Pulmonary reticulosarcoma			1		1
Suprarenal adenoma			1		
Fibroadenoma of the breast			3		
Total of pleural tumors			1	24 (54.54% m±7.5)	

Females 52.170% m±10.4
Males 57.14 % m±10.8

Results from the experiments conducted indicate that synthetic chrysotile asbestos possesses very weak blastomogenic properties. Whereas in experiments with natural chrysotile, tumors have been found in 65.5 percent of cases (L. N. Pylev), in experiments with the synthetic analog, a benign fibrous pleural mesothelioma was found in only one rat.

Synthetic Na,Mg-hydroxyamphibole also turned out to be considerably less blastomogenic than natural asbestos. When 3 20-mg doses of commercial magnesium arfvedsonite were administered to rats intrapleurally at 1-month intervals, pleural mesothelioma was found in 77 percent plus or minus 5.4 cases.

As we have already indicated, the degree of fineness of these dusts was about the same. However, the mixtures differed in regard to chemical composition. In the chrysotile we studied there were more iron oxides (1.25-5 percent by weight) than in the synthetic analog (0.53 percent). In the natural asbestos there was also a mixture of the oxides of various other metals (Ni, Al, Cr, Mn). There were also substantially greater numbers of iron oxides in the natural magnesium arfvedsonite (12.5 percent) than in the synthetic Na,Mg-hydroxyamphibole (2 percent).

A number of writers (Cralley; Morgan and Cralley; Morgan and Holmes) link the blastomogenic nature of asbestos with contamination by various metals, in particular, Ni, Cr and Fe. The carcinogenic activity of Ni and Cr is well known (Ya. M. Grushko, P. P. Dvizhkov and V. I. Fedorova; A. V. Saknyn and N. K. Shabynina; V. I. Fedorova; Hueper and Conway). Evidently iron itself is not carcinogenic, but in complexes with dextran, dextrin, sugars and glutamic acid it acquires carcinogenic properties (Hueper and Conway). The idea has also been suggested that the relationship between trivalent and bivalent iron plays an important role in the mechanism of blastomogenic action in asbestos, and moreover, carcinogenicity is linked with a low relationship (Harington and Roe).

Evidently the idea that metallic impurities have a role in asbestos blastomogenesis is not without foundation, as our experiments show. However, it is hardly possible to use this alone to explain the malignant action of asbestos on the mesothelium. Synthetic Na,Mg-hydroxyamphibole still induced mesothelioma in 54.5 percent of cases, and this indicates its strong carcinogenicity. This is also indicated by the experiments of Gross and Harley, in which the percentage of pleural tumors in rats was the same when asbestos was administered without metallic impurities or enriched with metals.

The morphologic picture of the premesothelioma and mesothelioma changes found did not differ from the experiments with other kinds of asbestos we have described elsewhere (L. N. Pylev; L. M. Shabad et al), and we therefore consider it possible that in this paper we need not dwell on them in detail. The diffuse hyperplastic processes in the mesothelium were characterized by the appearance across extensive areas of the pleural surface of first or second order epithelial-like or fibroblast-like cells with a basophilic cytoplasm and light or hyperchromic nuclei. The sites of mesothelial cell proliferation were distinguished by the marked polymorphism of the structure. There were solid, papillary, glandular or mixed structures in the proliferation of epithelial-like and, infrequently, fibroblast-like cells. Carcinoma-like mesotheliomas were of a solid, glandular and glandular-papillary structure. They consisted of large polymorphous cells similar to epithelial

cells (figure 1). Their mesothelial origin was indicated by the large number of intracellular and intercellular vacuoles containing hyaluronic acid found in them. Since the mesothelial cells have a specific function of secreting this acid mucopolysaccharide (Stout and Lattes), a test for hyaluronic acid is now suggested as a diagnostic test for mesothelioma (Boersma et al; Kannerstein et al; Wagner and Berry; Wagner et al; Winslow and Taylor). In terms of the histologic structure, sarcoma-like mesotheliomas of the pleura did not differ from those we have found elsewhere. They were both fusiform and polymorphic; secretions of hyaluronic acid were also found in them. The mixed-structure mesotheliomas possessed the greatest polymorphism. They may be divided into predominantly carcinoma-like, where products typical of carcinomatous mesothelioma were preponderant (see figure 2), and predominantly sarcomatous. The detection of hyaluronic acid in the cytoplasm of the cells and intercellular vacuoles in these tumors indicated their mesothelial genesis.

Pleural mesotheliomas elicited in rats as the result of administering asbestos are similar in structure to those described by many authors (Churg; Hourihaue; McCaughy; Thomson) in man. Further study of the blastomogenic activity of various kinds of asbestos and the pathogenesis of the pleural tumors they induce will assist in the development of measures to prevent the occurrence of these neoplasms in man.

Conclusions

1. The administration of synthetic chrysotile asbestos into the pleural cavity of rats elicits very weak blastomogenic activity.

2. Synthetic Na,Mg-hydroxyamphibole induced pleural mesotheliomas in 54.5 percent of the rats.

3. The lower blastomogenic activity in the pleural mesothelium of rats caused by synthetic asbestos is possibly explained by the absence of various impurities in them (metals, rock and so forth). However, the high carcinogenicity of Na,Mg-hydroxyamphibole indicates its significance in the mechanism of the action and in the basic structure of the substance.

4. The morphologic picture of premesothelioma changes and of pleural tumors was similar to that found in experiments with natural asbestos.

5. Results from the experiments with synthetic asbestos indicate that in principle it is possible to make less carcinogenic asbestos materials.

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PHYSIOLOGY

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AUTOMATION OF NEUROPHYSIOLOGICAL EXPERIMENTS

Leningrad AVTOMATIZATSIYA NEYROFIZIOLOGISHESKOGO EKSPERIMENTA in Russian 1979

[Annotation, foreword, introduction and table of contents from a monograph by K. N. Dudkin and V. Ye. Gauzel'man, edited by V. D. Glezer, Izdatel'stvo "Nauka", 1650 copies, 160 pages]

[Text] On the basis of their own and published materials, the authors analyze new approaches to the organization and performance of neurophysiological experiments with the use of automation and computing machinery. They describe methods of automatic control of experiments, simulation and identification of neuron structures. An analysis of the methods of express processing of neurophysiological data is given. New designs of electronic equipment for the automation of neurophysiological studies, circuits of devices and instruments, and their operating principles are described. Bibliography -- 128 items, figures -- 83.

Foreword

At the present time, probably, no physiologist doubts that the use of automation and computing machinery in physiological studies raises them to a higher level and broadens the limits of creative thinking of the investigator who can propose and verify more complex hypotheses much faster and accelerates the process of maturation of new ideas, thus increasing considerably the effectiveness of investigations. However, this is not the only importance of the automation of experiments. The use of computing equipment makes it possible to obtain a practical output of the results of physiological studies connected with the development of models of data control and processing principles in physiological systems. It can be assumed that such models are urgently needed in modern technology, for example, in developing various robots.

It is evident that there is also no doubt that automation and computing machinery produce the highest degree of effectiveness in physiological studies when they become the usual everyday tool of the scientists. This goal was set during the organization of the Biological Computation Center in the Institute of Physiology imeni I. P. Pavlov. The ten-year experience of the

existence of the computation center in the Institute of Physiology has shown that such a center is a scientific subdivision uniting the creative efforts of biologists and physiologists in solving practical problems and in constructing theoretical principles of the functions of living matter. The experience of the work of the computation center has shown also that the introduction of automation and computing machinery in physiological studies is accomplished in several stages. At the present time, one of the urgent needs is the automation of physiological experiments.

The monograph by K. N. Dudkin and V. Ye. Gauzel'man is undoubtedly important because it formulates many aspects of the automation of experiments in a physiological laboratory and shows on concrete examples the possibility of accomplishing such experiments.

The monograph is particularly valuable because it shows how the use of automation and computing machinery makes it possible to solve the problem of the analysis of electrophysiological data in a new way. Apart from the classical methods of the processing of physiological information in the process of the experiment, it is possible to solve a number of new problems one of which is the identification of neuron structures based on the experimental data. This method leads to a direct practical result -- development of bionic models. The authors used concrete examples of their work to show the unquestionable advantages and merits of such an approach.

The publication of this monograph is timely due to the rapid introduction of mathematics in physiology which increasingly broadens the use of automation and computing machinery in it and the increasingly acute problems of practical realization of the results of physiological studies.

K. P. Ivanov

Introduction

It is urgently needed to increase the effectiveness and methodological level of modern neurophysiological experiments. There is no doubt that the solution of this problem depends on the degree of the application of automation and computing machinery in studies. It is possible to isolate three aspects in the problem of the automation of neurophysiological experiments.

The first aspect is connected with the automatic control of experiments, the second has to do with automatic registration of the experimental data, and the third is formulated as automatic processing and analysis of the bioelectric activity. The solution of these problems depends on the technical facilities in physiological laboratories and institutes. In the process of modern electrophysiological experiments, the investigators obtain a huge amount of data whose processing, undoubtedly, must be conducted automatically in the process of the experiment, which is impossible in the absence of appropriate computing machinery. It is also obvious that, in order to set up a controlled experiment, it is necessary to use not only electronic computers, but also various external devices for the recording, coding, and introduction of information into the computer.

Our experience in the work on the problem of automation of neurophysiological experiments makes it possible to conclude that at the present time there is a gap between the needs of modern electrophysiological experiments in increasing their effectiveness and methodological level and the state of affairs which formed as a result of or the absence of computing machinery in physiological laboratories, or its limited use.

A considerable progress in the solution of this problem was made by the organization within physiological institutes of subdivisions similar to the Biological Computation Center created in the Institute of Physiology imeni I. P. Pavlov. The organizational principles and scientific goals of such a computation center were clearly and exhaustively formulated in the monograph by K. P. Ivanov and A. S. Kleshchev [44]. The analysis of the operation of the Biological Computation Center shows that such scientific subdivision increased greatly the effectiveness of physiological studies. First of all, it became possible for the physiologists to process experimental data by computers, to gain considerably in time, and to use mathematical methods of analysis which were inaccessible before. Moreover, there appeared new aspects of studies connected with the identification and simulation of neurophysiological mechanisms. These methods are a bridge between the fundamental direction of studies and the direction connected with the introduction of the results of studies into practice. In fact, formalized descriptions and models of physiological mechanisms serve as a good foundation for developing methods and devices for information processing, i.e., a new technique based on physiological principles.

There is no doubt that we cannot imagine physiological institutes of the present and the future without such scientific subdivisions as a computer center with one or several large electronic computers. However, there still remain many unsolved problems with regard to the automation of experiments which, along with the above-mentioned approach, require a somewhat different methodological approach.

Experience of the Biological Computation Center shows that, in practice, neither controlled experiments with the use of a large digital computer, nor data processing in the process of the experiment have been used widely [44]. Evidently, there are deeper reasons than merely a shortage of large computers. The point is that one of the notable phenomena in modern computer techniques is the tendency toward distributing computations and information processing, and spreading a computing and controlling operations over numerous points of the system.

From this viewpoint, the most modern facility is a neurophysiological facility with distributed automatic controlling and computing devices which has access to a large central digital computer. However, there are no systems for controlling physiological experiments with such devices.

A good example of what a fully automated experiment can be is the modern physical experiment with the use of computing and controlling systems which fully satisfy the needs of the experimenter [49]. This became possible

as a result of the development of new directions in computer engineering based on the achievements of integrated electronics. Minicomputers and microprocessors were developed which found wide application in various computing and controlling devices. Computing potentialities of minicomputers and microprocessors and their relatively low costs are the main prerequisites for their mass penetration into technology and science in the future, including physiology. However, even in this case, there will still remain specific peculiarities and difficulties of the automation of neurophysiological experiments which researchers will have to solve.

The purpose of this book was to share some experience accumulated by the authors in the process of such work.

The authors are deeply grateful to V. D. Glezer, under whose direction they started many years ago to work on the most fascinating problem -- the problem of visual perception, for his constant help and support in their work. The authors are also sincerely grateful to K. P. Ivanov for his support in the work on this book, to N. F. Baskina, V. A. Kislyakov, T. G. Malinnikova, V. D. Rodinov for reviewing, constructive discussions and criticisms, as well as to all their co-workers: I. V. Anan'yeva, Ya. A. Bedrov, S. K. Yegorov, V. A. Ivanov, A. S. Kleshchev, N. B. Kostelyanets, L. I. Leushina, A. A. Nevskaya, N. N. Nikitina, G. I. Novikov, M. B. Pavlovskaya, A. I. Panin, Zh. A. Pershin, N. F. Podvigin, N. V. Prazdnikova, V. L. Temov, I. V. Chuyeva, Yu. Ye. Shelepin, L. V. Shperl, P. Ya. Fink, and T. A. Shcherbach.

Contents

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DYNAMICS OF VEGETATIVE RESPONSES WITH VOLUNTARY CONTROL OF ALPHA RHYTHM

Moscow FIZIOLOGIYA CHELOVEKA in Russian Vol 5, No 5, 1979
pp 927-930

[Article by V. G. Markman, Institute of Physiology imeni I. P. Pavlov, USSR Academy of Sciences, Leningrad, received by editors 5 Dec 77]

[Text] The problem of the connection of voluntary changes in the alpha rhythm with changes in the vegetative indexes still remains insufficiently studied. Recently an attempt was made to establish connection between changes in the intensity of alpha rhythm during voluntary control, the heart rate, and the cutaneogalvanic reaction measured simultaneously [1]. As a result of this, it was proposed that the interaction between these parameters, if it exists, must occur with a definite time shift. The purpose of this work is to verify this assumption.

Method

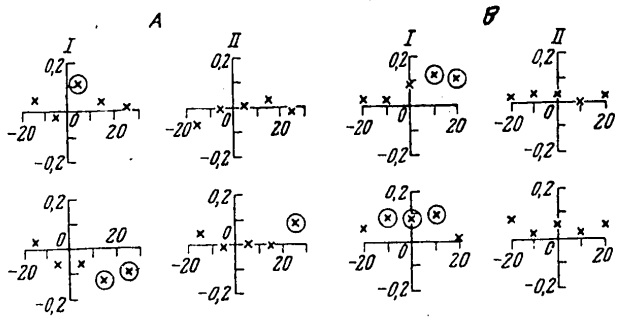
The method of the experiment was described by us earlier [1, 2]. For the values of parameters of the alpha rhythm intensity, the R-R interval of the EKG, and the constancy of skin resistance obtained in the initial background and in tests with feedback (OS) for each 10 s, the coefficient of the correlation between momentous values and during shifts of values of vegetative indexes in relation the values of the alpha rhythm by one and two 10 s sections in the direction of advancement or delay were calculated in pairs. Due to the special technical characteristics of the method, the value of the R-R interval was measured at the beginning of the following 10 s section. This delay by 5 s in relation to the value of the integral of the alpha rhythm envelope was taken into consideration in plotting the points on the chart.

Thus, it was possible to evaluate both the degree of the connection of changes in the vegetative indexes and the alpha rhythm in the process of training and the time of interaction between them.

The obtained correlation coefficients were averaged by nine tests with OS of three sessions separately for Group I (five subjects who were able to cope with the problem of the alpha rhythm increase) and for Group II (five subjects who were unable to cope with the problem). The significance of the difference of the averaged coefficients from zero (at a 5% level) was checked by Student's t-criterion.

Results of Studies

Figure (A) shows the data on the connection between the intensity of alpha rhythm and value of the R-R interval in the initial background and in tests with OS for two groups of subjects. Analogous data on the connection between the intensity of alpha rhythm and the constancy of skin resistance are also shown (Figure B).



Average values of the coefficients of the correlation of the intensity of alpha rhythm with the value of the R-R interval of the EKG (A) and with the constancy of skin resistance (B) for groups of subjects I and II in the background (upper row) and in tests with OS (lower row). Along the X-axis -- the value of the shift of the values of vegetative indexes in relation to the values of the alpha rhythm (in s); ("-" -- advancement, "+" -- delay). Along the Y-axis -- average value of the correlation coefficient. Values differing significantly from zero are circled.

Places occupied by five subjects of Group I by the degree of training, expression of the studied correlation, and the number of times the OS signal was turned off

Effectiveness of training	Contribution to correlation	Number of times the OS signal was turned off
1	5	5
2	1	1
3	4	4
4	3	2
5	2	3

On the average, Group II was characterized by values of the coefficients which did not differ significantly from zero, while the values of the correlation coefficients in Group I often differed significantly from zero. There was no positive difference between the parameters in the initial background and in the tests with OS for Group II, while Group I showed structural changes in the connection between the intensity of alpha rhythm and the length of the R-R-interval of the EKG. The positive values of the correlation coefficient which are characteristic for the initial background

at a 5 s delay shift are replaced by negative correlation at a 15-25 s delay which differs reliably from the background correlation. The positive correlational connection between the intensity of alpha rhythm and the constancy of skin resistance in the background does not change its nature in changing to tests with OS, shifting only by 10 s in the direction of advancement.

When analyzing the obtained data, it is necessary to keep in mind that Groups I and II differed reliably with respect to the average intensity of alpha rhythm in tests with OS in relation to the background (1.15 and 0.89; $t = 4.284$; $p < 0.01$) but did not differ in the relative values of the R-R-interval (0.98 and 1.00; $t = 0.683$; insignificantly). However, a lesser variability of the mean values of the vegetative indexes was observed for Group II as a whole [1].

The figure and the time parameters of the correlations of the intensity of alpha rhythm with the value of the R-R-interval and the constancy of skin resistance in the background in the subjects of Group I are characteristic for activation (depression of alpha rhythm, tachycardia, increased KGR [galvanic skin reflex] caused, to all appearances, by the orienting reflex or by the readiness to work. It will be recalled that the feedback indicator in the background test was turned off and could not be the cause of activation. The change to work with the OS signal (for which we used the change of digits on the indicator during the period when alpha rhythm exceeded the threshold level) caused a sharp structural change in the connection of alpha rhythm with the R-R-interval. The sign of correlation changed from positive to negative, i.e., the increase of alpha rhythm in the tests with OS was accompanied by tachycardia.

In order to find out whether or not this connection depends on the training, the subjects were arranged in order of decreasing effectiveness of training and this order was compared with the order of the degree of expression of negative correlation at +15 s (first and second columns of the table). The class correlation index for this pair of columns is -0.4, i.e., this dependence is not connected directly with the degree of increase in the alpha rhythm under these conditions.

It was assumed that this dependence is a component of the emotional response of the subject to the stopping of the digits on the display board at the end of the outburst of alpha rhythm. Indirectly, this is indicated by the latent period of its manifestation increased against the norm [3]. Therefore, the third column of the table gives the place occupied by the subject with respect to the number of the stopping of digits on the indicator board (stopping for a time less than 1 s was not taken into consideration). The class correlation indicator for the second and third columns is 0.9, which also confirms the above-mentioned assumption.

Discussion of Results

The idea that the reproduction of positive emotional experiences can be accompanied by an increase in alpha rhythm was confirmed by the data of many experimenters. Nevertheless, in the operant determination of alpha rhythm, the question was never posed directly about the possibilities of emotional reaction to the OS signal itself, although it was often mentioned that the trained parameter changed similarly under the effect of instructions or a false OS. Therefore, it is quite appropriate to assume that at least in some subjects the mechanism of the alpha rhythm increase in

the appearance of an emotional response to the OS signal. But the on and off positions of the indicator in the tests do not occur in isolation, but follow one another quite frequently. In this case, it is evident that there must occur interference of emotion-producing stimuli which, with various time structures of the OS signal, can weaken or intensify the emotional reaction whose role is usually underestimated in experiments with OS. For a more strict verification of our assumption, it would be necessary to examine the characteristics of the reinforcement (its probability) and the motivation level of the subject [4], as well as to have an evaluation of the vegetative reactivity during emotional states.

The background of the subjects of Group I had a complex of conjugate changes involving both the cortex (changes in the intensity of alpha rhythm), and the vegetative nervous system. There is no doubt that the hypothalamus participates in the organization of such reactions because it is the control center of vegetative functions and, moreover, it is capable of diffusely stimulating the cortex [5]. Vegetative manifestations of emotional responses in the process of work with OS are also realized through the hypothalamus. The subjects of Group II, on the contrary, did not have any marked signs of orientation or emotional responses. But regardless of whether or not the detected peculiarities of the functional organization of hypothalamocortical connections are based on the differences between the groups, they are of interest in themselves both for preliminary selection of subjects, and for professional selection of special groups. A sufficiently large number of classifications of human operators on the basis of the properties of the central and vegetative nervous systems are known [6-8].

It is still difficult to understand why negative correlation is maintained at a shift of +25 s in Group I. But the assumption about the emotiogenic effect of the OS signal makes it possible to explain the absence of analogous correlation in Group II partly by the fact that, due to the marked depression of the alpha rhythm, the OS display was turned on in this case much rarer. The positive correlation at a shift of +25 s which was noted in Group II reflects a vigorous contribution of one subject and is not characteristic of the group as a whole.

As for the differences in the background between the groups, they cannot be explained by the changes in the state of the indicator, since the latter was disconnected. They observed lesser changeability of the mean values of the vegetative indexes in the subjects of Group II is supplemented by the absence of dynamic connections in the intensity of the alpha rhythm with the indexes of the vegetative nervous system. The environment and the experimental conditions were, of course, identical for both groups. The average values of the R-R interval (0.84 and 0.85 s) were practically identical ($t = 0.209$; insignificant), the average variation coefficients of the value of the R-R interval were also of the same order -- 7.2 and 5.3% ($t=1.666$; insignificant). The variation coefficients of the alpha rhythm intensity also did not differ significantly -- 14.2 and 13.9% ($t=0.147$; insignificant). Thus, the absence of the correlation of the alpha rhythm intensity and the value of the R-R interval which is characteristic of the orientation response cannot be explained by their lower variability.

Conclusions

1. The ability of the subjects to increase their alpha rhythm in the experiment with feedback is reflected in the dynamic correlational connection of alpha rhythm with shifts in the vegetative indexes.

2. The differences in the subjects, evidently, reflect the differences in the functional organization of the hypothalamocortical connections and can serve as a criterion for preliminary division of the subjects during professional selection.

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HEMISPHERIC ASYMMETRY OF P_{300} WAVE IN RESPONSE TO UNRECOGNIZED EMOTIONAL WORDS

Moscow ZHURNAL VYSSHEY NERVNOY DEYATEL'NOSTI in Russian Vol 30, No 3, 1980
pp 467-475

[Article by E. A. Kostandov and Yu. L. Arzumanov, Central Scientific Research Institute of Forensic Psychiatry imeni V. P. Serbskiy, Moscow, submitted 6 Apr 79]

[Text] Numerous studies of individuals with a "split brain" revealed that when visual information is delivered only to the right hemisphere it is not verbalized or recognized [7-10]. At the same time, the same studies established that analysis and synthesis of verbal signals take place not only in the left, but in the right hemisphere, although to a substantially limited extent in the latter. R. Sperry [9] believes that people with a "split brain" have two independent areas of consciousness. In his opinion, each hemisphere has its own area of consciousness with regard to perception, cognition, volition, learning and memory. This applies to the right hemisphere as much as to the left, although the latter can "speak." Eccles (see [12]) critized this opinion of R. Sperry. He believes that the right hemisphere is able, like a computer, to perform complex discrimination, recognition and learning acts, but is entirely wanting in conscious experience.

We expounded a hypothesis, according to which activation of temporary associations, with involvement of structures of the motor speech zone of the left hemisphere [1, 2], is of decisive importance to perception ["recognition, realization"] of any exogenous stimulus to explain the neural mechanisms of the effects of unrecognized emotional words. We believe that mental reactions to unrecognized signals, with their somatovegetative and bioelectric components, can develop as a result of a difference in thresholds of activation of temporary associations making up the functional system that reflects and emotiogenic situation. In cases of prolonged and strong experiences of negative emotions, the most plastic changes apparently occur in the neurons of the brain that are related to emotional behavior. As a result, there is marked increase in excitability of temporary associations between sensory elements of the neocortex which perceive emotional signal stimuli, in particular verbal ones, and structures of the limbic system, in which there is integration of neural mechanisms of negative emotions. This could lead to excitation of the above temporary associations, even under the influence of a stimulus that is physically very weak but emotionally meaningful, and development of the corresponding emotion, without activation of temporary associations with the motor speech region in the left hemisphere, as a result of which the stimulus would not be recognized.

More recently, M. Gazzaniga and J. LeDoux [8] arrived at an analogous assumption of the decisive role of the "verbal system" of the left hemisphere to perception of an exogenous signal, on the basis of psychological experiments on individuals with a "split brain." In essence, they repeat the above point of view concerning the conditioned reflex mechanism of so called unaccountable emotions, when their cause is not perceived by the subject.

Some authors believe that there is a rather direct [straight] correlation between unconscious mental phenomena and activity of the right hemisphere [6, 11]. In addition to the works cited, which refer to studies on people with a "split brain," these authors refer to some clinical and electroencephalographic data to confirm their view: patients with a lesion to the right hemisphere have virtually no imaged dreams; at the stage of REM sleep, when there is the highest probability of dreams, greater activation of the background EEG is observed in the right hemisphere [11]. In our opinion, the view, according to which the right hemisphere is the "source" of unconscious motivation but, at the same time, that it makes a typical contribution ("its own voice") to performance of mental functions on a conscious level [5], is more acceptable. This opinion is consistent with the conception of mutually complementary "collaboration" between the two hemispheres in the process of performance of any mental function, and of the predominant role of one hemisphere only at a certain phase of this function.

We were unable to find any works dealing with comparison of cortical activity of the left and right hemispheres during perception of unrecognized stimuli or other unconscious mental activity. Yet the direct registration of cortical activity could be of substantial help in understanding the role of a hemisphere in physiological mechanisms of the unconscious. In the past, we recorded the averaged evoked cortical potential from the left occipital region in response to unrecognized words delivered to the center of the field of vision [3]. We demonstrated changes in the P_{300} wave related to the unrecognized emotional word, and this served as grounds to use recording of the P_{300} wave to study interhemispheric relations in the course of perception of unrecognized verbal stimuli.

Methods

We studied 11 men ranging in age from 18 to 39 years (mean age 24.5 years) who were right-handed and had normal vision. All of the subjects were in a difficult conflict situation. Six tests were conducted with each subject. During the experiment, the subject was in a semireclining position in a special chair, in a soundproof cubicle, with their eyes open. The Nova-2/10 of the Data General Company (United States) computer was used to control the experiment, record and average bioelectric activity, following a program that was specially prepared by our colleague, S. A. Pogrebinskiy. The visual stimuli were neutral words ("field," "heat," "rice," etc.) and emotional ones which had a bearing on the subject's conflict situation ("wife," "knife," "children," "court [of law]," etc.). The verbal stimuli appeared on an electroluminescent screen that was 80 cm away from the subject's eyes. The stimuli were delivered at irregular intervals, with random pauses (3 to 10 s), out of order and in random order to different halves of the field of vision, 5 cm to the right and 16.5 cm to the left of the fixation point in the middle of the screen counting from the beginning of the projected word. We realize that, for an obvious and inevitable reason, the angle of vision is not the same on the left (10.5°) and right (3.5°) if measured in relation to the beginning of a word. The stimuli were exposed for 15 ms. The letters in a word measured

4×2.5 cm each, and words consisted of 3-5 letters; words with the same number of letters were presented to different visual fields in the course of one test. Illumination constituted 0.05 lux ±20% in the vicinity of the screen. The light was green. The subject was not aware of the stimuli at any time, as we determined from his verbal report after each test. All of the subjects stated that they saw a dull flash on the screen. The experiment was begun after 5-min dark adaptation. The following instructions were given in advance: "Look attentively only ahead, at the luminescent point; do not turn your head; words will appear from time to time to the right and left of this point, try to identify them and remember how many times they appear."

The exploring electrodes were placed on the vertex, on the occipital part of the skull (2.5-3 cm above and 3 cm to the left and right of the occipital protuberance), in the left and right "associative" regions (halfway between Pz in the international system 10-20 and the mastoid process); the last derivation, we believe, was from the region of the angular gyrus at the boundary between the occipital parietal and temporal regions. The reference electrodes were situated on the left and right mastoid processes. The potentials were fed, through amplifiers of an ME-132 electroencephalogram of the Nihon-Kohden Company (time constant 0.3 s), to the input of a Deytel analog-digital converter, with analysis epoch of 1024 ms and frequency [sampling rate] of 1024/s. In order to determine the EEG isoline, averaging of bioelectrical activity was started 300 ms before delivery of a stimulus. Averaging was performed per 50 reactions, separately for stimuli delivered to the right and left half of the visual field. In the course of the experiment, the current averaging of evoked potentials was flashed on the graphic NR 1311A display for visual monitoring and, at the same time, it was recorded on the magnetic tape of an Ampex (United States) digital recording device.

The latency period (LP) and amplitude of positive wave (P_{300} component) of the averaged evoked potential (AEP) were measured automatically by the computer after determination by the experimenter of its peak and peak of preceding negative oscillation on the graphic display. The results obtained were submitted to variance analysis, and we calculated the reliability of differences according to Student.

Results

A P_{300} wave with LP of 353±2.6 ms is derived from the left occipital region and 347±4.5 ms from the right occipital region in response to presentation of an unrecognized neutral word to the contralateral visual field (Figure 1). The difference is statistically unreliable ($p>0.05$). No significant interhemispheric difference in latency period of P_{300} is demonstrable with analogous presentation of unrecognized emotional words (LP 342±5.3 ms on the left and 346±3.3 on the right; $p>0.3$). However, in this case there was one distinction: LP of P_{300} is almost reliably shorter for the left occipital region in response to emotional words ($t = 1.92$ according to Student; $F = 4.79$ according to Fisher; df - 1/10; $p>0.05$) than neutral ones; this is not observed in the right hemisphere.

We failed to demonstrate appreciable interhemispheric differences in LP of P_{300} in response to neutral and emotional words in the "associative" region (as we suppose this is the region on the boundary between the temporal, occipital and parietal regions) (Figure 1). In the region of the vertex, LP of the P_{300} wave is unrelated to the visual field to which the stimulus was presented or to the signal meaning of the stimulus. For example, LP constituted 355±4.2 ms in response to a neutral word in the left visual field and 353±3.4 ms in response to an emotional word.

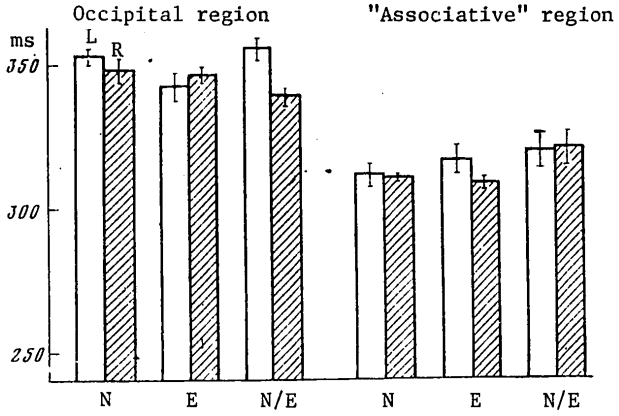

Figure 1. Latency period of P_{300} wave in left and right hemispheres in response to unrecognized words presented to the contralateral field of vision

Key:
- L) left hemisphere
- R) right hemisphere
- N) neutral words
- E) emotional words
- N/E) neutral words against the background of "unaccountable" emotion

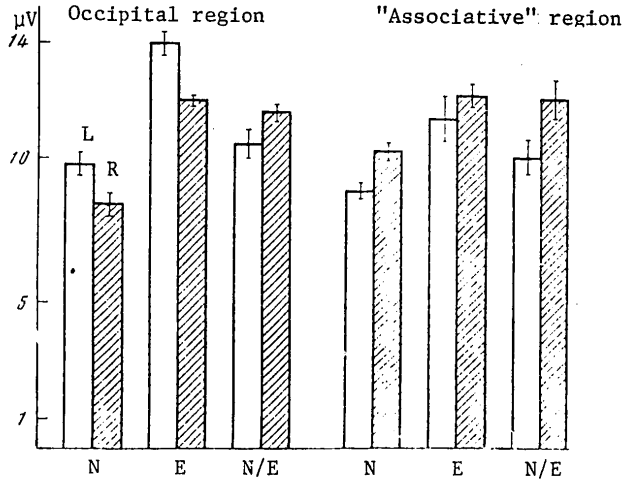

Figure 2. Amplitude of P_{300} component in left and right hemispheres in response to unrecognized words delivered to contralateral field of vision. Designations are the same as in Figure 1.

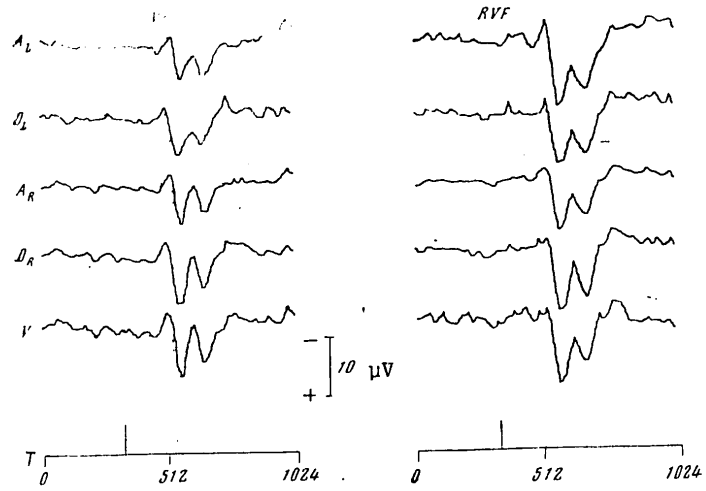

Figure 3. Averaged evoked potentials in response to unrecognized neutral verbal stimuli. Subject D. LVF--left field of vision; RVF--right. The word "field" delivered to left visual field and "sea" to the right. The line going from the time scale indicates time of stimulation

Key: A_L, A_R) associative regions of left and right hemispheres
O_L, O_R) occipital regions of left and right hemispheres
V) vertex
T) time scale, ms

Considerably greater differences are observed in amplitude of P_{300} wave, both between hemispheres and between neutral and emotional words (Figure 2). In response to exposure of a neutral unrecognized word to the contralateral visual field, P_{300} constitutes 9.8±0.38 μV in the left occipital region and 8.4±0.35 μV in the right ($p<0.01$).

There is significant increase in ampliutde of P_{300} wave in the occipital region in response to an unrecognized emotional word, as compared to a neutral word ($F = 118.9$; df - 1.10; $p<0.001$). As can be seen in Figure 2, this increase occurs in both hemispheres, as a result of which the interhemispheric difference is retained: the P_{300} wave is substantially larger on the left than the right (14.0±0.36 and 11.9±0.17 μV, respectively; $p<0.001$). One can also see the increase in amplitude of P_{300} wave when one compares Figures 3 and 4, which illustrate the AEP curves in response to a neutral and emotional word, respectively.

An increase in amplitude of P_{300} in response to an emotional stimulus is observed not only in the occipital region, but in the "associative" ($F = 16.9$; df - 1.5; $p < 0.01$). The amplitude of the potential in response to emotional words also increases in the vertex, regardless of the visual field to which they are presented (Figure 4). For example, the value of P_{300} in the right visual field is 10.6±0.48 μV

in response to neutral words and 14.7±0.59 μV ($p<0.001$) in response to emotional ones; in the left visual field, the values are 10.5±0.46 and 12.6±0.36 μV, respectively ($p<0.001$). Thus, there is an increase in the P_{300} wave in response to an unrecognized emotional word in all regions of the cortex we recorded, without appreciable changes in interhemispheric correlations that are observed under the influence of unrecognized neutral stimuli.

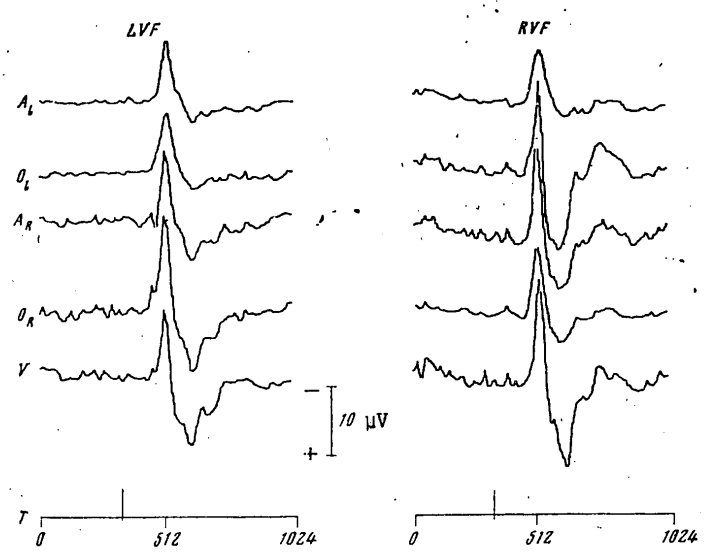

Figure 4. Averaged evoked potentials in response to the unrecognized emotional word, "wife." Subject D. Designations are the same as in Figure 3.

Other correlations were demonstrated in response to unrecognized neutral verbal stimuli delivered against the background of "unaccountable" negative emotion. Figure 1 shows that the LP of the P_{300} wave in response to neutral words presented against an "unaccountable" emotional background differs somewhat (it is longer or shorter) than the LP of the potential in response to the same stimuli, which is recorded in a "calm" state. The influence of an emotional background is also demonstrable in variance analysis of LP of potentials in the occipital ($F = 6.7$; $df - 1.10$; $p<0.05$) and "associative" ($F = 11.2$; $df - 1.5$; $p<0.05$) regions. However, these changes are quite vague and concrete analysis shows them to be statistically unreliable. Thus, the change is more marked in the right occipital region (Figure 1), but it also fails to reach statistical significance ($t = 1.86$).

An "unaccountable" emotional background has a more definite effect on the amplitude of P_{300}. It increases in all of the regions we recorded, as compared to a "neutral" background, but there are substantial interhemispheric differences (Figure 2). The increase in amplitude of potential is insignificant and does not reach statistical reliability. For example, in the left occipital region, the amplitude of P_{300}

constitutes 9.8±0.48 μV in response to a neutral word in the contralateral visual field against a neutral background and 10.5±0.48 μV against an emotional background; in the associative zone, the figures are 8.9±0.3 and 10.2±0.6 μV, respectively. In the right hemisphere these differences are overtly more marked: the amplitude of P_{300} is 8.4±0.35 with a neutral background and 11.6±0.28 μV with an emotional one ($p<0.001$); the figures for the associative region are 10.3±0.3 and 12.1±0.7 μV, respectively ($p<0.05$). The uneven increase in amplitude in the left and right hemispheres leads to inversion of interhemispheric amplitude differences in P_{300} (Figure 2): the P_{300} is more marked in the right hemisphere against the background of "unaccountable" emotion, rather than the left, as observed in response to the same stimuli delivered against a neutral background or under the effect of unrecognized emotional words.

The P_{300} wave in response to neutral unrecognized words presented against an emotional background is also larger in the region of the vertex, as compared to the wave in response to analogous stimuli in tests against a neutral background. The degree of this increase is overtly related to the visual field to which the stimulus is presented: in response to a stimulus delivered to the right visual field, amplitude of P_{300} is 10.6±0.48 μV against a neutral background and 11.8±0.51 μV with an emotional one ($p<0.2$, i.e., the difference is insignificant); if the stimulus is delivered to the left visual field, i.e., information is delivered directly to the the right hemisphere, the amplitude constitutes 10.5±0.16 and 14.1±0.53 ($p<0.001$).

Thus, against the background of "unaccountable" emotion induced by an unrecognized word, we observe a diffuse increase in evoked potential of P_{300} in response to neutral signals, but it is significantly greater in the right hemisphere, and this leads to a change in interhemispheric relations.

Discussion

Unrecognized emotional words having a bearing on a subject's conflict situation induce considerably larger P_{300} in the cortical hemispheres than neutral words. The increase in potential is diffuse; it is observed not only in the occipital and "associative" regions, but in the vertex. These data confirm the previously obtained facts concerning reflection of the results of semantic analysis of an emotional stimulus on the unconscious level in evoked cortical activity [3].

The potential increases almost identically in both hemispheres, and for this reason interhemispheric relations remain the same as in the tests with neutral words, i.e., its amplitude is obviously greater in the left hemisphere than the right. Analysis of the latency period of the P_{300} wave also failed to demonstrate that an unrecognized emotional verbal stimulus affects interhemispheric relations.

The tests with recognized emotional words revealed overt changes in interhemispheric relations in analysis of the latency period and amplitude of P_{300} wave [4]. A recognized emotional verbal visual stimulus elicited lateralized local cortical activation, more marked in the left occipital region, rather than the right, as in the tests with neutral words. Stimulation of emotional integrating mechanisms in the limbic system led to displacement of local activation in the direction of the left hemisphere. There was only diffuse cortical activation under the influence of unrecognized emotional words, which was almost identical in both hemispheres, and for this reason interhemispheric relations did not change. One comment is indicated

here: When we refer to the absence of changes in interhemispheric relations in the course of perception of unrecognized emotional words, obviously they are not demonstrable with our method of analyzing these relations by means of the time and amplitude parameters of the P_{300} wave. Perhaps a different, more refined analysis would demonstrate some distinctions with regard to asymmetry of the hemispheres related to the processing of unrecognized, emotionally meaningful verbal information. With this comment, by no means are we suggesting to question the efficacy of this method for studies of functional asymmetry of the hemispheres. On the contrary, as shown by analysis of the amplitude of the P_{300} wave in response to neutral stimuli delivered against a functional background, induced by unrecognized emotional words, this method demonstrates quite effectively the changes in interhemispheric relations.

Numerous works (see [2]) have demonstrated the influence of unrecognized words on various physiological and psychological functions. In particular, unrecognized emotionally meaningful words may elicit so-called unaccountable emotions, when the subject is not aware of their cause [2]. In this study, we believe that it was demonstrated for the first time that there is a significant change in interhemispheric functional relations under the influence of an unrecognized emotional word. Activation of mainly the right hemisphere leads to inversion of interhemispheric relations observed in a "calm" state. We cannot state how long this effect of an unrecognized emotional word lasts, since the test neutral stimulus is delivered only 3-10 s after the unrecognized emotional word. Additional studies are needed to answer this question.

Interestingly enough, the above-described consistent effect of an emotional word on interhemispheric relations, in the form of unilateral activation of the right hemisphere, is not observed in tests where such a word is recognized. In this case, there is mild activation of both hemispheres limited chiefly to the occipital region [4].

Thus, two aspects of the problem emerge when one studies the link between unconscious mental phenomena and functional asymmetry of the hemispheres. In the first place, this refers to interhemispheric relations directly in the process of perception of an unrecognized emotional stimulus. We failed to demonstrate any distinctions here, so that we cannot refer to the predominant or special role of a hemisphere in the processing of unrecognized verbal information. In all likelihood, the perception process on the unconscious level also occurs with interaction of both hemispheres, each of which makes its contribution to integral function. The second aspect refers to interhemispheric relations that occur after an unrecognized emotional word, as a result of its effect. The distinct functional asymmetry of hemispheres then observed is indicative of the predominant role of the right hemisphere in organization or cortical control of such an unconscious mental function as unaccountable emotion.

Conclusions

1. The late evoked potential of P_{300}, which appears in response to an unrecognized emotional word, increases diffusely in both hemispheres, as compared to the response to a neutral word. This is not associated with any change in interhemispheric relations.

2. Unilateral activation of the right hemisphere is observed in the period of aftereffect of an unrecognized emotional word.

3. The right hemisphere plays a predominant role in cortical organization of unaccountable emotions.

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THE NORMAL AND DISEASED HUMAN BRAIN

Leningrad ZDOROVYY I BOL'NOY MOZG CHELOVEKA in Russian 1980 (signed to press 4 Jun 80) pp 2-11, 208

[Annotation, introduction and table of contents from book "The Normal and the Diseased Human Brain", by Natal'ya Petrovna Bekhtereva, Izdatel'stvo "Nauka", 5500 copies, 208 pages]

[Text] In this monograph, factual material is presented which is based on a number of proven concepts of fundamental significance for the study of the structural-functional organization of the human brain, how the brain is responsible for various forms of activity and the role of the independently-shaped memory in these processes. The possibilities and prospects for the development of future studies on the mechanisms of the human brain are examined in the book. Bibliography--385 references; illustrations--19; tables--2.

Introduction

> In order to obtain success, it is necessary to establish goals somewhat higher than those which can be attained at the present time.
>
> Max Plank

A critical moment in the development of the field of human brain physiology occurred in the second half of this century. It stemmed from the results of fundamental and applied investigations and creative application of the theories of experimental physiology of the human organism, taking into account its qualitative uniqueness and the special development of the field of brain physiology. Experimental study had been all but impossible in this discipline.

Developed by synthesizing knowledge of the processes for life activity of the diseased and healthy human organism, thereby guaranteeing exceedingly rapid growth of the methodologic

possibilities for study of the molecular, cellular, organ and organism mechanisms, physiology of the human brain has been transformed into a more productive aspect of the field of theoretical medicine. The results, conceptually valuable and adequately organized for neurophysiological investigations, are used in neurosurgery and neurology. The development of specific directions in fundamental physiological research has also led to understanding of the underlying physiology upon which well-founded treatment of psychic disorders is based. Data on the physiologic provisions for psychic processes are utilized more widely by philosophers to resolve the problems of the material bases of the ideal.

Progress in physiology of the human brain is important not only for therapeutic practices. It is necessary for expansion of the possibilities of preventative medicine and the proper organization of pedagogical processes in this century of the scientific-technical revolution.

Interest in the mechanisms for the activity of the human brain is long-established. In essence, this question lies at the foundation of various world-view and philosophical constructions.

The first real scientific representation of brain responsibility for certain human functions dates back to the nineteenth century. There are well known results from clinical-anatomical correlations, giving support to--and now we have the right to state--hard data showing that some structures of the brain are related principally to these functions. The experiments led to some basic corrections in the initial theories, however their place in the history of human brain physiology is still of undisbuted importance.

The works of I.M. Sechenov and I.P. Pavlov have enormous significance for the study of human brain physiology. There is no doubt that creative study of their contributions must and still can yield new "ripe fruit" for practical medicine. The concept of P.K. Anokin on the mechanisms of the brain are significant for general biological governing principles and are valuable, especially given its practical orientation, not only for understanding of but also for directed mobilization of the reserves of the brain. In analyzing the mechanisms of the healthy and diseased brain, it is necessary to consider the concept of D.K. Belyayev on the influence of factors in the external environment and those which arise in the reconstruction of the organism during the development of its genetic properties.

The physiology of the human brain is related closely to psychology because one of the branches of psychology--neuropsychology--

can be considered as a related discipline of equal importance to the fields of psychology and physiology. However, it would be incorrect to underestimate, in the development of the field of physiology of the human brain, the role of its connection with biochemistry, molecular biology, mathematics, physics and cybernetics. Thus, data from clinical-anatomical correlations, general biological theory and the broad possibilities of various scientific fields were fundamental to the construction of a foundation for the field of physiology of the human brain.

These disciplines and data obtained from their application were of special importance when the physiological approach was applied to the brain, providing new means for penetrating into its mechanisms.

Until recently, in fact up to the last decade of this century, physiolcgy did not have the key to study the detailed neurophysiological mechanisms of the human brain or its neurophysiologic dynamics. Now, because of the possibilities opened by stereotaxic neurosurgery and modern technology, productive ways to study the structural-functional organization and neurophysiology of the human brain have been found. Use of the discipline of physiology of the human brain yielded much material and provided new directions of research.

However, study of the most complicated of organs--the human brain--will,for a long time,produce a greater collection of questions than answers. Simple comparison of results from physiological and morphological studies sometimes not so much reveals the secrets of the brain as establishes a blind alley for the scientist. Thus, undoubtedly, a special examination of the problem of transfer of information within the human brain is necessary. Data obtained by analytical means is very difficult to interpret using an integrative approach. It is also difficult to compare the properties of a single neuron with those of an assembly of neurons; even functionally united assemblies acquire new qualities which do not arise as a result of simple stimulation of the properties of separate units.

Evidently, there exists in the brain of humans and animals innate, genetic determinants which,as a result of ontogenesis,are responsible for the properties needed to detect certain direct signals. During ontogenesis, the human begins to distinguish a multitude of signals from the outside world, including quite complex vocal ones. A human can not only distinguish,but can also utilize brain images of a signal as operative units. This occurs primarily because of the influence of the nerve assembly and the systems for independently shaped (long-term) memory which organize the activity of a specific assembly responsible for completing a task. Are such circuit networks known? Bio-

chemists consider the protein S=100 to be the most probable candidate, however, it has not been linked to a specific activity. The specificity arises from the particular organization of the system (Hyden, 1978), however, the specificity at the biochemical level is still unclear. The significance of this question, which assumes the influence of memory on the function of the brain, led to the development of research on modulation, directed by the mechanisms of memory, although the very mechanisms for these influences were not yet examined. This approach was successful and some of the prospective lines of research could be used to study neuropeptides. To date, however, there is still no basis to expect a quick, easy and complete victory.

The most difficult questions concerning brain activity are related to the global sequence. Modern sociologists are anxious for the human brain to cope with the abundance of information, with the growing and ever-increasing requirements for it. The creative brain power of geniuses and talented individuals is a pre-requisite for dealing with the scientific-technical revolution. This scientific-technical revolution, built on the work and talent of millions, in turn makes enormous demands on the brain. An enormous flow of information is conducted through man's eyes and ears. His brain, whether he wishes it to or not, reacts to this flow. Is there a real danger that the human brain can not deal with such a complex information flow?

The theoretical aspects of experimental physiology led to an hypothesis for basic principles, by which the brain develops an inter-dependence with the external environment. Human neurophysiology must try to answer the following questions: in what form will occur the possibility of not only colossal individual advancement, exhibiting the potential of an individual's brain, but also a sharp transformation to a new level of interaction with an increasingly complex environment? In less than two generations, the human brain has been shown to be capable of adapting to an almost entirely new world.

What will become of the human brain if the load on it increases with more enormous acceleration? Will the brain develop mechanisms for self-preservation and self-protection? Will its development and organization systems be more vulnerable? Will the system which provides emotion surrender to those which provide intellectual activity? Or, on the other hand, will it fail to protect its intellectual functions from overload? Will it become necessary to "neutralize", to suppress the system which provides emotion and presumably thereby expand the scope of the intellect? Or will the brain somehow become attuned to signals for distress of this protective valve?

Among the most complex problems are those which require clinical solutions for protracted disorders of the brain. Actually, in such cases, would the disease begin to fight against the doctor, against the treatment?

Thus, for example, the doctor tries to eliminate the focus and origin of epileptogenesis--the area of anatomical damage to the brain. The doctor utilizes anti-epileptogenic therapy to combat the disease, always prepared to deal with the formation of new foci of epileptogenesis. Unfortunately, the doctor does not always conquer the disease. While the source of epileptogenesis is eliminated locally, without inflicting new sources for disease provocation, in other, previously quiescent regions of the brain, sources of epileptogenesis are activated. Is the epileptic brain conditioned genetically, is it influenced by various external and internal cuases, including the very disease which alters the organism and alters the brain?

A surgical procedure for Parkinsonism has been conducted successfully. The patient is satisfied and the doctor is pleased. However, the doctor knows that it is necessary to wait before being assured of success. Even after success at the operating table, signs of a supposedly exhausted disease could appear again after several weeks, when edema of the brain, evidently already long passed, reappears. The disease can resist stubbornly, circumventing the surgical and pharmacological traps set for it by the doctor.

Examples of this type fill clinics for somatic medicine. They include hypertonic disease, for which the use of pharmacologic agents and their doses vary all the time, ulcer disease and many other protracted disorders. However, in the clinics for treatment of diseases of the brain, they are especially unexpected. In the human brain, both in the majority of cells and cellular connections, many cells and cellular ensembles are originally poly-functional; that is, prepared to serve the functions of both emotional and intellectual activity. Where are these reserves when they are especially needed? Could they be controlled? Are there brain mechanisms not only for prophylactic protection from damage, mentioned above, but also defenses to combat the existing affliction? Supposedly there are, but how can the doctor make use of them?

These questions do not represent an exhaustive list and in fact, no such list exists. But it is necessary to try to answer them. The sooner the better.

Of great significance in a scientist's life is making a contribution to the treasury of science, to rightfully have his name

linked with some factor or theory, to be recognized as having opened slightly the heavy door to the mysterious life of nature. In this pursuit, there is happiness and despair, flights of thought and struggles to find the truth with oneself, with colleagues, with opponents and living and dead authorities. So it is. There are troubles in the otherwise very fortunate fate of the scientist-theoretician. However, the fact that the scientist works both in the field of theory and in close proximity to sick people, thereby sharing with the doctor the responsibility for the patient's fate or answering for it, can make up for the difficulties and misfortunes of the endeavor.

"Right" solutions in science are not recognized ("solutions" are not recognized!). Mistakes are detected in your own work or in someone else's (by the way, it is still not known which category has greater numbers). The doctor is unable to save the sick. He does everything but can not anticipate all eventualities, or allow for all possibilities. Not all the facts are always brought to his attention. Or he can not risk fighting with the disease. Or he is unable to help because, as stated in other instances, medicine in that area has not advanced far enough. The first case is a result of the judgement of a few people. The second case is the result of the incurability of the specific disease. It is the responsibility of the scientist to try to resolve these problems. In the literature, the problem of responsibility for not being an accomplished person is, in my opinion, fully and beautifully shown by Ibsen in "Peer Gynt".

The incomplete problem always has a precise address in the sphere of production, but no known one in the field of science. This question is very complex. Unresolved and undecided problems exist today for which a good deal remains to be done.

One should emphasize that in the field of physiology of the healthy and diseased human brain, as well as in other fields of science, it is now especially important to correlate and examine critically existing assets and prospects, to evaluate the level and degree of resolution of problems and their definition.

At the end of 1962, at the Institute for Experimental Medicine of the USSR Academy of Medical Sciences, a section was created to study various theoretical problems. This led to the study of the physiology of the human brain. In close contact with neurologic and neurosurgical clinics, together with physicians from municipal treatment establishments, K.K. Rodionov and L.I. Nikitina and their scientific co-worders began to develop approaches to and principles for the study of human neurophysiology, to assimilate materials accumulated in previous experi-

ments, to translate it and to create new technical-methodologic solutions.

For the past two decades, a large amount of multi-planned material in this field has been accumulated, correlations have been carried out and concepts which open up new scientific directions have been advanced and confirmed. From the very beginning,physiologists in the section worked with doctors, neurosurgeons and neuropathologists with the highest qualifications. Also, from the outset, a large number of the co-workers in the section were specialists with technical training.

The overwhelming majority of the problems in neurophysiology can be resolved only by the study of man directly. The precise study of the mechanisms of the human brain is being conducted on people with diseases, the treatment and diagnosis for which are accomplished with the aid of methods used in stereotaxic neurosurgery.

From the outset, one firm law regarding the work of the section was the absolute priority of solving tasks necessary both for diagnosis and treatment of a particular disease. The co-workers at the section knew that,above all, each study and each procedure must serve a specific disease entity. Not one measure which might negatively influence the patient would be carried out. No potential use of "great" science on patients was allowed if the act could be potentially harmful or not justified in the best interests of the given patient.

By following this approach, scientific material, revealing many mechanisms of the diseased and healthy brain,was accumulated. Diagnostic and therapeutic investigations were organized in the form of collection, correlation and analysis of material. The first aspect of the question--the safety of the patient and medical ethics--was controlled entirely by the neurosurgeons and neuropathologists of the section, and the second aspect was resolved by a creative collaboration of physiologists with engineers, mathematicians, physicists and cyberneticists. Thus for example, in one complex method for treatment of a specific disease, a multitude of long-acting electrodes were used. As is known, this process was used in the 1960's without the combined application of precise calculations or co-ordinated with stereotaxic techniques (Bickford et al., 1953; Bates, 1961; Walter, Crow, 1961 and others).

The introduction of electrodes in the early stages of work of the section was accomplished not only on the basis of stereotaxic calculations, but also with the aid of electronic computers. The computer not only accelerated the calculations and made them

more precise, but in time led to the creation of stereotaxic methods, competitive with all others. Data obtained from one patient on the use of calculations for placement of electrodes were shown to be comparable with data obtained in subsequent tests. The findings of the studies at the clinics showed that physiological investigation of patients in analogous conditions can be accomplished with the aid of certain methods (electroencephalography or recording of neuronal activity) or a combination of methods (EEG + neuronal activity + evoked potential --EP). All possible physiological indices for brain activity were recorded (EEG, ESKoG [not further identified], neuronal activity, EP, low-velocity electrical processes (LEP), the voltage of oxygen (pO_2), local blood flow, impedance and a series of others) both at rest and the dynamics of the physiological state of the test individual who was given various functional tasks. Data were obtained in conditions of direct contact with the brain through activation of the electrodes, expanded by results of studies on the state of capillaries, dermato-galvanic response, electrocardiography and others. These same indices were recorded for diagnostic and therapeutic electrical potentials through activated electrodes. This approach not only increased the volume of obtained information but provided the opportunity to correct the location of the electrodes in relation to individual variations of the brain, to obtain related additional data on the state of various structures of the brain and finally, to provide optimal methods or a complex of methods for study of one or another function. Thus, the limitation of a single method approach to the study of various phenomena of brain activity was overcome. This work, done in close creative contact with representatives of other scientific fields, allowed adaptation and development of methods for goal-oriented extraction of information from data on physiological observation and use of telemetry--to expand the scope of examined physiological and pathological states. A polymethodologic approach to the organization of research studies promoted a significant growth in existing scientific directions and created a number of new ones for various aspects of physiology of the human brain.

Thus, for example, in the study of the structural-functional organization of the human brain, data accumulated by section members were substantially increased. In fact, stereotaxic neurology, used by the section at the outset of the study on the structural-functional organization of the brain, is, in its very exactness and detail, already a qualitatively new direction in this field, similar to the relationship of clinical biochemistry to molecular biology.

If the study of brain provisions for psychic activity led to

elucidation of the role of deep structures of the brain in this process, then, consequently, general principles of the brain organization for a given system were uncovered and the presence of apparatus for fixed and flexible networks was shown. In depth investigation of the given problem, in turn, led to development of a new direction--study of the brain code for psychic processes.

Study of the neurophysiology of psychic processes, naturally, requires an in depth examination of the problem of memory--originally it was considered conditio sine qua non. Results of electrical stimulation of the brain and recording of its physiological indices laid the ground work for a more serious approach to this problem. Up to the present time, neurophysiological study of memory represented an independent direction of study, an ideological spur for concepts on the regulation and self-regulation of the processes of memory.

Study of the emotional sphere of the brain has produced a multitude of concepts which underscore different aspects of the problem. Many of them can be examined as related additional concepts, however, some of the related and not-so-related ones in psychology were not based on, prior to our work, knowledge of internal human brain neurodynamics, which develop for emotional reactions and states. If the study of brain provisions for intellectually supported processes is simply not possible in animal experimentation, then, in terms of brain participation in emotion, extrapolation of experimental data to human processes is far from correct at all times. Perhaps, it is more correct to state that data on brain provisions for human emotion help to understand more fully unclear results from animal experimentation.

By this time, the first neurophysiological studies on patients with activated electrodes had generated exceptional interest and valuable material which demonstrated the similarity between functions of the brain system in emotional and basic intellectual activity and highlighted their differences. The inseparable emotional and psychic spheres in man can and must be studied from an analytical approach to neurophysiological phenomena. Its components should be studied separately and from integrated approach. Presently, members of the section have compiled unique material on brain neurodynamics, directly related to its involvement in emotional reactions. A hierarchy of connections in a given brain system has been outlined. However, the study of neurophysiological participation in emotion is far from complete. It must be continued as is true for work in fields of other related problems. It would be dangerous and incorrect to consider that complete data have been obtained on the brain

provision for emotion. However, there are, at the present time, results which allow a scientific approach to the study of this problem on a qualitatively new level.

In terms of theory, some of the most important problems are far from new, such as the problem of the characteristics of the functional state of the brain and its relation to realization of brain function. This problem became particularly important with the accumulation of data on the poly-functionality of many neurons and neuronal populations. Much energy has been spent,with a relatively low return,on attempts to utilize EEG recordings for the purposes of obtaining identical characteristics of the functional state of the brain. Full-fledged characteristics were not obtained even with the aid of supplemental information provided by instrumentally-mathematical methods. The possibilities for reliable study of the mosaics and dynamics of the functional state of the brain were expanded by using, in addition to EEG recordings of separate components of the low-velocity electrical processes, relatively stable and weaker ones--and correspondingly more dynamic signals. This approach not only opened up new possibilities for theoretical study of the problem but also presented a whole series of practical approaches to existing questions.

A poly-methodologic approach to the study of brain physiology expanded knowledge of the physiological principles governing the healthy and diseased brain. As a result, data were compiled, although not completely analyzed and reviewed, on the relationship and inter-dependence of various physiological processes of the brain. Thus, new possibilities for probing the physiological nature of recorded electrical and non-electrical processes were created. As is evident from what has been shown, this is far from a complete list of the directions of physiology of the human brain. Their development must and can serve to elaborate the most important questions in theoretical physiology of the brain.

The accumulation of facts on the dynamics of protracted pathological processes can lead to advancement in understanding the role of resistent pathological conditions and reactions, which, in the pathogenesis of protracted diseases of the brain, is of central importance. New methods have been proposed for treatment of diseases of the brain and scientifically based possibilities for use not only of reserves but also the protective forces of the brain have been uncovered.

The development of the field of brain physiology has not only enriched medical and pedagogical theory and practice. The discipline has provided new treatment for sick people and new data for the improvement of technical systems. Now physiology of the

human brain has begun to serve cybernetics. In the long process of evolution, the human brain was created as a system capable of devising other systems to serve it. For all its merits, the modern computer is still not capable of reproducing all the properties of human brain function. Revelation of the laws according to which the brain realizes its own special properties and the formalization of them, can and must serve as the basis for development of technical systems.

The basic stages of research on the physiology of the human brain have been reflected in published reports, collections and monographs in various degrees of similarity. The task of the present work is to present, on a new level, the most important aspects of the problem, taking into account its development in our laboratory and in other USSR laboratories and in foreign centers. In relation to the terms "analytical and integrative", this book attempts to present an integrative approach to that which constitutes the present basic nucleus of the scientific discipline of physiology of the human brain.

Contents

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9139
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ANIMAL AND HUMAN BIOCHEMISTRY

Kiev BIOKHIMIYA ZHIVOTNYKH I CHELOVEKA. VYPUSK 4: BIOKHIMIYA BELKOV NERVNOY SISTEMY in Russian 1980 (signed to press 25 Jun 80) pp 2-3, 93-94

[Annotation, foreword and abstracts from book "Animal and Human Biochemistry", edited by Ye. T. Tal'nova, Izdatel'stvo "Naukova dumka", 1000 copies, 94 pages]

[Text] This collection contains survey articles that shed light on the distinctive features referable to composition, physicochemical properties, metabolism and functions of nervous tissue proteins, including neurospecific proteins. Much attention has been devoted to a description of the distinctions of levels, properties and functional activity of proteins during sleep, learning and development of memory. Some articles discuss protein metabolism in the brain as related to different functional states of the organisms, while others deal with the role of proteolytic enzymes in metabolism of central nervous system proteins under normal and pathological conditions, as well as under the effect of ionizing radiation and antibrain antibodies.

It is intended for workers concerned with problems of biochemistry, physiology and pathology of the nervous system.

Foreword

1980 will mark the 95th birthday of the founder of the school of Soviet neurochemists, Aleksandr Vladimirovich Palladin. For this reason, the office of the Scientific Council for the Problem of "Animal and Human Biochemistry" of the Ukrainian Academy of Sciences has decided to dedicate this collection to questions of neurochemistry and to publish articles by prominent Soviet scientists who are working on pressing problems of protein metabolism in the structures of nerve tissue. The editorial board tried to select articles that would shed different aspects of protein metabolism in nerve tissue under normal conditions, in the presence of various physiological, extreme and pathological states in animals, as well as during learning, which is a specific function of the brain.

At the different stages of development of functional neurochemistry in our country, work on many of the above-mentioned problems was begun in the laboratory of A. V. Palladin. The main results of these studies are briefly summarized in the survey by Ya. V. Belik. Studies of nerve tissue proteins, their physicochemical and biological properties, including functions specific to nerve tissue, distinctions of protein metabolism in the brain in the presence of different functional states of the nervous system, which were started in the laboratory of A. A. Palladin were then developed extensively in neurochemical laboratories of institutes and chairs of VUZ's of our country. The advances in these branches of neurochemistry were

described in the survey articles of G. Kh. Bunyatyan et al., P. A. Kometiani, N. G. Aleksidze, N. B. Kozlov et al., I. A. Sytinskiy, S. Kh. Khaydarliu, M. B. Shtark et al. Analysis of data pertaining to the properties and role of enzymes of protein catabolism under normal conditions and in the presence of certain pathological states of the nervous system is made in two of the articles in this collection (by G. A. Vilkov et al., and A. D. Reva et al.).

Abstracts

UDC: 612.8+547.96+155.3

"Protein Metabolism of the Brain During Learning," by N. G. Aleksidze, pp 4-11

Experimental data are submitted that deal with metabolism of cerebral proteins during the learning process. The opinion is voiced that the proteins synthesized in the brain during training should not have signal significance. Specific proteins and enzymes are used in processes of formation of temporary contacts to create informational ensembles of neurons.

Protein synthesis in the brain is strictly controlled by the level of excitability of informational and regulatory systems. The changes in protein metabolism will vary, depending on the nature of training and alteration of functional organization of the brain, as a result of changes in the specific effect of the physiological load on the genetic system.

Bibliography lists 82 items.

UDC: 571.1:612.822.1

"From Chemical Topography of the Brain to Neurospecific Proteins and Their Functions," by Ya. V. Belik, pp 11-22.

This survey briefly describes the main results of many years of research conducted by the founder of Soviet neurochemistry, Academician A. V. Palladin, and his disciples; it also summarizes data characterizing the topographic distribution, fractions, heterogeneity of rates of in vivo renewal of proteins, as well as the properties, distribution and activity of intracellular proteinases in morphologically and functionally different macrostructural and microstructural elements of nerve tissue, its subcellular and suborganoid structures, in the presence of different functional states, in philogenetic and ontogenetic aspects. A special place is occupied by the results of studies of neurospecific proteins, particularly the physicochemical, immunological and therapeutic properties of the main encephalitogenic protein, myelin, and its antigenic determinant.

Tables 2; bibliography lists 92 items.

UDC: 612.82+612.015.348:616-001:15

"State and Metabolism of Brain Proteins During Exposure to High Ambient Temperature," by N. B. Kozlov, T. V. Alenina and N. M. Stunzhas, pp 22-28.

Data are submitted that describe protein metabolism in different parts of the brain and some low molecular nitrous compounds as related to different degrees of

overheating of the organism. The obtained results indicate that during exposure to high ambient temperature there is increased dissociation and, on the contrary, diminished rate of protein synthesis in the brain. Studies of levesl and reactivity of different functional groups, as well as of general ultraviolet spectra of brain proteins revealed that overheating of animals is associated with profound structural changes in proteins of the brain, which have a complex mechanism of development and are related to the degree of hyperthermia and functional distinctions of different parts of the brain. These changes cannot be induced by direct heating to 45°C of isolated brain tissue or heating of proteins extracted from it in vitro.

Bibliography lists 29 items.

UDC: 612.-8.015+577.23

"Mechanisms of Involvement of the DNA-RNA-Protein Triad in Functional Activity of the Brain," by P. A. Kometiani, pp 29-39

An effort was made to prove that the genetic system participates in memory phenomena by synthesizing functional proteins, inhibited biosynthesis of which impairs memory. Neurotransmitters, in particular biogenous amines, play the leading role in gathering neurons into ensembles and activation of the genetic system. Their effect on the genetic system is implemented by 3-,5'-AMP. Specific changes in distribution of biogenous amines, and hence effects on behavioral acts can be induced by psychotropic agents and loading animals with small doses of free amino acids.

The information coded in the genetic system is reflected in behavior through biosynthesis of enzymes that regulate the levels of neurotransmitters in the brain.

Bibliography lists 112 items.

UDC: 616.832-002-097:612.015-348

"Proteolytic Activity of Brain Tissue in the Presence of Neuroallergy and Under the Influence of Antibrain Antibodies," by A. M. Mendzheritskiy, I. B. Vovchenko, G. A. Vilkov and R. A. Trapezontseva, pp 40-47.

The role of activation of acid proteases in demyelinization processes of an autoimmune nature--in the presence of multiple sclerosis and experimental allergic encephalomyelitis--is discussed. Most probably, penetration of antibodies into the main protein of myelin in the brain and thus induced activation of proteolysis is the initiating factor in development of demyelinization.

Tables 2; bibliography lists 54 items.

UDC: 547.963

"Copper-Containing Proteins of the Brain," by R. M. Nalbandyan and G. Kh. Bunyatyan, pp 47-57

Four copper-containing fractions were isolated from extracts of cerebral acetone powder, two of which were in a highly purified state. It was demonstrated that

one copper-containing protein has the properties of cerebrocuprein I and is a cerebral copper and zinc containing superoxide dismutase. The other protein, which has strongly acid properties, differs from proteins heretofore described in the brain and other tissues, and it was named neurocuprein. Neurocuprein contains one atom of copper per molecule, the vicinity of which is very sensitive to pH. The possible significance of histidine, lysine, tryptophan and water is suggested as ligands of copper. Studies were made of the reaction of neurocuprein with epinephrine and norepinephrine, and it was demonstrated that they are oxidized by neurocuprein in a stoichiometric proportion (2:1).

Copper has been demonstrated in mitochondria, vessels and myelin. Cytochromoxidase of mitochondria is more active than that of the myocardium, although the optic and EPR spectra, subunit composition, copper and heme content, as well as activity are identical.

Figures 11; tables 2; bibliography lists 50 items.

UDC: 577.156.612.8.015

"Enzymes of Protein Catabolism in the Brain," by A. D. Reva, V. A. Berezin and M. T. Gengin, pp 57-63.

In this survey of the literature and the authors' experimental data dealing with peptide hydrolases of nerve tissue, there is discussion of the subcellular localization, methods of isolation and role of lysosomal cathepsins in degradation of specific proteins and peptides of the brain. It is stated that neutral peptide hydrolases of the brain have been less studied. A study was made of the phenomenon of multiple molecular forms of neutral peptide hydrolases that hydrolyze protamine, glycylglycine, glycylglycylglycine demonstrable by gel chromatography and disk electorphoresis.

Figures 2; bibliography lists 50 items.

UDC: 612.613.81

"Metabolism of Proteins and Nucleic Acids of the Central Nervous System Under the Influence of Ethanol," by I. A. Sytinskiy, pp 63-69.

This survey discusses the acute and chronic effects of ethanol, manifested by depression of protein synthesis in subcellular structures of the brain of experimental animals, due to predominant impairment of enzymatic activity of aminoacyl-tRNA synthetase. Ethanol inhibits incorporation of 5-^{3}H-orotic acid in subcellular RNA fractions (nuclear, transfer, ribosomal, mitochondrial). The change in RNA metabolism in the presence of chronic alcoholization is related to inhibition of RNA polymerase of the brain. Five elements were demonstrated in the effect of ethanol on the cAMP system in neurons and, accordingly, on the process of phosphorylation of the proteins of neuronal membranes. The severity of clinical signs of impairment of protein metabolism in alcoholics is related to the severity of manifestation of this disease.

Figures 4; bibliography lists 26 items.

UDC: 612.822:616-001

"Neurocytochemical Characteristics of Protein and RNA Metabolism as Related to Stress," by S. Kh. Khaydarliu, pp 70-75

The literature and the author's own data are discussed, which deal with the quantitative changes in RNA and protein content, and proportion thereof in cellular elements of the central nervous system in the presence of stress factors. It was shown that the initial reaction of the central nervous system to stress is characterized by a greater diversity of effects of stressors than at the later stages of stress, which occur against an altered hormonal "background." The latter are characterized by prevalence of the process of RNA and protein dissociation in most cellular elements of the central nervous system, and there is more reduction of proteins than RNA.

Figures 2; bibliography lists 32 items.

UDC: 612.8-017.1

"Immunophysiological Study of Neurospecific Proteins (Antigens) of the Central Nervous System," by M. B. Shtark and N. V. Piven', pp 76-83

This article deals with methodological bases and results of studying the physiological role of neurospecific protein-antigens. It submits the results of work done in the authors' laboratory on the characteristics of brain-specific antigenic spectrum in the intact organism, nerve tissue culture and individual, identified neurons of invertebrates, and its relation to electrogenesis. There is discussion of the mechanisms of effects of antibrain antibodies that develop on the level of the membranes and entire brain. The results of studies of localization of a number of neurospecific proteins on the surface membrane of neuronal and glial cells are submitted. There is discussion of the question of synaptic induction of synthesis of neurospecific proteins in the postsynaptic cell and its role in mechanisms of memory and learning.

Figures 6; bibliography lists 22 items.

UDC: 612.8.015:612.58+591.543.42

"Brain Proteins of Warm-Blooded Organisms at Low Body Temperatures," by E. Z. Emirbekov, R. A. Abdullayev and I. A. Ismailov, pp 84-90

Date from the literature and the results of the authors' own research are submitted, which deal with renewal of proteins, proteolysis thereof, electrophoretic lability, amino acid composition, as well as amide group levels in proteins and activity of enzymes of nitrogen metabolism in brain tissues during forced cooling and hibernation.

Bibliography lists 35 items.

[151-10,657]

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CSO: 1840

UDC 612.821

CHANGES IN VARIOUS PHYSICAL INDICATORS DURING ASSIMILATION OF INCREASING VOLUMES OF VISUAL INFORMATION

Moscow ZHURNAL VYSSHEY NERVNOY DEYATEL'NOSTI in Russian No 4, 1980 pp 765-771

[Article by V. V. Gorbunov, Kiev, submitted May 28, 1979]

[Text] The extensive use of various methods of information gathering in existing automated systems points out the need for an objective evaluation of the difficulties related to the assimilation of various volumes of visual information. Most researchers have resolved this problem by measuring the degree of psychoemotional stress in humans during work performance. They used electrocardiogram indicators [1, 2, 10, 12, 15, 19, 22, 24, 25], electromyograms (EMG) [3, 9, 10, 20], EEG [8, 16, 17, 21, 23, 26, 28], and other physiological indicators [6, 7, 11, 13, 14, 18]. Since these studies dealt with activities that included mental stress produced by the absorption and processing of visual information that has not been quantitatively accurately defined, and omitted personal characteristics of the individuals, the results obtained were not uniform and sometimes even contradictory.

The objective of this study is to devise quantitative criteria for the difficulties of operational activity based on the evaluation of the physiological load of work. We studied the correlation between the indicators of the basic physiological systems that participate in the operational activity and the level of mental stress related to the processing of increasing volumes of visual information. The study dealt with the following aspects: Objective quantitative control of mental stress; simultaneous recording of the indicators of basic functional systems of the organs during work activity, and indirect indicators of efficiency and intensity of performance; individual records of the characteristics of the test subjects.

Methods

The experiment was carried out on 147 subjects, age 19 to 25 years. The operator activity affected by the assimilation of increasing volumes of visual information was measured by the PNN instrument (processed by OKP institute of physiology of A. A. Bogomolets, USSR Academy of Sciences) by a method described earlier [4].

Words representing animals, plants or objects were flashed on the screen. In response, the subject had to press a button with his right or left hand or not respond at all. The rate of the word signal projections was raised from 30 to 160 per minute. We informed the participants on their performance at regular intervals; at the end of the test we announced their general level of efficiency compared with the other participants.

Prior to the tests we trained the subjects at five different speeds ranging from 30 to 70 signals per minute. We measured the maximum rate of effective assimilation of visual information. We established as a criterion for successful performance an error rate below 5 percent of the total number of projected signals. On this basis, the test subjects were divided into three groups.

The condition of the subjects was evaluated by a 30 second analysis of the amplitude of EMG (Σ EMG) of m. extensor carpi radialis brevis of the left hand, total EEG (Σ EEG) registered between C_4 and O_2 [27] and its frequency components of beta-, alpha-, theta- and delta-rhythms, cardiac contraction rate (CCR) and respiration rate (RR). We calculated the number of errors (Er), the number of responsive movements (Σ Mo) and the index $K = \Sigma$ EMG/Σ Mo. The registration and analysis were carried out with an 8-channel recorder USCh 8 and an EEG apparatus (made by the Orion Company Hungary) consisting of an electroencephalograph, automatic frequency analyzer and integrator. The background conditions of the subjects were recorded before and after the tests.

The obtained data were processed by methods of mathematical statistics, using an EVM, model "Mir-2".

Results of the Investigation

Based on the determination of the maximum rate of effective assimilation of visual information, the subjects were divided into groups according to their ability to respond successfully to consecutively accelerated visual signals. The maximum rate of effective information assimilation in the first group of 47 subjects ranged from 70 to 80 signals per minute; in the second group consisting of 54 subjects, from 90 to 100, and in the third group of 46 subjects, from 110 to 120 signals per minute.

The acceleration of the signal projections increased thenumber of errors in all groups (Fig. 1). The number of errors grew and reached high proportions in individuals with lower test efficiency. In the velocity range of 30 to 80 signals per minute, successfully handled by all subjects, the differences in the number of errors of the three groups were insignificant. The differences were more marked at velocities of 130 to 160 signals per minute at which rate all subjects had failed (Fig. 1). Close correlations between the errors and the signal projection rates are evident in all groups (Table 1). As for the number of responses, the differences between the groups were very small (Fig. 1). An increase in the velocity produced a unidirectional increase in the number of responses in all groups; this was confirmed by the high coefficients of correlations among these indicators (Table 1).

Table 1

Correlation Coefficients Between the Studied Indicators and the Projection Rates of Visual Signals for Different Test Groups

Velocity	Error	Σ Mo	Σ EMG	K	CCR	RR
			First Group			
number of signals/min	0.96***	0.96***	0.69**	-0.79***	-0.78***	0.34
			Second Group			
same	0.93***	0.97***	0.72**	-0.85***	0.55*	0.57*
			Third Group			
same	0.89***	0.97***	0.69**	-0.89***	0.19	0.71**

Velocity	EEG Indicators				
	Σ EEG	beta	alpha	theta	delta
		First Group			
number of signals per minute	0.32	0.57**	0.78***	-0.19	0.79
		Second Group			
same	-0.83***	0.84***	0.66**	-0.76***	-0.81***
		Third Group			
same	0.39	0.79***	0.56*	0.65**	0.25

*probability 0.95
**same, 0.99
***same, 0.999

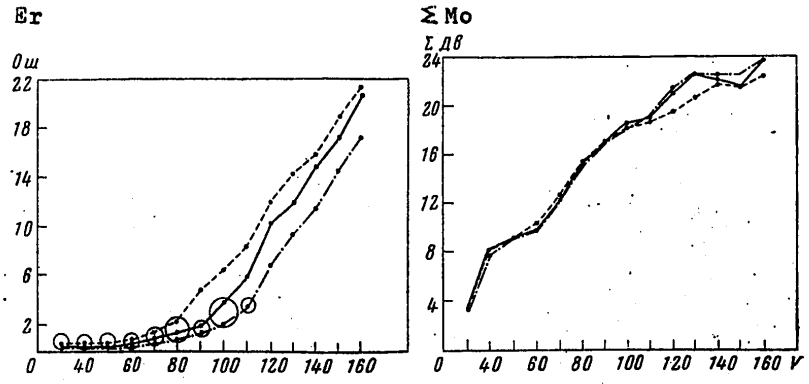

Fig. 1. Variations in direct performance indicators of all groups with increased projection rates. Dashed line--first group; solid line--second; dash-dotted line--third group. The circles represent rates of successful performance. The abscissa--the visual projection rate V, signals per minute; the ordinates--the number of errors (Er), and the number of responsive movements (ΣMo).

In the velocity range of 30 to 100 signals per minute, the amplitude of EMG rose markedly in all groups and then declined moderately although the number of responses continued to increase (Fig. 2). The most significant changes in the EMG occurred in the first group; they were average in the third, and smallest in the second group (Fig. 2). Statistical analysis of the correlation confirmed a link between the projection rate and the EMG amplitude (Table 1). The correlation between the index K levels among the different groups is the same as for the EMG (Fig. 2), but it is indirectly proportional to the velocity rate (Table 1).

In all groups, the cardiac contraction rate increased markedly at the beginning of the test and decreased significantly at the end (Fig. 2). The CCR increased during the initial projection rates, and then decreased. The analysis of the data indicates an indirectly proportional correlation between the CCR and the projection rate for the first group, a linear correlation for the second, and the absence of any significant correlation for the third group (Table 1).

The respiration rate (RR) sharply increased at the beginning of the test and it fell sharply after completion (Fig. 2). In the 30 to 70 signals per minute range, the RR increased and them remained practically unchanged. The comparison of the respiration rates indicated insignificant differences between the groups. The correlation between the projection rates of the signals and the RR was closer when the test results were more successful (Table 1).

The highest level of total EEG activity was registered by the first group of contestants; it was considerably lower in the second and third group (Fig. 2). A correlation between the projection rate and the amplitude of the total EEG could not be confirmed for the first and third group (Table 1). In the second group,

an increase in the projection rate was accompanied by a decrease of the ΣEEG index (Fig. 2); a definite indirectly proportional relationship was confirmed statistically (Table 1). The acceleration of the signal projection rate produced an increase of the beta-rhythm index (Fig. 2); this was more pronounced in the second and third groups, and less in the first group. (Table 1). In all groups, the alpha activity fell considerably at the beginning and increased sharply at the end of the tests (Fig. 2). Acceleration was accompanied by a tendency of the amplitude of the alpha rhythm to increase in all groups (Fig. 2). This tendency becomes more evident as the test scores fall (Table 1). The study of the theta activity indicates similar changes in its values for the first and second group of contestants. Consecutive acceleration of the signal projections at first increased, and then reduced this indicator (Fig. 2). However, the tendency to reduction is more evident in the second than in the first group. The third group showed a tendency of increased theta activity (Table 1). The delta activity in the first and third groups generally increases, although it declines somewhat during some initial test rates (Fig. 2). This tendency is clearly seen in the first group and is less evident in the third (Table 1). The delta activity markedly decreases during performance at higher velocities in the second group; this confirms the indirectly proportional correlation of the studied indicators (Table 1).

Evaluation of Results

The projection rate of visual signals was the criterion of mental stress produced by the reception and assimilation of visual information. The higher the rate, the higher is the stress; and it requires greater effort for successful performance, i. e. the harder the work, the greater is the physiological strain. The efforts of the contestants were reflected by changes in all the recorded physiological criteria. However, variations in the results greatly hinder a uniform interpretation. Therefore we tried to evaluate the performance with the aid of an integral index, the level of behavioral activity (BA) reflecting the reaction of the physiological systems that directly participate in the specific operation.

We ranked the physiological indicators before, during and after the test. For each indicator, we assigned one point to the lowest value, two for the next higher, and so on. The highest point value was given to the maximum value of the respective indicator. Alpha activity was ranked in a reverse order (Table 2). Levels of behavioral activity were determined by the summation of all the point values of the physiological indicators in each group, at rest and at all projection rates (Table 2). The BA value increased noticeably for the 30 to 80 signals per minute range in which the contestants of all groups performed successfully.

In the range of 90 to 120 signals per minute, the BA varies for the individual contestants. In the 130 to 160 signals per minute range, in which all the contestants failed to perform satisfactorily, the BA level tended to decrease (Fig. 3).

Looking at the physiological strain of the test that determines the BA level as an objective criterion of difficulties of performance, we find that the mental stress of the members of all groups increased in the 30 to 80 signals per minute range as the task became more difficult. This is confirmed by the high coefficients of the ranking correlation according to Spirman [5], according to groups,

between the BA level and the projection rates ($r_1 = 0.92$; $r_2 = 0.83$; $r_3 = 0.89$), the number of errors ($r_1 = 0.91$; $r_2 = 0.77$; $r_3 = 0.89$), and the number of responses ($r_1 = 0.99$; $r_2 = 0.83$; $r_3 = 0.89$). In spite of the increased mental load, the contestants exerted less effort in the 130 to 160 signals per minute range, i. e. the work seemed to be less difficult. This could be attributed to their gradual failure to perform due to the excessive complexity of the task and the virtual impossibility of successful performance.

Thus the level of behavioral activity reflects more clearly the functional state of the contestant, and it is determined by the difficulties of the task. This is confirmed by the unidirectional changes and the high degree of correlation of these criteria with the mental stress and the direct indicators of work during successful performance of the task.

Table 2

Ranking of the Physiological Indicators of the Different Test Groups During Test Performance

V	Фн (1)	30	40	50	60	70	80	90	100	110	120	130	140	150	160	Фк (2)
						(3) Первая группа										
Σ EMG	2	3	4	5	6	8	12	14	16	9	10	13	7	15	11	1
CCR	2	8	12	14	10	13	11	9	13	7	5	5	6	3	4	1
RR	2	3	4	5	8	11	12	10	13	14	6	6	7	9	6	1
Beta	6	1	2	3	4	4	7	9	10	12	11	8	4	5	7	13
Alpha	2	15	14	13	12	11	8	7	7	4	3	5	9	10	6	1
Theta	2	1	3	4	9	9	10	13	13	14	11	12	8	6	5	7
Delta	11	4	3	5	2	1	2	8	6	8	7	13	12	9	10	14
BA	27	35	42	49	51	57	62	70	78	68	53	62	53	57	49	38
						(4) Вторая группа										
Σ EMG	2	3	4	5	6	7	9	13	16	15	14	11	12	8	10	1
CCR	2	4	3	5	7	8	12	12	11	14	13	13	10	9	6	1
RR	1	3	4	5	7	12	14	12	13	15	9	10	6	11	8	2
Beta	6	5	1	2	4	6	6	6	11	10	7	9	11	11	8	3
Alpha	1	9	10	6	9	8	9	5	5	5	5	7	8	3	4	2
Theta	6	6	8	10	11	12	9	9	7	4	5	13	3	4	2	1
Delta	13	14	16	15	11	12	10	6	8	3	2	7	9	5	4	1
BA	31	44	46	48	55	65	69	63	71	60	55	70	59	51	42	11
						(5) Третья группа										
Σ EMG	2	3	4	5	6	8	11	12	14	16	10	15	13	7	9	1
CCR	2	4	3	10	9	8	9	12	11	10	7	13	8	5	6	1
RR	2	3	4	5	6	9	7	8	14	12	11	10	13	7	8	1
Beta	5	3	7	1	4	1	2	6	8	7	11	10	12	13	9	5
Alpha	2	9	8	9	9	12	13	11	10	14	4	6	5	7	3	1
Theta	2	4	6	6	8	5	9	7	3	7	11	12	8	8	10	1
Delta	8	13	10	4	5	1	2	12	6	11	9	5	9	7	14	3
BA	23	39	42	40	47	44	53	68	66	77	63	71	68	54	59	13

Key: 1--condition before test; 2--condition after test; 3--first group; 4--second group; 5--third group

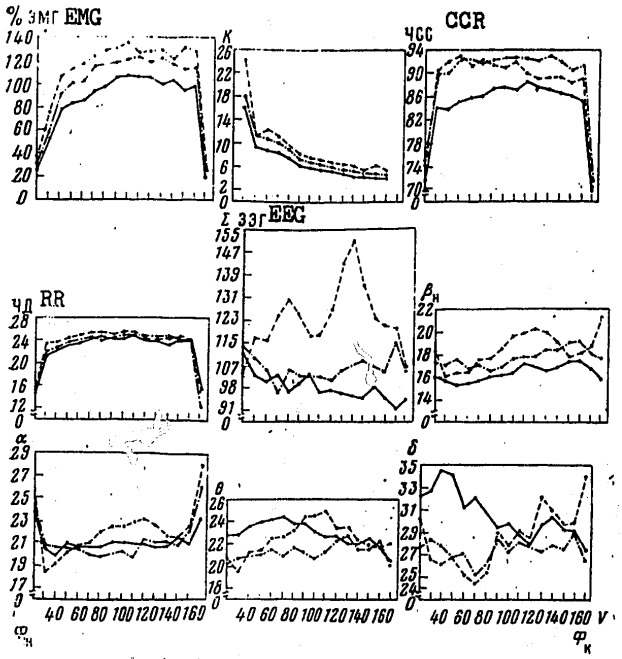

Fig. 2. Variations in the physiological indicators of the different test groups with increased visual projection rates. Abscissa--same as in Fig. 1; ordinates--various physiological indicators; ϕ_H condition before, and ϕ_K condition after test.

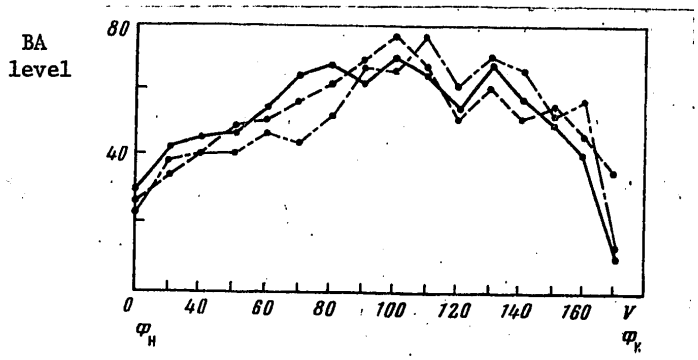

Fig. 3. Variations in the BA level of the contestants of the different groups during the assimilation of visual information, projected at increased rates. Abscissa--as in Fig. 1; ordinate--level of behavioral activity (BA); ϕ_H--condition before, and ϕ_K--condition after test.

Conclusions

1. All groups comprising subjects with varying capabilities to assimilate increasing volumes of visual information, exhibited most significant correlations between the level of mental stress and the integral amplitudinal indicators of EMG, beta- and alpha-rhythms of EEG and the indicator K.

2. The behavioral activity level reflects the intensity of the function of the physiological systems responsible for the concrete work performance; it more fully characterizes the difficulties of successful performance related to the assimilation of visual information projected at increasing rates.

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HUMAN FACTORS

COMPUTERIZED RADAR OPERATOR TRAINERS

Moscow TRENAZHERY DLYA PODGOTOVKI OPERATOROV RLS S POMOSHCH'YU EVM in Russian (signed to press 5 Dec 79) pp 2-4, 125-126

[Annotation, introduction and table of contents from book "Computerized Radar Operator Trainers", by Anatoliy Nikolayevich Romanov, Voyenizdat, 6,000 copies, 127 pages]

[Text] This book examines the basic technical principles of building computerized trainers, and it presents the requirements imposed on trainers. Methods for modeling targets and interference on a display with the assistance of a computer are described, as are the principles of signal simulation in trainers.

Some problems associated with operator psychological training are illuminated, the techniques of teaching operators with trainers are described, and the methods for evaluating their preparedness are presented.

The book is intended for military specialists involved in the development and operation of trainers.

Introduction

Radio engineering troop units and subunits possess the most sophisticated combat equipment embodying the latest achievements of Soviet science. This imposes high requirements on the training level of personnel servicing this equipment.

A high professional level permits operators to successfully assimilate modern radar equipment and automated control systems (ASU), and to competently exploit the combat potentials designed into such equipment.

Life has necessitated a search for ways to train radar operators more quickly.

Reducing specialist training time is only one part of the problem. The other is that of upgrading the quality of work done by operators with combat equipment. Organizing and conducting combat training, commanders, political workers, and staff officers base their efforts on the fact that the continually growing power and complexity of military equipment is intensifying the dependence between the degree to which this equipment is assimilated by the personnel and the effectiveness of its combat use.

The proficiency of radio engineering subunit crews directly influences the accuracy with which antiaircraft missile troops and fighter aviation perform their missions. Therefore one of the most important requirements imposed on crew proficiency should be stated as detecting targets at maximum range, providing radar information with maximum precision, and fully exploiting the possibilities of the combat equipment when determining the composition of airborne targets.

The progress of science and technology in recent years has led to broad proliferation of complex technical systems. The human operator plays the decisive role in such systems, and the complexity of analyzing information and of performing control functions has made it necessary to upgrade operator training and instruction quality. This problem is especially important in radar applications, where operator training based on real systems involves considerable outlays of resources and significant expenditures of materiel.

Despite the rather broad use of simulators and trainers as technical devices to teach operators the habits of controlling various systems, the effectiveness of their use was inadequate until recently. An analysis of the development of trainers showed that at first, their designers tried to simulate the situation in the air with simplified models which permitted training only within a limited range of operating modes. The requirements on the quality and teaching possibilities of trainers increased, making it necessary to raise the completeness and accuracy of use of dynamic and information models, which necessitated inclusion of electronic computers into the trainers.

Among the merits of computerized stimulators and trainers we should include the possibility for simulating any aerial situation, for making it more or less complex, for changing the target projectory parameters on a real time scale, for reusing the information models of the aerial situation, for studying such models in parts, and for automatically obtaining an objective score of operator proficiency and monitoring the course of operator training.

These merits and advantages of computerized trainers promote more-effective training, they raise its quality, and reduce its time. The results of operator training sessions can be used as a basis for evaluating how well an operator is suited to controlling a concrete system, and preparing operators for the purposes of their selection.

Contents

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FLIGHT SIMULATORS

Moscow AVIATSIONNYYE TRENAZHERY in Russian 1978 (signed to press 5 Jul 78) pp 4-6, 190-192

[Annotation, introduction, bibliography and table of contents from book "Flight Simulators", by Vasiliy Afanas'yevich Bodner, Rafael' Abdullovich Zakirov and Inna Ivanovna Smirnova, Izdatel'stvo "Mashinostroyeniye", 3600 copies, 192 pages]

[Text] Annotation

This book describes the fundamentals of designing aircraft simulators and mathematical modeling of aircraft systems. It deals with questions of dynamic and informational similarity, and it describes methods of synthesis of simulator characteristics. Mathematical models of an aircraft and its onboard systems are submitted; questions of planning experiments on simulators, methods of recording data, evaluating quality of piloting performance and fundamentals of theory of training on simulators are discussed.

This book is intended for engineers and scientific workers dealing with the planning and operation of aircraft simulating complexes.

Introduction

Flight simulators reproduce the conditions to which a crew is exposed during flight. The instrument readings and information about the visual situation, accelerations and other factors, to which the crew members are exposed, characterize the fight of an aircraft and operation of its systems, which are described by differential and finite equations. Reproduction of these equations with due consideration of the effects of the above factors on crew members constitutes the task of mathematical modeling executed in the simulator. A computer is used to solve these equations on a real time scale, to output the necessary readings to instruments and simulators of physical flight factors as a function of controlling and perturbing effects on the aircraft.

For a long time, analog computers were used in aircraft simulators. In such computers, the dynamic properties of the aircraft are simulated by means of a set of appropriate units that execute different mathematical functions or partial operations (addition, multiplication, solving equations for longitudinal, lateral movement, solving engine equations, etc.). The accuracy of modeling using analog computers is rated at a 20-25% error factor.

Flight simulators with digital computers, which have processers that have a mean calculation rate of at least 250,000 op. [operations]/s and an immediate access storage of at least 64 kbytes, have greater capabilities with regard to both solving problems of flight personnel training and questions of studying new aircraft models. One can experimentally test piloting techniques, performance of aerobatics, group flights and pilot behavior in unusual situations on such simulators, at minimal expense and in safe conditions for the pilots.

A number of problems come up when designing flight simulators: elaboration of quantitative criteria of dynamic and informational analogy with due consideration of psychophysiological characteristics of pilots; elaboration of methods of technical execution of analogy criteria in analog modeling; development of algorithms and software programs for digital modeling; development of reasonable simulators of the visual situation, accelerations and background noise; development of a mathematical model for training on a simulator, and others.

In this book, the quantitative criteria of analogy [similarity] have been formulated, and methods for synthesis of optimum simulator characteristics were outlined on the basis thereof, with due consideration of human psychophysiological distinctions.

A significant place is devoted to technical executation of simulators having the required characteristics. For this purpose, complete equations of motion are discussed; reasonable means of analog simulation of mathematical functions are outlined, and methods are offered for calculation of hardware of the analog type.

Attention is focused mainly on the software for simulators with digital computers, development of algorithms and operation programs. For this purpose, equations for motion are reduced to a rational form, which facilitates solutions on digital computers, analysis is made of computation methods and recommendations are offered on the choice of computing procedures and characteristics of digital computers.

It is impossible to provide conditions simular to those of an aircraft in a simulator without simulation of the visual situation and accelerations. These questions are solved to some extent in the book, in both the theoretical (providing for informational similarity) and practical (consideration of possible technical executions) respects. Questions

of planning of experiments and distinctive features of training on simulators are also discussed.

The issues covered make it possible to undertake substantiated designing of simulators.

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Contents

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MEASUREMENT OF LOCAL INDICES OF OPERATOR PERFORMANCE IN THE TRACKING MODE

Kiev KIBERNETIKA I VYCHISLITEL'NAYA TEKHNIKA in Russian No 45, 1979 manuscript received 13 Apr 78

/Article by V.A. Chernomorets, Cybernetics Institute, Ukrainian SSR Academy of Sciences, Kiev/

/Text/ At the present time, one of the most common components of operator work is activities related to the realization of the tracking mode. This type of activity is dominant during the control of transportation, technological processes and so on. In order to obtain prognostic data on an operator's efficiency under these conditions, we use the results of a modeling of his activities. In connection with this, as the basic initial data we use evaluations of the effectiveness of the operator's processing of service information.

The direct measurement of the qualitative indices of an operator's informational activity involves the registration of a number of characteristics of the dynamics of the psychic processes that insure the realization of the information handling process. The difficulties involved in this consist of the special features of the functioning of the physiological systems of the human operator's body that exclude the elimination of a number of essential parameters of these processes. Therefore, in the observable structure of the operator's activities there are a number of unknown components, including the amplitude-time characteristics of the quantification processes for incoming analog signals and the distribution of time expenditures among the stages of the control cycle, plus others. As a result of this, at the present time -- as a rule -- we use evaluations of the efficiency of his controlling actions, as based on the relative deviations of the control process's actual parameters from some idealized ones, as the indices of the quality of his processing of information. These reference values of the quality indices of the operator's activities are based on a formalization of the requirements stipulated in the instructions for an operator of a specific system. Such evaluations of the efficiency of an operator's informational activities are adequate for a comparative analysis of monotypical ergaticheskiye /translation unknown/ systems, for the determination of the relationship between the certified characteristics of systems and the professional training of the operators, and for other purposes that are

related to the relative constancy of the characteristics of man and machine /2/.

In order to improve the resolving power of the methods for describing the human operator's purposeful behavior, it is necessary to use empirical data that adequately reflect the quality of the operator's activities in specific situations that arise successively during the functioning of an ergaticheskaya system. If there are no special restrictions, for this purpose it is possible to use an artificial quantification of the observed analog processes and regard the operator's activities as the process of realization of a sequence of control cycles within the limits of the quantification intervals. In connection with this, however, there appear a number of metrological processes that are related to the substantiated choice of these intervals and the reference values of the indices of the quality of the realization of the corresponding control cycles.

Let us discuss a possible approach to the solution of these problems, using as an example the activities of an operator in the compensating tracking mode, which is one of the most complicated types of operator work.

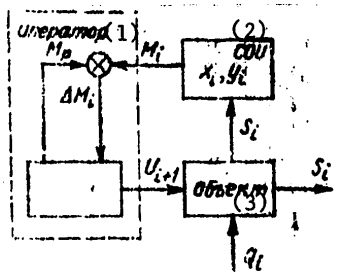

Figure 1. Block diagram of operator's activities in the compensating tracking mode.

Key: 1. Operator
2. Information display system
3. Object

In the psychological plan, the operator's activities in this mode consist of controlling a dynamic object acted upon by different disturbances (Figure 1). For the i-th control cycle, $S = f(\varphi,\psi, \theta,Q)$ = state of the object; $U = f(p,g,r)$ = vector of the controlling actions; φ,ψ,θ = angular coordinates of the object; X,Y = rectangular coordinates of the object in the corresponding units of the information display system (SOI); M_p = upper limit of the required coordinates in the SOI (threshold value); Q = = disturbing influence.

In the structure of the operator's activities in the compensating tracking mode, the leading place is occupied by operations for measuring the object's current coordinates and, when necessary, operations to work out and issue the appropriate control actions. The representation of the operator as two structural units (see Figure 1) also reflects the fact that he realizes the functions of a unit for comparing the object's current coordinates (possibly their modulus M_i) with the threshold area M_p, as well as the functions of choosing and issuing the control actions U_{i+1}. In this case, the presence of a fixed threshold M_p predetermines the choice of the components of the operator's activities' quality index, which can include the time for achieving the area M_p by the controllable coordinates, the mean-square error of the deviation of M_i inside a window with radius M_p in the SOI, and other factors /3/.

The components of a quality index computed in this manner are global in two respects. On the one hand, they are evaluations of the operator's actions within the limits of the entire time of their registration; on the other, they are evaluations of the quality of the realization of all the stages of the control cycle, regardless of the object's state S_i by the beginning of the i-th control cycle. Meanwhile, it has been established that the human being's purposeful behavior is formulated on the basis of achieving certain local indices of the quality of his activities that reflect the specific initial conditions and the personal experience and current psychological state of the subject /17/. In this case this can mean that in making the decision about the choice and issuing of certain U_{i+1} control actions is guided by a scale of reference values M^0_{i+1} that does not (in the general case) coincide with the threshold values M_p. Thus, a certain local quality index I_i for the realization of the i-th cycle that is actually achievable in the given cycle corresponds to each $S_i \in S$. In realizing this cycle, however, for a number of natural reasons the operator will unavoidably admit some deviations in the selection of the optimum controls, so the state S_{i+1} into which the object is converted will differ from the maximally possible approximation to area M_p. This means that the local quality index for the operator's actions will be lower than the theoretically possible one.

Methodologically, the problem of determining the local quality index for the operator's activities consists of a comparative analysis of the results of the realization of the operator's appropriate control cycles and some optimum controller that works out the values of the theoretically possible approximation of the object's current coordinates M^0_{i+1} to the given area M_p. The calculated values M^0_{i+1} of the coordinates and the controlling actions U^0_{i+1} that correspond to them are regarded as reference values for the realization of the i-th control cycle. The physical meaning of the index I_i that is computed on the basis of these values is that it reflects the values of the reserves that the operator had at his disposal, during each cycle, for the minimization of the object's coordinates. The system that realizes the functions of the generator of the control actions' and coordinates' reference values is natural considered to be the standard system (ES) for the given type of activity.

In order to obtain reference values U^0_{i+1} and M^0_{i+1} that make physical sense, the functioning of the ES must satisfy some obvious requirements: 1) for the selection of U^0_{i+1} the ES must use the same class of functions that the operator used; 2) for the ES and the operator there exist common initial conditions, common restrictions on the variables that are used, and common activity quality indices; 3) the ES's operating algorithm permits the use of the experience of highly qualified operators; 4) the indicator of the correct ES selection is the possibility of duplicating the operator's functions with activity of a better quality. With respect to the type of activity under discussion, the latter can manifest itself in that for any initial conditions, the object's theoretical trajectory of motion is constructed in such a fashion that its coordinates move toward the window with radius M_p along the shortest possible path.

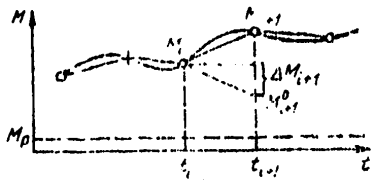

Figure 2. Principle of computation of the coordinates' reference values.

Practically speaking, the organization of the ES's functioning for the compensating tracking mode is as follows (Figure 2). The nonobservability of the components of the operator's actions gives us grounds for selecting Δt_i -- the duration of the i-th control cycle -- by diverging from its physical meaning (with, naturally, due consideration for the specific object's special features). If T is the time of registration of the object's trajectory, then by dividing into N sufficiently small time intervals, the initial continuous function $M = f(t)$ can be represented as a broken line with apices at points (M_i, t_i). In this case, $T = \sum_{i=1}^{N} (t_{i+1} - t_1)$, where t_i, t_{i+1} = the beginning and end, respectively, of the i-th interval. Empirical data make it possible to determine unambiguously the parameters S_i of the state at moment t_i and the parameters S_{i+1} of the state into which the object is transformed as the result of the effect on it of the control actions chosen by the operator during the given interval.

Using the parameters S_i of the object's state at moment t_i -- that is, by returning to the beginning of this interval -- let us reproduce the equation of our standard system. In order to determine U^0_{i+1} and M^0_{i+1} for the ES, it is necessary to determine p^0_{i+1}, g^0_{i+1} and r^0_{i+1}, which can insure the maximumally possible approximation of M_i to the threshold M_p during time interval Δt_i. This problem reduces to minimizing the object function criterion for m variables with restrictions, for the solution of which there exist a number of numerical methods. In this case, in order to speed up the search for the object function's minimum we use the deformable polyhedron method, which was developed for use in problems of nonlinear programming [4]. The flaw in it (which is also characteristic of other numerical methods) is that the iterative process reduces to one of the local minimums. The values of the variables p^0_{i+1}, g^0_{i+1} and r^0_{i+1} that are computed in connection with this may not satisfy the qualitative requirements for the change in trajectory during the given cycle. Therefore, the selection of the form of the criterion for minimization of the object function and the area in which the initial approximations of unknown components of the control actions' vector are given is a matter of considerable importance.

These data were developed as the result of a qualitative analysis of a specific object. With respect to the case under discussion, their selection can be substantiated from the following propositions. Since the search for the unknown values p^0_{i+1}, g^0_{i+1} and r^0_{i+1} reflects the representation of some idealized trajectory of motion of the object controlled by the operator, the object function minimization criterion is based on the formalization of the requirements for the operator's actions. It is not difficult to see that it follows from the operator's instructions that for him and, consequently, for the ES, for each Δt_i it is necessary to select values of p^0_{i+1},

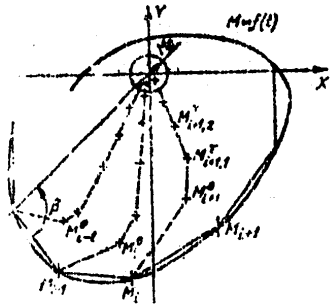

Figure 3. Fragment of empirical trajectory with reference M_i^0 and test $M_{i,k}^T$ points.

g_{i+1}^0 and r_{i+1}^0 that minimize the angle between the velocity vector and the shortest distance to M_p at moment t_i, which is angle β (Figure 3). This condition will be met if we use the following expression as the minimization criterion for the object function:

$$F = V\sqrt{R_1^2 + R_2^2} + k(R_1^2 - R_2^2),$$

where

$$R_1 = x_i - \Delta x_{i+1},$$
$$R_2 = y_i - \Delta y_{i+1}.$$

Also in an inexplicit form, in the instructions there is a requirement that the operator reduce the object's speed when $M_i \to M_p$. It is inadvisable to include it in the expression for the criterion. In this case it is more worthwhile to use our intuitive ideas that the velocity and direction of motion should depend on the value and sign of the controlling actions (although this is not always realized). For objects in the class under discussion, these data are known with accuracy up to that of the sign, which is completely adequate in order to determine the limits of the area of existence of the unknowns p_{i+1}^0, g_{i+1}^0 and r_{i+1}^0. By introducing boundary values for them that are, for example, linearly dependent on the area of existence of the control actions that satisfy the qualitative requirements for their values, for the i-th interval we can write

$$\bar{k}_1 \leqslant p_{i+1} \leqslant \overset{+}{k}_1,$$
$$\bar{k}_2 \leqslant g_{i+1} \leqslant \overset{+}{k}_2,$$
$$\bar{k}_3 \leqslant r_{i+1} \leqslant \overset{+}{k}_3.$$

Coefficients k_1, k_2 and k_3 are determined from the numerical restrictions on p, g and r (Figure 4.).

The computation process for U_{i+1}^0 and M_{i+1}^0 is constructed in the following manner. For moment t_i, the known values of φ_i, ψ_i and θ_i are used to calculate the rectangular coordinates x_i, y_i in the SOI and the control action vector components p_{i+1}^0, g_{i+1}^0 and r_{i+1}^0 that insure their minimization in an interval of time equal to Δt_i. The values ΔM_{i+1} of the increments of the angular coordinates that are obtained as the result of the search are used for a test check of the program's efficiency, assuming that the form of the function that described the disturbances at the beginning of the i-th interval will not change in the future. With that end in view, for moment t_{i+1} we compute new values of the angles and rectangular coordinates $\varphi_{i+1} = \varphi_i + \Delta\varphi_{i+1}$, $\psi_{i+1} = \psi_i + \Delta\psi_{i+1}$ and $\theta_{i+1} = \theta_i + \Delta\theta_{i+1}$, and then the equations for Δt_{i+1}. The process continues until $M_{i,k}^T$ is stably located in the area $M_{i,k}^T < M_p$. This situation is checked by a logic diagram of the

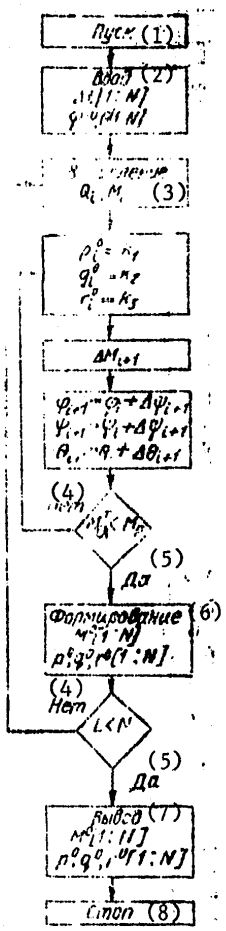

Figure 4. Block diagram of computation of reference values of coordinates M^0 and control actions p^0, g^0, r^0.

Key:
1. Start
2. Input
3. Computation
4. No
5. Yes
6. Formulation
7. Output
8. Stop

following form: ...if ($M^T_{i,k-} < M_p$) and (...) and ($M^T_{i,k} < M_p$) then go to... here d = 10. When the logic conditions are fulfilled, the testing of the ES's extrapolating properties is completed and the values of U^0_{i+1} and M^0_{i+1} that are regarded as the reference values for the i-th interval (see Figure 3) are derived. Thus, as the result of alternate control of the object by a human operator and an automaton, initial data are accumulated for the computation of the reserves that the human being has available, in each case, for the improvement of the qualitative indices of his own actions. Depending on the problems involved in the further processing of the experimental data, the local quality index can be represented in the form of errors in the selection of the control actions or as deviations in the object's trajectory of motion from the reference values of the coordinates.

The mode selected for time sharing between the operator and the ES is related to the realization of a method that is oriented to obtaining the initial data for the modeling of the operator's activities. In principle, however, there exist no limitations for the joint functioning of an operator and a system of this class, this being the case not only for tracking modes, but also for other types of operator work. The reference values for the control actions and coordinates that are obtained in connection with this can be used to optimize the education of an untrained operator or directly for control purposes.

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11746
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UDC: 57:53+612.13

CYBERNETIC ANALYSIS OF HEART RATE DURING EXPOSURE TO EXTREME FACTORS

Kiev NEYROBIONIKA I MODELIROVANIYE BIOSISTEM in Russian 1980 pp 98-100

[Article by G. A. Nikulina from book "Neurobionics and Modeling of Biosystems," Institute of Cybernetics]

[Text] Abstract: A method is described for evaluating the degree of tension and nature of regulation of functions in operators who work under conditions of impaired autonomic homeostasis.

Checking the heart rate is one of the mandatory and traditional procedures for examining sick and healthy men when performing a medical work-up. In the last 10-12 years, in view of development of cybernetic conceptions in physiology of circulation and introduction of computer technology into medicine, mathematical methods began to be used to analyze the heart rate, and it was established that its time organization is closely linked with the state of neurohumoral regulation of the heart and adaptive function of the body. At the present time, probabilistic analysis of dynamic series of heart intervals is used by many researchers. The diagnostic capabilities of mathematical and statistical analysis of heart rate have been demonstrated in the most diverse branches of physiology, clinical and sports medicine, balneology, engineering psychology and in industry. The use of mathematical methods for analysis of heart rate in space medicine is due to the specific nature of experiments conducted in space, which are methodologically oriented toward gaining maximum information about the status of an organism with a minimum amount of data. The heart rate is an integral indicator of neurohumoral regulation of the body, and when various extreme and subextreme factors are involved it is just as important to assess the general condition of an organism as to monitor different functions or detect some specific deviations.

We evaluated the degree of stress and nature of regulation of functions in the course of complex experiments where work and rest schedule was altered, with experimental disruption of autonomic homeostasis and prolonged clinostatic hypokinesia. Quantitative criteria of the process of regulation of the heart rate over a 24-h cycle in healthy subjects were obtained from dynamic observation of 30 experimenters, 20 athletes and 10 cosmonauts.

Evaluation of the degree of body tension and nature of regulation of functions is one of the important tasks in space physiology and for medical monitoring in space experiments. Mathematical analysis of heart rate was first performed when working with the data obtained during the flights aboard Soyuz-9 spacecraft and the Salyut-1 orbital station. Analysis of the data revealed that the reaction of autonomic homeostasis to the specific effects of weightlessness was the same in

cosmonauts. Some differences in values of mathematical and statistical parameters are apparently attributable to individual distinctions.

Analysis of data obtained during the flight aboard the Salyut-1 orbital station made it possible to determine that, according to the statistical characteristics of heart rate, all crew members presented marked tension of mechanisms of regulation of the rate of cardiac contractions at the first and final stages of the flight. As compared to the ground-based findings, all crew members presented a significant increase in amplitude of mode (AMo) and decrease of mode (Mo) and variational scatter (ΔX). On the 5th-6th flight day, the changes in statistical characteristics of heart rate were indicative of development of the process of adaptation to space flight factors (decline of AMo, rise of Mo and ΔX). These changes were analogous to those observed in the crew of the Soyuz-9 spacecraft.

The distinct manifestation of individual distinctions and absence of parameters exceeding the normal range inherent in each cosmonaut are indicative of retention of functional reserves of the system of controlling the heart rate in the course of space flights.

Mathematical methods of analyzing the heart rate were used to assess the condition of the crews of Salyut-4 and Salyut-6 orbital stations, and during the orbital flights aboard Soyuz-12, Soyuz-13, Soyuz-19 and Soyuz-22 spacecraft.

10,657
CSO: 1840/167

THE HUMAN FACTOR IN CONTROL SYSTEMS

Moscow NOVOYE V ZHIZNI, NAUKE, TEKHNIKE: SERIYA MATEMATIKA I KIBERNETIKA in Russian 1974 (signed to press 16 Aug 74) pp 2-6, 62

[Annotation, introduction and table of contents from book "The Human Factor in Control Systems", by G. L. Smolyan and K. V. Tobolev, Izdatel'stvo "Znaniye", 47,930 copies, 64 pages]

[Text] The booklet describes the characteristics of the functioning of the "human" link in automatic control systems. It also examines the training of operators with the help of the so-called algorithmic system control model and the evaluation of the effectiveness of the automated systems.

Introduction: In our country every year has seen an expansion of the use of EVM [electronic computers] in planning and control and in the processing of information. There is continual development of the base for electronic computer technology and other facilities for the collection, storage and processing of information; also for the means of communication. We have carried out series production of third-generation EVM, which have become the basis for the technical, programmed mathematical, and organization methodological unity of a large number of automated systems. The unified EVM system of the socialist countries is enabling them to achieve a meaningful increase in the capacity of the computer inventory and to significantly enhance the productivity and effectiveness of the use of the computer equipment facilities. We have begun the implementation of a broad program of work for the organization of automated control systems serving various purposes.

However, there is still a substantial quantity of resources relating to effectiveness in the use of EVM planning, control and information.servicing. We are not always exercising rational judgment in selecting the problems to be

resolved by employing EVM. There still persists a tendency to "overautomation," wherein we try to saddle the ASU [automatic control system] with nearly the entire complex of tasks of planning, control and monitoring. There are often attempts today to skip over tomorrow's ASU and a failure to take full cognizance of the human factors and the psychological aspects of the control.

Automation of control by EVM means is a new form of organization of operative intellectual processing of large masses of information, a system which was called into being by the requirements of the present-day scientific technical revolution.

The use of EVM in control has been directed to the accomplishment of the following basic tasks. First, improvement of the administrative supervision and control by enhanced objectivity and validity of the man-made solutions applied in consequence of the operational recording of a considerably larger mass of data pertaining to the preparation of the solutions. Second, enhancement of the quality and efficiency of the transmission of the information needed for the preparation and making of decisions. Third, achievement of a new, higher level of quality and coordination of the plans and the economic and production-technological processes. Fourth, enhancement of the effectiveness of the monitoring of the systems which operate in an actual time context. Finally, fifth, automation of the computations and engineering calculations and increased accuracy of the formulation of the control problems by codifying them and thereby generating enhanced forms of the organization of mental work in general.

We can single out the following basic classes of automated systems employing EVM:

1. The large systems for transmission and processing of data (information) of the territorial type. These systems are set up for the purpose of improving the economic management and the nationwide administrative supervision of the national economy sectors, the large economic regions, and the All-Union and republic industrial associations.

2. The automated enterprise control systems (ASUP)--the systems for collection transmission and processing of economic planning and accounting information at the enterprise. In these systems the EVM solution of information problems is combined with the automated preparation of data for the solution of management problems.

3. Automated systems of information servicing in the fields of public health and education, in scientific research and scientific-technical information, in transport, etc.

4. Automated control systems for the technical processes--systems for the optimization of the continuous production routine and the monitoring of the energy systems, the air traffic, the production control service, etc.

5. Automated systems for monitoring moving objects with an active role played by the human operator, as for example, on transport facilities. A system for monitoring lunar motion is an example of this.

On a natural basis, all these systems can be subdivided into two types. First, the systems for data processing (SOD). In these EVM functions as a tool and a means of preparing the solutions adopted by man. The first three classes of systems are of this type. The second type is, strictly speaking, the ASU, where the EVM not only fulfills the functions of preparation of solutions but also participates in the working out of an optimum solution. Although here too the adoption and approval of a solution is still largely a function of man, it rather fulfills the role of observer and controller. The fourth and fifth classes of systems are systems of this type.

The ASU for technological processes or moving objects can be considered machine--man--machine systems. It is these systems that the discussion below is concerned with. Man is here included in the control process, which under simple or normal circumstances can proceed under his supervision and control. The ASU operator makes decisions in emergency or unforseen situations.

These systems make great demands on the technology but also no less great demands on man; man must be considered not simply a special "human" link in the overall control system (as was the case in the initial stages of the development of the cybernetic technology) but as the basic central intellectual link embodying the "mind" of the system.

Despite their rapid and remarkable development, the EVM are not of themselves capable of creating the entire intellectual potential necessary for the preparation, adoption and implementation of decisions in the automated systems. As things have turned out today, for complicated situations this objective can only be achieved in the context of a sufficiently flexible interrelationship between man and EVM and when this interrelationship is little dependent on previously predetermined programs. This kind of organization of the interrelationship, if unusual, is still a completely realistic and effective method of merging people's intellectual potential with the intensification of their creative capacities.

In recent years the views of the control system developers with respect to man have undergone considerable changes. There is now no need to hail man as a "magic black box" capable of restoring the operational capacity of the system while rejecting its elements and capable of finding correct solutions in unexpected situations. Doubts as to the need to use man in the control system have receded into the past. The doubts manifested at this time pertain on the contrary to the potentialities of the EVM. In various instances and for various problems the attitude toward EVM in the control systems is today going through, as one specialist expressed it, four stages:

--"No, no, no!"

--"Ha, ha, ha"!

--"Yes, yes, yes"!

--"O-ho-ho!"

It is our profound conviction that the last stage can be attained only by way of rational organization of the interrelationship between man and machine. The various aspects of this problem are also delineated in the booklet

Table of Contents

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UDC: 612.82+821.821.8+612.822.3

DYNAMICS OF SLOW ELECTRICAL ACTIVITY OF THE HUMAN CEREBRAL CORTEX, AND PERCEPTION ERRORS

Moscow ZHURNAL VYSSHEY NERVNOY DEYATEL'NOSTI in Russian Vol 30, No 3, 1980
pp 602-605

[Article by A. M. Ivanitskiy, I. A. Korsakov and L. V. Matveyeva, Laboratory of Electrophysiology, Central Scientific Research Institute of Forensic Psychiatry imeni V. P. Serbskiy, Moscow, submitted 15 May 79]

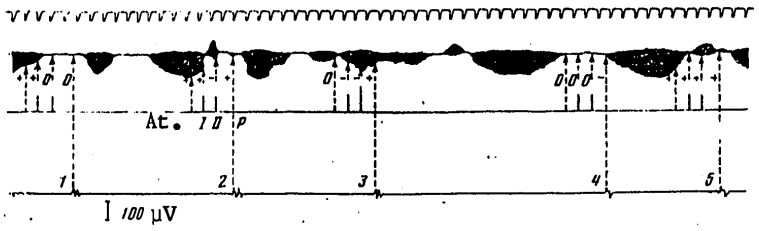
[Text] The hypothesis was expounded, on the basis of analysis of the possible physiological mechanisms of perception errors made in our preceding work [2], that slow oscillations of cortical potential may play an important role in the genesis of perception errors. Slow activity of the cerebral cortex was recorded in a psychophysical experiment dealing with differentiation of light flashes according to brightness in order to make an experimental verification of this hypothesis.

Experiments were conducted on 16 healthy subjects who were put in a dark, soundproof chamber during the test. Pairs of light flashes were delivered at intervals of 1.2 s between the two flashes 1 s after giving the subjects the command, "attention." The interval between pairs of flashes was 4-10 s. Half the flashes were of the same brightness (energy of light flux 0.18 and 0.18 J) and half of different brightness (0.18 and 0.27 J). The pairs of flashes (total of 100 pairs) were delivered in random order. The subject had to react to delivery of flashes differing in brightness by depressing twice on a button and to flashes of the same brightness by depressing once on the button.

The subjects' reactions were evaluated as follows: "detection of signal," when the subject perceived different flashes as being different; "false alarm," when the subject perceived identical flashes as being different; "missed signal," when the subject perceived different flashes as being the same; "correct negation" or "rest," when the subject perceived identical flashes as being identical. Consequently, "detection of signal" and "correct negation" were the correct reactions, while "false alarm" and "missed signal" were incorrect.

Electrical activity was recorded with electroencephalographic electrodes placed over the occipital cortex along the midline, 2 cm above the inion. The reference electrode was on the right mastoid process. The biopotentials were amplified with a BU-1 amplifer with frequency response of 0.1 to 10 Hz. The active input resistance of the amplifier constituted at least 10 MΩ. Slow potentials were fed from the BU-1 output through a vibropack, at a chopping frequency of 12/s, to the input of an

MB 5202/B electroencephalograph (produced in the Hungarian People's Republic). The Figure illustrates the type of tracing we recorded.



Slow electrical activity of the human cerebral cortex and subject's reactions to light flashes. Top to bottom: time mark 1/s, slow activity, marks of flash delivery, marks of subject's reactions. When the reactions are correct the sign of the derivative of slow ac ivity does not change, when they are wrong, the sign of the derivative changes

Key:
At.) time of giving the command, "attention"
I, II) time of presentation of first and second flash
p) mark of subject's reaction
+, -, 0) signs of first derivative of slow activity
1, 2) false alarm reaction
3) correct detection reaction
4, 5) correct negation (rest) reaction

In control experiments, when the electrodes were put in saline, we observed some drift of potential for 1-2 min, after which it stabilized, and we failed to demonstrate any oscillations of potential comparable in amplitude and time parameters to the tracing from the skin.

When recording slow electrical activity from the scalp, the question of distortion of this activity may arise because of fluctuations of galvanic skin reaction (GSR).

In order to determine the extent to which the slow activity recorded in our experiments was free of the GSR component, we conducted special control experiments. We made parallel tracings of slow activity from an electrode situated on the scalp, as well as a subcutaneous needle electrode isolated over its entire length, with the exception of the tip. This tracing failed to reveal significant differences in nature of activity in both instances. The needle electrode was inserted at a distance of 3-5 mm from the superficial one. Nor did we demonstrate significant changes in amplitude and time parameters of slow waves recorded from the skin surface after ionophoretic administration of 0.1% atropine solution for 20 min at the site of either the active or referent electrode. At the same time, significant reduction of GSR was noted on the wrist [or hand] after ionophoretic administration of atropine.

The data in the literature also confirm that the slow activity recorded from the scalp does not undergo significant distortion due to GSR because of mild expression thereof [1, 5]. The foregoing warrants the conclusion that the slow activity we recorded is chiefly of cerebral origin, especially since it differed appreciably from GSR parameters in its amplitude and time characteristics.

The recorded activity was characterized by aperiodic waves in the frequency range of 0.15-0.3 Hz and mean ampliutde of about 50 μV. Analogous activity had been described by several authors [1, 3], who observe that oscillations of this frequency and amplitude are dominant in a waking state.

In our study, we determined the amplitude and direction of shift in slow electrical activity, change therein in the direction of positivity or negativity (i.e., sign of first derivative) at the time of issuing the order, "attention," delivery of the first and second stimuli, and the subject's reaction.

Subject's reaction as a function of change in sign of first derivative of slow activity (percentage of total number of tests)

Time interval	Correct reactions		Erroneous reactions	
	correct detection	rest	missed signal	false alarm
"Attention"--first light flash	64.0	65.2	64.7	64.6
First--second light flashes	31.5	37.0	68.3	75.4
Second flash--depression [of button]	44.8	46.7	45.7	48.0

A comparison of data referable to electrical activity and the four possible results of the psychophysiological experiment is shown in the Table. We see that, in a high percentage of cases, the subjects' erroneous reactions were associated with a change in sign of the first derivative in the interval between stimuli. At the same time, we failed to demonstrate a correlation between the subjects' reaction and frequency of change in sign of the first derivative of the potential in the intervals between the "attention" command and first flash of light, as well as between the second flash and the subject's reaction. In this series of experiments, we also failed to detect a link between the direction of change in potential (positive or negative direction) and nature of the subject's reaction.

It must be noted that, in the situation of correct detection, there was a decrease in number of cases of change in sign of the first derivative of activity, as compared to the background. While the direction of the potential changed in 72% of the cases in the background, in relation to the total number of tests (readings were taken for 350 points picked at random divided by the time equaling the interval between flashes), in the case of correct reactions the percentages were 31.5 and 37.0 (see Table). In this case, we observed some extension of the period. In this respect, it is also interesting that the subjects who made fewer mistakes presented a lower background frequency of slow waves. In the case of incorrect reactions, the percentage of changes in sign of the first derivative did not differ from the background. It can be added that the slow activity we recorded was the opposite of the GSR with regard to this parameter. It is known that GSR increases with delivery of stimuli [5], while the slow potentials were usually stabilized in our experiments.

Thus, the results of the experiments indicate that perception of the intensity of stimuli (in our experiments the light flashes) is modulated to a significant degree by slow electrical activity of the cerebral cortex. Correct detection is implemented by a certain stabilization of slow electrical activity, as a result of which both stimuli of a pair coincide with unidirectional change in potential. With a change in sign of the first derivative of potential, the perception of brightness is distorted in the interval between flashes, which leads to mistakes in assessing the stimuli perceived.

It is known that changes in the slow cortical potential are associated with a change in excitability of cerebral structures, and this was demonstrated in studies of evoked potentials [7] and of the activity of single neurons, as well as in studies of conditioned reflexes [4, 6].

Evidently, the conditions under which perception takes place must be stable for adequate perception of flashes of light differing little in intensity. Stability of the direction of change in cortical potential is apparently one of these conditions.

It is assumed that the considerable stabilization of cortical potential with correct perception of intensity of stimuli may be indicative of the presence of an active regulatory mechanism, which makes it possible to stabilize the functional state of the analyzer. In this sense, stabilization of potential may be one of the components of physiological implementation of adequate perception of the physical parameters of stimuli.

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CSO: 1840

UDC 62.50.23

ERGATIC CONTROL SYSTEMS

Kiev ERGATICHESKIYE SISTEMY UPRAVLENIYA in Russian 1978 (signed to press 27 Dec 78) pp 2, 61-64

[Annotation and abstracts of articles from the book "Ergatic Control Systems", edited by Professor V. V. Pavlov, doctor of technical sciences, Institute of Cybernetics, Ukrainian SSR Academy of Sciences, 500 copies, 65 pages]

[Text] Annotation

The results of investigation of a control system with a human operator in a control circuit are presented.

Questions of the optimization of processes of identification are examined, as are methods and ways to expand the possibilities of a human operator in solving navigation tasks and ways to estimate operator load in ergatic aviation control systems.

The collection is designed for specialists in the areas of cybernetics and agronomy. It can be useful to graduate students and students of senior classes in the corresponding specialties.

UDC 62.50.23

INVESTIGATION OF ALGORITHMS FOR STATIC SIMULATION OF OPERATOR LOAD IN AN ERGATIC NAVIGATION COMPLEX

[Abstract of article by Nakov, N. I.]

[Text] The article examines the task of estimating operator load in solving tasks of navigation during flight. The method of statistical simulation was used to obtain a quantitative estimate of the dynamic loading of the operator. The proposed numerical algorithms for determination of operator load during the performance of navigation tasks are described in FORTRAN IV. Bibliography: 2 items.

UDC 62.50.23

ERGATIC SHIP POWER PLANT CONTROL SYSTEM

[Abstract of article by Lanchukovskiy, V. I.]

[Text] The state of the question of improving the maneuvering properties of a ship propulsion complex is analyzed. The task of investigating dynamic models of contemporary automated engines and their control algorithms. Equations of some ship engine plant regulators are presented. Bibliography: 5 items.

UDC 62.50.25

INFORMATION APPROACH TO EVALUATING AN OPERATOR'S READING OF INSTRUMENT INDICATIONS

[Abstract of article by Kurochkin, V. V.]

[Text] The quantity of information per measurement and the information transmission (readout) rate are examined as information criteria. Correlations are presented for obtaining the mean conditional entropy for cases of discrete and continuous states and messages. Bibliography: 4 items.

UDC 62.50.23

ERGONOMIC SOFTWARE FOR REMOTE CONTROL OF A SHIP'S SLOW-SPEED DIESEL ENGINE

[Abstract of article by Filonenko, D.]

[Text] An investigation is made of how the realization of the problem of control of a vessel's motion from the pilot's cabin by means of automated systems changed the ship operator's activity algorithm. Practical analysis of the operation of main engine automated control systems, the interaction and interconnection of ship operators with the main engine under real operating conditions makes it possible to conclude that it is necesssary to consider some properties of the human factor in the realization of low-speed diesel control posts. The developed proposals permit increasing to a certain degree the effectiveness of main diesel engine control. Bibliography: 1 item.

UDC 681.51:629.7.015.3

OPTIMUM ESTIMATION OF A 'MAN-MACHINE' SYSTEM

[Abstract of article by Kas'yanov, V. A., and Zautashvili, V. G.[

[Text] Questions of the optimization of processes in the identification of dynamic systems on the basis of implicit algorithms synthesized from the

stability conditions are examined. Minimax optimization criteria are proposed, which permits considering the degree of prior information about the parameters to be estimated. A solution is obtained for optimization of the process of identification of the aerodynamic characteristics of aircraft under the conditions of limitations connected with the realizability of the laws of pilot control. Bibliography: 1 item.

UDC 62.50.23

PROBLEMS IN THE AUTOMATION OF NAVIGATION

[Abstract of article by Stafeyev, A. M.]

[Text] The article examines questions in the creation and operation of automated navigation systems on large-capacity ships. A definite disproportion is noted in the technical level of the equipping of ships. Positive results and shortcomings are noted in the experimental operation of imported automated navigation systems installed in recent years on Black Sea Steamship Company ships. Bibliography: 1 item.

UDC 629.735.051.5

ESTIMATING THE PRECISION OF EXECUTION OF THE TASK IN ARGETIC AVIATION SYSTEMS

[Abstract of article by Kovaruk, V. V., and Khrisanov, S. M.]

[Text] An analytical method of determining the possible precision of aircraft navigation along routes with deviations is described. Analytical recurrent correlations are presented which permit estimating longitudinal and lateral deviations of aircraft in any section of the route according to known errors of its initial position and errors of readout of coordinates during flight. The vectors of total and partial deviations of aircraft are presented in matrix form. Bibliography: 1 item.

UDC 62.50.23

OPTIMUM HEADING CORRELATION TO HOLD A SHIP ON A TRAJECTORY

[Abstract of article by Vagushchenko, L. L.]

[Text] An algorithm is proposed for the correction of the given heading of a heading hold syste, one which permits with a minimum mean-square error assuring holding of the vessel on a trajectory according to discrete observarions of lateral deviation. The given heading is changed at intervals which permit making those changes manually if necessary. Besides the above, a description is given of a method of correlation which permits minimizing the dispersion of corrections for a given precision of holding on trajectory and by the same token avoiding considerable elongation of the ship's path due to heading changes. Bibliography: 1 item.

UDC 62.50.23

ALGORITHMS AND STRUCTURES OF ACTIVITY OF NAVIGATION PERSONNEL IN THE PROCESS OF SOLVING THE TASK OF SHIP CONTROL

[Abstract of article by Khovrachev, G. G.]

[Text] An analysis is given of the activity of navigation personnel in ship control. Decomposition of a typical voyage into stages is examined, as is the formation of tasks to be solved in navigation and control functions entrusted to ship ergatic control systems in separate stages. On the basis of analysis of the functioning of ship ergatic control systems a consolidated algorithm has been constructed for the activity of a navigator solving the task of controlling a ship in the open sea. Bibliography: 2 items.

[364-2174]

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CSO: 1840

PSYCHOLOGY

RESEARCH METHODOLOGY IN ENGINEERING AND LABOR PSYCHOLOGY

Leningrad METODOLOGIA ISLEDOVANIY PO INZHENERNOY PSIKHOLOGII I PSIKHOLOGII TRUDA in Russian 1974 pp 2-4, 148

[Annotation, preface and table of contents from book "The Methodology of Research in Engineering and Labor Psychology, Part 1", edited by Doctor of Psychological Sciences A. A. Krylov, Izdatel'stvo Leningradskogo universiteta, 148 pages]

[Text] Annotation--This collective monograph deals with the basic problems connected with the methodology and methods of research on engineering and labor psychology. It examines the most important ways of studying the operator's activity in receiving and processing information, the methods of evaluating the status of the individual in various activity aspects, and questions relating to training and determining vocational fitness.

The book is designed for specialists who work in engineering psychology, labor psychology and ergonomics.

Tables--10, Illustrations--27, Bibliography--180 items.

Editor's Preface--The need for simultaneous development of all the fields of human knowledge is a characteristic feature of the current period of revolutionary changes in science and technology. Psychology is one of the sciences where the progress achieved in recent years enables us to talk about a characteristic "psychological boom." The "psychological boom" is not a chance phenomenon. The most diverse knowledge concerning man as a subject of labor, as a subject of cognition, and as a subject of intercourse was necessary both in the planning of new technology, the accomplishment of social planning, the development of new forms of instruction and methods of vocational training, etc. Among the psychological scientific disciplines

which are of particularly great interest one would be justified in listing the psychology of labor and engineering psychology.* This is primarily due to the fact that the results of the research carried out in the field of labor psychology and engineering psychology are used on the level of 'reification" in the realm of physical production.

To date the fields of engineering psychology and labor psychology have carried out an enormous number of research projects which, on the whole, have been directed to a search for optimum solutions in the designing of technical units and equipment to be used by man; research for the creation of favorable conditions in the external environment; for improvement of the methods of vocational screening and training; for a search for ways of monitoring and controlling the status of the individual in the period of his work activity, etc. These research projects vary as to level and direction. They are often based on a simplified perception of man and his activity when they stem from direct analogies with the functioning of the technical devices, as for example, control automatic machines. This sometimes generates mechanistic tendencies in comprehending the nature of the operation of the cerebral system and a dogmatic approach to the implementation of the psychological recommendations. If we bear in mind also that as things stand now the problem of providing qualified psychologist and research personnel is still a long way from a full solution and that the psychological and engineering psychology research is now being carried out by specialists in various fields of knowledge, then we would have to recognize the special urgency of the development of the methodological aspects of engineering psychology and labor psychology. There are now good resources for this purpose, engendered on the one hand by the achievements of the science of psychology in the field of theory and methodology and, on the other hand, by the wealth and diversity of the empirical material and the growing need for practical utilization of the results obtained.

The main purpose of genuine collective labor is generalization and systematization of the knowledge concerning the research project in engineering psychology and labor psychology, analysis of the basic methodological approaches and some of the methodological techniques, evaluation of the potentialities for utilization of the results of the research, etc. The authors make use of the results of their own experimental and theoretical research as well as the domestic and foreign published literature on the subject under study.

*Engineering psychology, which formulates the principles of optimum activity of man on the basis of a study of the operation of the brain as an information system, is now characterized by the profound and specific nature of the methods of experiment and the theoretical concepts and approaches. Engineering psychology therefore actually represents an independent scientific discipline and is not a division of the psychology of labor although historically it is linked with precisely this field of the science of psychology.

The nucleus of the authors' collective comprised associates of the ergonomics and engineering psychology departments and the engineering psychology laboratory of Leningrad University. In addition, for the writing of a number of the sections of the book we recruited scientists who had participated directly in the research done in the psychology department of LSU [Leningrad State University]. The first part of the authors' collectives' work as presented in this book was written by the following: Gl. [Chapter] I (Introductory)--A. A. Krylov; Gl. II No. 1--M. A. Dmitriyeva, No. 2--M. A. Dmitriyeva and G. V. Sukhodol'skiy, No. 5--G. V. Sukhodol'skiy, No. 3--V. A. Ganzen, No. 2--A. I. Naftul'yev, No. 6--G. S. Nikiforov; Gl III, No. 7 and 9--V. L. Marishchuk, No. 8--G. N. Khilova, No. 10--N. N. Obozov; Gl IV, No. 11--A. A. Krylov and V. G. Naberezhnykh, No. 12 and 13--I. D. Rozhanskaya.

The editor and the author's collective feel obliged to express their gratitude for the help given them in the process of preparation of this book by APN [Academy of Pedagogical Sciences] USSR corresponding member Professor B. F. Lomov, who provided direct supervision in the initial period of the creative activity of many of the associates of the ergonomics and engineering psychology departments and the engineering psychology laboratory of Leningrad State University.

Doctor of Psychological Sciences
A. A. Krylov

Table of Contents

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UDC 615.814.1.015.4:613.863

EFFECT OF ELECTROACUPUNCTURE ON MANIFESTATIONS OF PAIN-GENERATED EMOTIONAL STRESS

Moscow BYULLETEN' EKSPERIMENTAL'NOY BIOLOGII I MEDITSINY in Russian No 1, Jan 81 pp 18-20

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[Text] Research on the mechanisms behind operation and triggering of endogenous stress-protective systems, which include, according to present ideas, the positively reinforcing and antinociceptive systems of the brain (4), has important significance to the search for ways to prevent emotional stress. It may be hypothesized that one of the possible ways for triggering these antistress systems may be to influence certain acupuncture points, inasmuch as presently available data show that acupuncture can relieve distress in certain situations (8).

The objective of this investigation was to study the stress-protective action of acupuncture in comparison with the effect of a typical antistress preparation from the benzodiazepin tranquilizer group--diazepam, which has a distinct influence upon the positive reinforcement system and antinociceptive mechanisms (2, 5).

Research Methods

The experiments were performed on 73 male rats weighing 250-300 gm. Stress was induced by a modification of Zabrodin's technique (7): Immobilized rats were subjected to electric stimulation at the base of the tail (20 pulses/sec, 10 msec, 30 w) with needle electrodes for 3 hours, the pattern being 30 seconds of stimulation every 2.5 minutes.

Electroacupuncture was performed with standard acupuncture needles at the analog of acupuncture point Da-Zhui (TM-14) throughout the entire time of stress influence. Choice of this point was based on clinical data indicating the broad spectrum of effects (including sedative) that could be achieved by activating this point, and its high effectiveness in the treatment of neuroses. We also considered the central location of this point in the "collar zone", which contains such extensive reflex associations (6). The stimulus parameters included a frequency of 1 pulse/sec and a duration of 1 msec, and the stimulus intensity was selected individually for each animal, enough to cause slight fibrillation of muscles in the vicinity of the needle.

The consequences of stress influence were assessed on the basis of erosive-ulcerous injuries to the stomach (7) as well as on the basis of change in the emotional reactivity and aggressiveness in response to, correspondingly, seizing the animal with the hand and bringing a metal rod near the animal, in accordance with techniques described earlier (1, 9).

We devised a scale based on the frequency of arisal of appropriate components of an integrated pain reaction in order to assess the pain reaction arising in rats permitted unrestricted behavior while experiencing stimulation of gradually increasing intensity at the base of the tail (3). The base of the tail was stimulated with bipolar electrodes contained in a flexible sheath, using short bursts of pulses with parameters 10 pulses/sec, 1 msec, 1 sec, and 30-100 w. Diazepam was injected intraperitoneally at a dose of 2.5 mg/kg, 30 minutes prior to the start of the experiment. The results were subjected to statistical treatment using Student's t-test.

Research Results

Stress produced significant change in the emotional and somatic status of the animals. As we can see from the table, erosive-ulcerous injuries appeared in the gastric mucous membrane of the rats, and their emotional reactivity and aggressiveness declined.

Effect of Electroacupuncture and Diazepam at a Dose of 2.5 mg/kg on Manifestations of Pain-Induced Emotional Stress in Rats ($M \pm m$)

Experimental Conditions	No. of Experiments	No. of Erosions	Emotional Reactivity, Points	Aggressiveness, Points
1. Control	10	0	1.20±0.13	1.20±0.20
2. Stress	10	8.6±1.0 $P_{1-2}<0.001$	0.10±0.10 $P_{1-2}<0.001$	0.50±0.17 $P_{1-2}<0.05$
3. Stress + diazepam	10	2.80±0.53 $P_{1-3}<0.001$ $P_{2-3}<0.001$	0.60±0.22 $P_{1-3}<0.05$	2.40±0.27 $P_{1-3}<0.01$ $P_{2-3}<0.001$
4. Stress + electroacupuncture at the acupuncture point	10	3.00±0.75 $P_{2-4}<0.001$	0.70±0.21 $P_{2-4}<0.05$	2.70±0.30 $P_{2-4}<0.001$
5. Stress + electroacupuncture outside acupuncture points	5	14.00±2.09 $P_{1-5}<0.001$ $P_{2-5}<0.05$	1.20±0.73	1.80±0.73

Diazepam reduced the pathological influence of the stressful situation. This was manifested as a statistically significant decline in the number of erosions. We concurrently noted a significantly lower decline in emotional reaction to external stimuli, in comparison with animals subjected to stress without diazepam premedication. Moreover the animals of this group exhibited heightened aggressiveness, expressed by more-frequent arisal of directed attacks against the provoking object.

Emotional reactivity was scored by the following number of points: 0--no reaction, 1--weak squeals or attempts to get free, 2--squeals and attempts to get free, 3--squeals and attempts to bite the hand. Aggressiveness was also scored with points: 0--no reaction, 1--turns away, 2--sniffs the rod, 3--single bites, 4--attack and numerous bites.

Electroacupuncture had a distinct stress-protective action comparable to the effect of diazepam (see table). Among rats subjected to stress on the background of electropuncture, the number of ulcerous stomach injuries was significantly lower than among control animals subjected to stress. Reduction of emotional reactivity was simultaneously forestalled, and aggressiveness increased similarly as in the series involving diazepam premedication.

A series of special experiments demonstrated that at a dose of 2.5 mg/kg, diazepam does not elicit significant changes in the structure of the pain reaction, while when electroacupuncture is applied to the point Da-Zhui, a relatively small increase in the thresholds of arisal of certain components of a response reflecting an emotional-behavioral reaction to intense nociceptive influence is noted.

Thus the research results show that electroacupuncture has a stress-protective action comparable to the effect of diazepam. Data obtained indicating absence of pronounced analgesia in response to diazepam and electroacupuncture permit the conclusion that the stress-protective effect is not associated exclusively with the painkilling action of the latter.

The antistress effect of diazepam is explained from the standpoint of its influence upon the positive-negative reinforcement system and the antinociceptive systems of the brain (4). It has recently been demonstrated that the antinociceptive effect is not only a mechanism of central analgesia, but it is also an operant method of self-regulation and self-protection against stressful influence, and that this effect manifests itself as a decrease in the intensity of ascending nociceptive transmission, and as correction of emotional-behavioral reactions (5). Influencing antinociceptive systems, diazepam typically modulates the exclusively emotional-behavioral components of the reaction to a stressful influence, and suppresses the activity of negative reinforcement systems, simultaneously activating the zone of "positiveness" (2).

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THE PSYCHOFUNCTIONAL TEST: MENTAL PREPAREDNESS EVALUATION IN ATHLETES

Moscow PSIKHOFUNKTSIONAL'NYY TEST: SPOSOB OTSENKI PSIKHICHESKOY PODGOTOVLENNOSTI SPORTSMENOV in Russian 1979 pp 3-23

[Excerpt from book "The Psychofunctional Test: A Means of Evaluating the Mental Preparedness of Athletes", by Anatoliy Vasil'yevich Alekseyev, Order of Lenin Central Institute for Advanced Training of Doctors, USSR Ministry of Public Health, passages enclosed in slantlines printed in boldface]

[Text] It is common knowledge that to an enormous degree the success of performances at competitions depends on the quality of the athlete's mental preparedness.

With every year the importance of psychological adjustment is steadily increasing. This is explained, first, by the never-ending rise in sport results; maximum mobilization of all the powers of the organism (physical and mental) are required to achieve and surpass them. Second, competitive pressure at sport matches is increasing from year to year, especially at important, prestigious ones, among which the Olympic games take first place in importance.

In response to the question of whether they know how to handle psychological preparation for competition, as a rule the overwhelming majority of athletes answer in the affirmative. Unfortunately, the results of competitions very often refute such affirmations, for example, the soccer matches at the 1978 international competitions where it was precisely poor mental adjustment of the players of our teams which prevented them from winning.

The discrepancy between a subjective opinion of good mental preparedness and inadequately mobilized behavior in the competitive arena requires the introduction into daily practice of objective (using instruments) criteria which would make it possible to evaluate the degree and quality

of athletes' mental preparedness even before the beginning of the competitions.

The present procedural manual presents one of the techniques for controlling the quality of mental preparedness which has received the designation of "the psychofunctional test" (PFT).

The Essentials of Mental Preparedness

In analyzing the process of mental adjustment it is not difficult to see that first there occurs a deliberate "review" of details of the situation which may arise at the impending competition. Thus, for example, a boxer imagines the ring and his opponent and deliberately plays over particular moments offensively or defensively. The discus thrower deliberately "sees" the nature of the ground in the circle and predicts the atmospheric temperature and the direction and force of the wind at the stadium where the competitions are to be held, etc.

Simultaneously with analysis of the future situation at the competitions the process of forming a personal attitude toward it occurs. But, as is well known, the formation of an attitude is always accompanied by the emergence of specific feelings and emotions. Thus, for example, a boxer imagining his opponent may experience the most diverse feelings--from timidity and anxiety to absolute confidence. A similar thing happens with each athlete.

The process of forming a personal attitude and the feelings which emerge as this takes place are the cornerstone of mental preparedness for competitions. If only positive emotions predominate, then, as a rule, success is guaranteed. In those cases when the athlete proves to be in the power of negative emotions, then he is doomed to defeat beforehand. For positive emotions, such as confidence, courage and joy, have a mobilizing, inspirational effect on man, and negative ones (anxiety, fear, uncertainty, etc) demobilize and disorganize his behavior.

There are a number of means and methods for overcoming negative emotions in athletes. As far back as 20 years ago and earlier, different medicinal preparations were in great demand. Some of them suppressed such feelings as fear and anxiety; others activated the organism's potential powers for the competitive fight. In our day such methods can no longer be used to solve the problem under consideration, since most of the preparations with such directivity are now classified as doping. Those which can be used, e.g., valerian, may have a completely unexpected effect, for in many ways the result of the action of the preparation depends on the /athlete's condition/ at the time he takes the drug. And these conditions have still not been adequately studied. For example, for this reason instances are known in which an overexcited athlete, wishing to get a good night's sleep before a competition, took soporifics and then got practically no sleep at all.

Psychologists who study athletic activity long ago proposed their own ways of mental adjustment. These include, among others, such devices as self-encouragement, self-persuasion and self-commands. The essence of such methods amounts to the fact that the athlete, having carefully interpreted the impending competitive situation, and having imagined himself in it, finds the thoughts, feelings and words he needs and then with their help organizes his condition and behavior.

Examples of self-commands in a long-distance runner might be such thoughts and words as "Endure, endure! Whatever happens, I must endure it!"

An example of self-persuasion in a fighter: "Everything will be all right. I am well informed about my opponent's leading techniques. Yesterday, watching how he fights, I saw with my own eyes that his arsenal of techniques hasn't changed recently. I have always won against this fighter. That means I'll also win this time."

An example of self-encouragement in a discus thrower: "Everything will go as it should. I am well prepared and hit the mark very well."

Such mental techniques are used more or less consciously by all athletes.

It must be admitted, that the methods of psychological self adjustment are valid and provide substantial help quite often, but unfortunately, not always. The fact is that often cases are seen in which the organism does not submit to self-encouragement or self-commands, i.e., after the athlete says very correct thoughts and words to himself, the necessary physiological changes do not take place in his organism. Without these changes the psychological beginning (the thoughts and words) remains unrealized. Suppose an athlete has ordered himself to calm down but his heart continues to beat feverishly, his respiration remains rapid and shallow, his muscles tense and his thoughts "race" chaotically in his head. This is an instance of the correct and necessary words "calm down" (the psychological component) failing to link up with the organism's other systems--nervous, cardiac, cardio-vascular, respiratory and muscular (with the physical component) and to restore them to a state of calm. Thus no effect was obtained from the self command.

Only when the necessary and appropriate physical changes occur in the organism following the psychological beginning (thoughts and words) does the athlete become as he should be. But how can an effective association between the psychological and physical components of the organism be ensured? In order to find an answer to this question it is first necessary to become acquainted with the theory of functional systems developed by Academician P. K. Anokhin.

The Functional Systems of the Organism

During the last decade of his life Academician P. K. Anokhin (1898-1974) definitively formulated the theory of the functional systems of the organism. In simplified form this theory is as follows:

When a person engages in some activity changes determined by this activity begin in his organism. Thus, when he ascends a staircase to an upper floor his heart begins to beat more rapidly, respiration deepens, the activity of the work of the muscles (especially the muscles of the legs) increases, and a whole series of other changes occur in the organism which are necessary in order for the goal (ascending to the necessary floor) to be achieved. The /totality/ of all these changes in the organism is directed at achieving the /necessary result/ and constitutes a /functional system/ which unites all the most characteristic elements of the person's condition at the given time.

Thus, by functional system we mean the joint action of the most diverse systems of the organism (nervous, cardio-vascular, respiratory, muscular, etc) which are united for the time necessary to perform the task set. As soon as it is performed the particular functional system falls apart, and the individual organs and systems which were part of it can now unite in other combinations according to the requirements of the next task. Thus, e.g., while the staircase is being ascended the activity of the gastro-intestinal tract is minimal. But now the person has reached the necessary floor, entered his apartment and sat down to eat. Now the most active organs become those which carry out the procedure of food intake and processing--the hands, teeth, masticatory muscles and the glands which secrete the enzymes necessary for chemical processing of the food.

Naturally, other organs, especially the heart, lungs and the muscles of the body also continue to function in a person who is eating. But since the process of eating does not require high activity of these organs, while entering into the functional system of the digestive act they occupy a different, one might say subordinate, position in it.

Thus, during the ascent of the staircase the heart, lungs and muscles of the legs were the major elements in the functional system performing the physical work, and the gastro-intestinal tract was in the background. At the table, however, during the process of eating, a new functional system was formed, and active work of the organs necessary for performing this new function--food intake--came into the foreground.

In the same way, during any successful activity, precisely those functional systems of the organism which ensure achievement of the desired result are activated. At the same time, it should be emphasized that the formation of different functional systems is determined by the ultimate goal which must be achieved. According to the theory proposed by P. K. Anokhin, it is precisely the /desired/ ultimate result which "sets up" the

structure of the next functional system, i.e., determines how and in what combinations the different organs united in the particular functional system will act.

To a certain extent the re-forming of functional systems in the organism can be compared to the reorganization which occurs with the bits of colored glass in a kaleidoscope--the bits of glass remain the same but each new turn of the tube of this toy puts them together in a new and harmonious combination. In a similar way each new task which emerges for a person leads to the activization in his organism of appropriate systems which are capable of solving exactly this task. And the activity of the other systems which are less needed in the given concrete case decreases simultaneously.

It is not hard to see that functional systems are unusually mobile; their internal structure may change in the shortest intervals of time--depending on the properties of the tasks which the person must solve. But how is such high mobility of the functional systems of the organism, which are different in structure and essence, achieved?

Autoregulation

As long ago as the early 1930's Academician I. P. Pavlov wrote in his "Otvet fiziologa psikhologam" [A Physiologist's Answer to the Psychologists], "Of course, man is a system (more crudely speaking, a machine) like any other in nature which is governed by laws which are inevitable and common to all nature; but a system which at the level of our current scientific vision, is /unique/ in having the highest degree of /autoregulation/. It is self-supporting, self-restoring and even self-improving" (emphasis by author).

Thus, even then, almost half a century removed from us, scientists saw that the living organism has been given such a remarkable property as /autoregulation/. It is exactly because of this property, developed by evolution that the changes which ensure performance of necessary actions and organize essential behavior occur as if by themselves in the active organism. But the fact that autoregulation is realized through the formation of special functional systems (such as are required by precisely the specific concrete case) in each individual case was most clearly and completely expressed only during the last decade in Academician P. K. Anokhin's school.

The research conducted in connection with the development of the theory of functional systems showed, among other things, that each functional system has vertical organization. This means that the plan (design, structure) of the next functional system originates in the brain, but the activity of this functional system is realized by switching the organs (heart, lungs, muscles, endocrine glands, etc) necessary for the performance of the contemplated task on and off.

The activity of the organs which participate in the functional system created may be very well coordinated, extremely harmonious. And then the person copes with his work successfully and easily. But unfortunately the joint activity of the different organs is not always coordinated. And different problems arise in the behavior of a person performing a particular task. For example, a student who is not very confident of his knowledge often begins to worry so much after taking his question card that he almost loses his gift of speech. Noncoordination is noted between the activity of the brain and the vocal muscles in this functional system which must become the basis for solving a quite specific task--successful completion of the examinations. In the same cases, when all components of the functional system are working harmoniously, in a coordinated manner, the student retains the ability to think clearly and present his knowledge concisely.

Most often disturbances in the activity of functional systems arise in healthy persons because of stress situations--i.e., at times when the organism, and, above all, its highest branch--the central nervous system--experience extreme tension, which is particularly distressing when negative emotions are present which are of important significance for that particular person. Consequently the mechanisms of autoregulation, which are built into us by nature are not absolutely reliable and far from always strong enough. On the other hand, medical and especially psychotherapeutic experience indicates that if a person specially prepares for impending stress influences he tolerates them much more easily. And despite the negative stress his functional systems continue to act with sufficient coordination and effectiveness, a result which promotes the maintenance of the satisfactory condition of the organism fulfilling the next task.

Thus, functional systems may act in two ways. Usually they arise and disintegrate as if by themselves, automatically, under the influence of particular requirements of the organism or influences of the environment. It can be said that in these cases the mechanisms of spontaneous /unconscious/ autoregulation are operating. But functional systems are also capable of changing their structures under the influence of a /consciously/ contemplated goal. Suppose that a fixed-target rifleman sets himself a specific objective and formulates it thus: "I will be completely calm at the upcoming competition." Practice convincingly shows that in people who have been /trained/ to use speech correctly and to utilize the power of words intelligently such a consciously formulated task as a rule helps the appropriate (harmonious) formation of the functional systems arising during the process of competition. And in harmoniously constructed functional systems, all their components act in coordination, ensuring a good result for the activity.

Let us make one important inference--human speech, through which we can concisely formulate a particular task, helps us/deliberately organize the coordinated work/ of individual components which compose integral functional systems of the organism. Accordingly, by using the resources

of speech it is possible to help the organism adjust its vital activities in the hardest situations.

Psychological Autoregulation

We said above that it is important for athletes to know how to govern their psychophysical condition /consciously/, to know how to organize the functional systems of their organisms which ensure the achievement of good results in the necessary way. It was also noted that even correctly selected words used in self-command, self-encouragement and self-persuasion do not always have the desired effect on the athlete's condition.

This is why in order to help the /pedagogical/ methods of psychological adjustment in sports it was decided to enlist /medical/ methods as having a greater power of influence on the psyche than self-commands or self-persuasion. As practice has shown, in the given case the most rational means in the arsenal of medicine is the method of /autosuggestion/.

Both self-persuasion and autosuggestion are methods of /psychological autoregulation/. In both cases the basic means of influencing the psyche is /words/ and /mental images/. There is an important difference between self-persuasion and autosuggestion, however. Thus, for example, when one depends on self-persuasion, i.e., logical inference, it is impossible to convince himself, as he sits in a room that at the given moment he is in a pine forest. But this task can be solved using autosuggestion, depending on such a psychological process as belief.

Autosuggestion is based on two main mechanisms. First the level of wakefulness of the brain must be lowered to a somnolent condition (first mechanism) and then, maintaining this somnolent condition under the control of peaceful consciousness, relaxed attention must be concentrated to the utmost (second mechanism) on the details of the problem being solved. For example, a contusion of the knee joint occurs, and there are no anesthetics at hand. Using autosuggestion it is not difficult to reduce the pain or completely stop it in the following manner: for several seconds immerse yourself in a remote, extremely peaceful condition on the verge of drowsiness and, with your attention focused on the knee, say (in a whisper or mentally), "The pain is going...going... it's becoming weaker and weaker...it is completely gone." And it really decreases or completely passes--everything depends on how well the skills of autosuggestion have been mastered.

Preliminary self immersion in a somnolent state makes the brain/unusually sensitive/to words and mental images which correspond to them. It is precisely by this mechanism, which is used in autosuggestion, that the technique is distinguished, first of all from self-persuasion in which speech acts on the brain in an ordinary, wakeful condition. This is why words used in autosuggestion have a much greater effect on a person than the same words used in the context of self-persuasion.

At the present day in many countries there are different methods of autosuggestion created specially for athletes. Of the Soviet methods, "Active Autosuggestion" (A. Romen, 1964), "Autogenic Training" (O. Chernikova and O. Dashkevich, 1967), "Psychoregulating Training" (A. Alekseyev and L. Gissen, 1968-1969), "Psychomuscular Training" (A. Alekseyev, 1973-1975), "Emotional-Volitional Training" (A. Filatov, 1975) and a number of others are particularly well known. So everyone may choose the method which he finds most appropriate for his own purposes.

Suppose an athlete feels that he has mastered one of the variants of autosuggestion and is well able to control his psychological condition. How can this be verified?

For many years the degree of mastery of autosuggestion was evaluated under laboratory conditions according to changes in a particular physiological index or indices, for example, according to how the skin temperature or pulse rate began to change before and after the use of autosuggestion. But as practice has shown, the ability to change the course of individual physiological processes in now way guarantees that autosuggestion will give the desired result under the stress conditions of competition. This happens for the simple reason that the optimal fighting condition (OBS) in which the athlete must be at the competitions requires a much more complex and specially individualized organization of the procedure of autosuggestion specially directed at the achievement of this optimal condition. Thus, if the athlete has learned to accelerate or decelerate his pulse using autosuggestion, this in itself is very good. But there is an enormous distance between such an ability and conscious organization of optimal fighting condition.

What is the essence of this distance? As has already been said, words and the mental images which correspond to them are the basic force which acts in psychological autoregulation. Thus, in order to produce, say, a rise in temperature in the skin of the forearms, after first going into a light somnolent state, one must think the words "the skin on my forearms is becoming warm" and deliberately "see" that hot sun rays are falling onto this region of the arms. Thus it is easy to produce a whole series of the most diverse sensations in oneself. But in order to put oneself into optimal fighting condition one must first /develop an efficient OBS structure/ and create a /full-fledged mental image/ of it. This is much more complex than the mental image used in regulating individual functions of the organism. With an efficient plan of his own specially individualized optimal fighting condition, the athlete may begin special psychological training directed at achieving OBS using autosuggestion during the precompetitive period.

Unfortunately, such work is still not being conducted on a wide scale. So far the quality of mental preparedness is being tested only at competitions. If an athlete performs well that means he has demonstrated the ability to master himself; if a failure befalls him, it follows that he has not learned to govern his psyche.

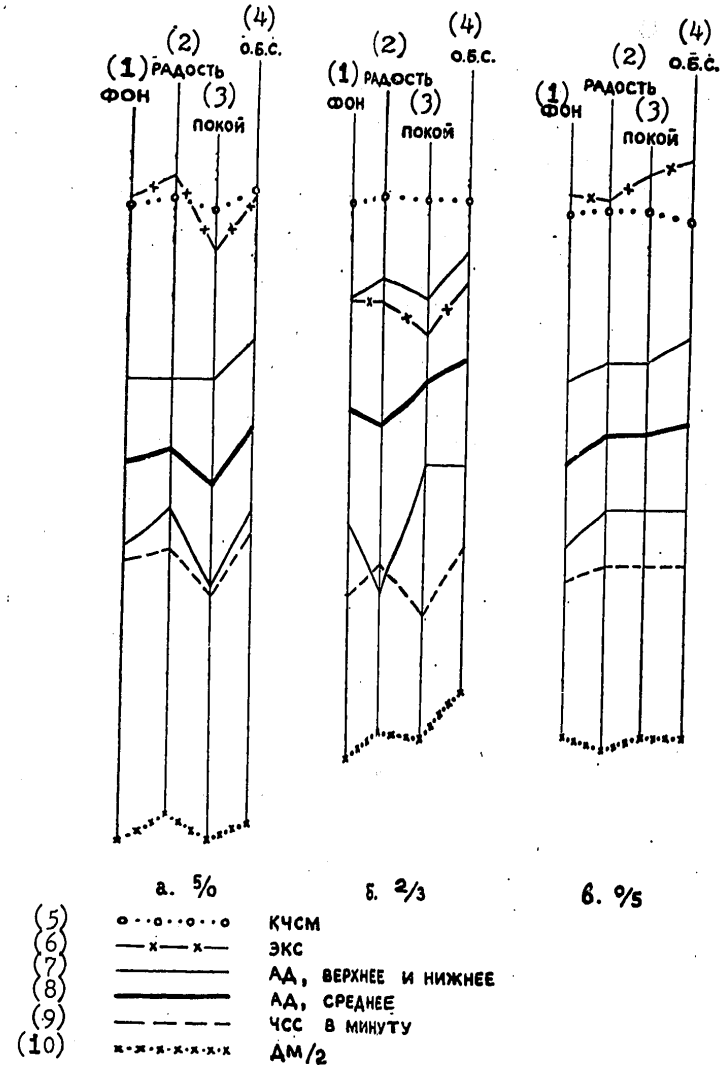

Figure 1.

Key:

1. Background
2. Joy
3. Calm
4. OBS
5. KChSM [critical frequency of light flashes
6. EKS [electrodermal resistance]
7. AD [arterial blood pressure], upper and lower
8. AD, mean
9. ChSS [heart beats] per minute
10. Dynamometry (DM/2)

Testing the degree of mastery of psychological autoregulation only at competitions, however, means exposing oneself to great risk. This risk must be approached fully armed with mental preparedness. But how can its quality be evaluated before the competition? In pursuit of an answer to this question a method was gradually developed which makes it possible to determine the degree of psychological autoregulation at the necessary moment. This method has been designated the "psychofunctional test" (PFT).

The Psychofunctional Test

As we said earlier, in the organism of a person engaged in some activity changes determined by this activity occur. The changes which occur in the organism in each specific case form appropriate functional systems. If the individual components of a given functional system act harmoniously, unidirectionally, the person copes successfully with the task. In the opposite case, when the individual components of a given functional system for some reason start working unharmoniously, in an uncoordinated manner, to some extent the activity always begins to go worse.

This conclusion from the theory of functional systems was made the basis of the psychofunctional test. Its essence is simple: it is suggested that the athlete perform a specific psychological task, and it is tested, using appropriate instruments, how harmoniously and unidirectionally the different systems of his organism participate in solving the psychological task set.

In the psychofunctional test the properties of the joint activity of the following systems of the organism are studied: nervous, cardio-vascular and muscular.

The degree of excitation of the cerebral cortex is evaluated using an instrument which determines the critical frequency of flashes of light (KChSM). This procedure takes 10-15 seconds.

The degree of excitation of the higher vegetative (subcortical) centers is determined using registration of electrodermal resistance (EKS) on the cushion of the fourth finger of the dominant hand. In all, 3-5 seconds are necessary for this study.

Arterial blood pressure (AD) is measured in 20-40 seconds using an ordinary medical tonometer.

The heart rate (ChSS) is established each time in 15 seconds by palpitation of the radial artery in the lower region of the forearm.

The muscular system (its power component) is evaluated using a standard hand dynamometer with a 90 kg range. Before beginning the studies the athletes squeeze the instrument once at full strength and then after several attempts learn to squeeze it at half strength. During testing

Table.

PFT Indices	First Tests	Second Tests	After Training In PMT and OBS
5:0	1	1	101
4:1	7	10	36
3:2	27	26	14
2:3	39	48	2
4:1	47	51	3
0:5	36	21	1

all further squeezing of the dynamometer is done at half strength. This changes according to the content of the psychological task. Each dynamometry (DM/2) study takes 5-10 seconds. Thus 1-1.5 minutes are required for a single study of all five indices.

Selection of the enumerated systems of the organism and instrumental methods was dictated by purely practical considerations which arose during work on psychological training of athletes for competitions. The information received from such tests gives a quite complete picture of how well the desired functional system is forming at the time of psychological adjustment to the competitive contest.

As for the instruments selected for conducting the given test, all of them fit into an ordinary briefcase and do not need to be connected to external energy sources. These circumstances (portability and independence from the electrical system) make it possible to conduct testing under any conditions, including field conditions.

In the psychofunctional test athletes (in standing position) perform three tasks during which they are supposed to use only psychological means, primarily those such as the processes of visualization, imagination and attention. They are not permitted to help themselves by active physical movements, but they may make small movements.

The first task is to put oneself into a state of "great joy" using visualization or imagination. The second task is to achieve a state of "complete calm" using the same psychological processes. The third task is to put oneself into "optimal fighting condition" (OBS), i.e., in what is the best psychophysical condition for this specific athlete at the time of competition.

All three tasks are performed successively in the order indicated here, without a break. At the time each of the three tasks is started, the five tested systems of the organism are examined using instruments. The data obtained indicate how unidirectionally and harmoniously the systems under study perform in each psychological task.

The time for performance of the test is not limited. Practice indicates that 5-10 to 50-60 seconds are required to perform one task. Consequently an average of 5-7--and a maximum of 10--minutes is spent on full testing of one person.

The three tasks which are part of the psychofunctional test were selected for the following considerations. The fact of the matter is that leaving aside most details, the basic essence of psychological autoregulation boils down to an extremely specific ability: to excite one's nervous system when necessary and to calm it when necessary. In order to excite or calm themselves using psychological means people employ only one power--that which is incorporated in thought, i.e., in

words and in the mental images associated with them.

Thus, for example, one may excite oneself by mentally visualizing or imagining some upsetting situation. But it is harmful for the organism to undergo the conditions determined by negative emotions (fear, grief, anxiety). This is why a pleasant emotion such as "great joy" was selected for the stimulus exciting the nervous system and, together with it, the entire organism.

Thus, the first task of the psychofunctional test is entering a state of "great joy", i.e., into one of the most useful emotional conditions. Athletes who know how to do this are thereby given a chance to use joy to drive out such negative emotions as, for example, fear and anxiety, which often arise before competitions and during them. So that a person who has learned to induce a full-fledged feeling of joy in himself under any conditions becomes invulnerable to the influence of negative stress situations. Besides, "great joy" plays a peculiar "warming up" role for the brain before the athlete enters into optimal fighting condition (after immersion in "complete calm").

The second task is immersion in "complete calm". The ability to calm oneself makes it possible to disengage from unneeded and hindering thoughts and feelings. This is especially important in order to escape from harmful emotional conditions. Moreover, complete psychological calm promotes the regeneration of energies. In those types of sports in which there are interruptions during performance--for example, between fights for fencers, between attempts for jumpers, etc.--these pauses are extremely useful to use for rest, for regeneration of energies by immersing oneself in deep psychological calm. The stage of "deep calm" helps one solve still another important task--in this condition, when the brain is freed of everything extraneous and it acquires increased sensitivity to information presented to it, it is possible to set about putting oneself into optimal fighting condition with the highest effectiveness.

The third task of the test is the ability to put oneself into optimal fighting condition--the final stage in psychological preparation of the athlete for competition. Naturally it is precisely this task, which completes the psychofunctional testing which is the most important. Depending on how well the athlete performs this task, it is possible to judge how well he controls himself and is able to adjust to the competition.

Before undergoing testing, each athlete not only thinks out the content of his personal models of joy, calm and OBS, but also describes them on a piece of paper--this gives the mental images concreteness and facilitates the testing procedure. Visualizing and fixing in writing the condition of joy and calm as a rule presents no difficulty. As for describing one's optimal fighting condition, this is a rather complex matter. Those who wish to obtain advice on this question should

familiarize themselves with the pertinent chapter of A. V. Alekseyev's book "Master Yourself!" (Fizkul'tura i sport, Moscow, 1978).

The data obtained from conducting the psychofunctional test are submitted to the simplest statistical analysis according to the following principle: the number which corresponds to the number of systems of the organism which participated in all three tasks of the test /unidirectionally/, harmoniously, becomes the numerator, and the number of systems which reacted /multidirectionally/ and conflictingly are placed in the denominator. Since five systems are being studied in the tests, with the best possible result a 5:0 ratio is obtained, and with the worst possible --0:5. Other ratios, e.g., 4:1, 2:3, etc., show how well the athlete has mastered the possibilities of psychological autoregulation, i.e. how well he can subordinate to himself the activity of the other functions of the organism using purely psychological means (thought, speech, attention, imagination).

If the data of the studies are plotted, it is possible to obtain an extremely graphic picture of the behavior of the different systems of the organism during performance of the psychofunctional test tasks.

Here are examples of graphs which show the results of the initial testing of the athletes (fig 1):

a. All five systems were stimulated by experiencing feelings of "joy" (the lines corresponding to them turned upwards) and quieted down during immersion in "calm" (the lines correspondingly went down) and were again excited during entry into optimal fighting condition (OBS). The test result is the highest possible--5:0.

b. Only two indices (heart beat--ChSS--and dynamometry--DM/2) reacted adequately to the test requirements. The other systems of the organism participated multidirectionally and inadequately in performing the task. Hence the result is 2:3.

c. All five systems of the organism reacted multidirectionally and inadequately during performance of the test tasks. The result is the lowest possible--0:5.

Of course, not only quantity, such as the uni- or multidirectivity of the individual indices but also the "degree of scope" with which a particular system of the organism reacts may be evaluated in the form of graphs. Thus, for example, the heart rate may increase by 4 and by 34 beats per minute during the experiencing of the feeling of joy (of course, the second figure indicates better functional "mobility" of the cardiovascular system). But this aspect of evaluation of the result obtained is a subsequent, higher stage in the analysis of the psychofunctional test results. When the special methods of psychological autoregulation are first mastered the indices of uni- and multidirectivity

of all five systems under study have the basic value.

The graphs in figure 1 show how individual athletes are able to control themselves by virtue of the capacities for psychological autoregulation given them by nature. Naturally the question arose of how such a method of psychological autoregulation as autosuggestion can influence the quality of the performance of the psychofunctional test tasks. Or, in other words, how much autosuggestion is capable of harmonizing the structure of functional systems which underlie the performance of specific psychological tasks, particularly those such as entering into optimal fighting condition.

In order to answer these questions, a special study was started in April 1977; its essentials amounted to the following: groups of athletes were examined three times using the psychofunctional test--first before training in autosuggestion, the second time a certain time (from several days to two months) after the first testing, also before training in autosuggestion (in order to learn how the training process alone influences athletes' psychofunctional condition) and for the third time after training in the fundamentals of autosuggestion.

This triple examination was undergone by 91 young sambo wrestlers (from the specialized Moscow school Sambo-70), 24 young judoists, 14 track and field athletes, 8 riflemen and 20 girls who play field hockey; in all, 157 persons.

Psychomuscular training (PMT) was used as the method of autosuggestion (A. V. Alekseyev, 1973-1975).

The table presents figures which show how the ratios of the different psychofunctional test indices (from 5:0 to 0:5) changed during the two years during which this work was conducted.

Most impressive in this table are the figures which reflect the dynamics of the best possible PFT index--5:0. While before training in autosuggestion only one of the 157 athletes proved to have such an indicator, after mastering the fundamentals of psychomuscular training as many as 101 began to perform the tasks of the psychofunctional test showing the same high result, 5:0. These data indicate with great reliability that mastery of the basics of psychological autoregulation sharply improves the course of the psychological processes and the physical ones associated with them in athletes. This is manifested subjectively in a pleasant feeling of good subordination, high "obedience" to his ego by different elements which comprise the athlete's psychological and physical state of health.

One of the most vexing difficulties encountered by those who performed the tasks of psychological autoregulation is that the expected results are not obtained immediately. The opinion exists that the psyche should submit immediately starting with the first demand imposed on it.

"And if it doesn't obey, then forget it, I won't waste time on any autosuggestion," many athletes reason, unfortunately.

But this is an enormous mistake! The brain, like any other system of the organism, needs special, systematic training in order to give results. And many athletes' problem is that at the present time they are being trained only for great /physical/ loads and absolutely do not know how to train /their brains/ correctly and consciously. Hence the sceptical attitude toward questions of psychological autoregulation and the lack of success in psychological training for competition.

With a serious attitude, psychological autoregulation gives extremely distinct results and quite rapidly. Figure 2 shows graphs of the data of psychofunctional testing of a decathlon athlete, P., examined three times over 10 days in all. During the first four days, studying under the guidance of a psychotherapist twice a day for 30 minutes the athlete mastered the basic calming and activating parts of psychomuscular training, something which immediately produced improvement in the PFT indices--3:2 in the second instead of 0:5 in the first test. In another five days, during which special training was conducted twice daily for 10-15 minutes in accordance with the developed formulas of optimal fighting condition (it was a question only of psychological adjustment to the first type of decathlon contest, the 100-meter race) the indices of psychofunctional testing became maximum, 5:0.

But such results are possible only where the athlete has a very serious attitude toward psychological autoregulation and works at it not only with a psychotherapist but also independently and "ties" the skills of autosuggestion to such training in the stadium and the gymnasium. Especially good results are obtained where the athletes' trainer uses the resources of psychological autoregulation in daily work with his students (as was the case in the example given of the decathlon athlete).

In summing up, it can be said that the studies conducted enable us to make the following conclusions:

1. Modern athletes, who perform under the most complex stress conditions, absolutely must have strong psychological autoregulation skills.

2. Each athlete should have a good knowledge of the specific psychofunctional components of OBS and be able to enter optimal fighting condition /consciously/ when this is required by the situation by using the resources of psychological autoregulation (autosuggestion).

3. The psychofunctional test is a simple and reliable method which makes it possible to determine /before/ competitions how well the athlete handles the skills of psychological autoregulation, how well he enters his optimal fighting condition, i.e., whether or not he knows how to subordinate to himself the /physical/ systems of his own organism

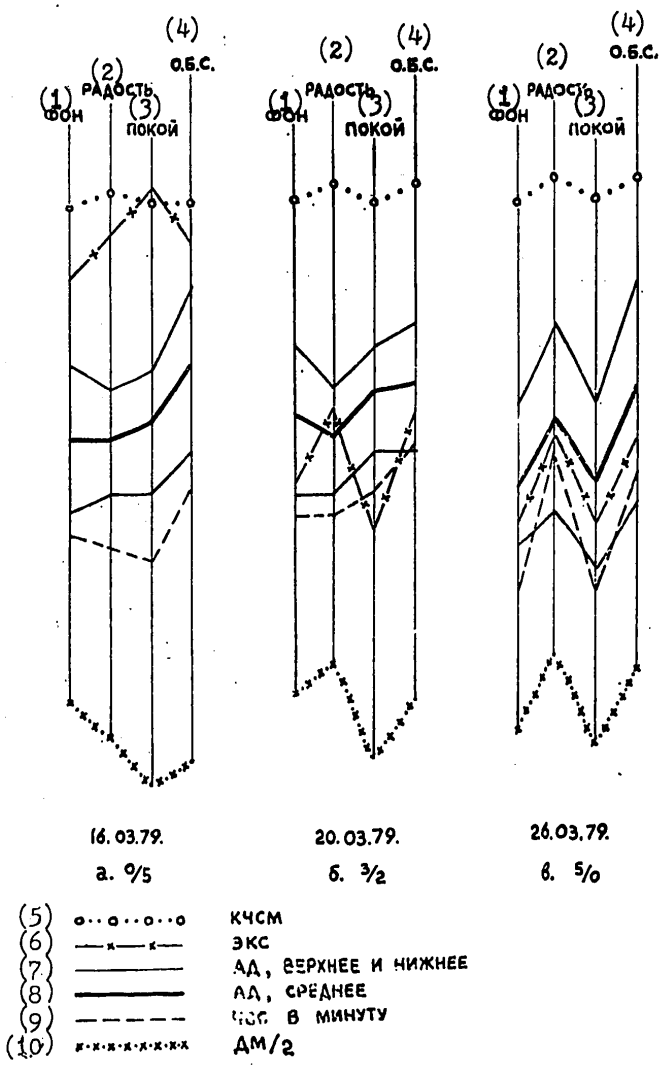

Figure 2.

Key:

1. Background
2. Joy
3. Calm
4. OBS
5. KChSM
6. EKS
7. AD, upper and lower
8. AD, mean
9. ChSS
10. Dynamometry (DM/2)

the activity of which is the basis for realizing the /psychological/ tasks dictated by the competitive conditions.

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THE MENTAL EXPERIMENT

Moscow MYSLENNYY EKSPERIMENT in Russian 1979 (signed to press 19 Nov 79) pp 2-6, 204-205

[Annotation, introduction and table of contents from book "The Mental Experiment", by Anatoliy Pavlovich Chernov, Izdatel'stvo "Nauka", 5,000 copies, 208 pages]

[Text] In this monograph, a theoretical analysis of problems related to the mental experiment is undertaken to show its interdisciplinary and complex character. Directions in current research are outlined and a methodology for mental experiments is proposed, thus enabling a description in objective terms of the structural, individual-typological and age-related parameters of mental experimentation.

The book is written for psychologists and scientists in related specialities.

Introduction

Concepts on the possibilities of mental experiments were formulated and expanded at the same time in the history of science as the development of natural-scientific experiments such as the specific method of research. The term "mental experiment" (Gedankenexperiment) entered into the vocabulary of the scientific revolution at the beginning of the Twentieth Century (355). Analysis of the psychological aspect of the process of knowledge and the creative theories of Galileo, Hyuygens, Newton, Maxwell, Karno and other classical thinkers in natural sciences demonstrated persuasively the essential role of the mental experiment in the course of formulating theoretical ideas. Moreover, wide spread dissemination of the Machist subjective-idealistic interpreation of a given heuristic process occurred. This approach was placed initially at the furthest point of of positivist spectrum concepts. Later, these concepts were used by P. Dyug' for analysis of the substance, purpose and structure of physical theory. P. K. Engel'meyer used it for the purpose of integrating the attempts to create evrology or

a general theory of creativity [100, 328, 329, 330]. The work of A. Einstein, N. Bor, V. Geyzenberg, E. Reserford and many other prominent scientists contributed a great deal to work in the area of the mental experiment. Because of their work, this process acquired the characteristics of an original method of theoretical analysis [38, 48, 67, 85, 323, 324, 344].

For a long period of time in Soviet philosophical literature, the problem of the mental experiment, as ackowledged by these same philosophers, was clearly underestimated and factually dismissed from the field of sensory investigation [58, 86, 318]. For many years, this methodologic concept was restricted to the field of psychology where it was disseminated in textbooks and general manuals [141, 189, 247, 278]. However, because of the absence of concrete materials to characterize the genesis and exact process of mental experimentation--its structural, age-related and individual characteristics--this heuristic process has been examined by psychologists primarily as an abstract-theoretical plan without proper critical interpretation and was not based on a framework of introspective description. The number of studies of this problem in special experimental and theoretical research has, up until now, been few.

The mental experiment is used in problematic situations when ordinary discursive-logical abilities to solve tasks are shown to be inadequate and a need arises to establish mentally a system of inter-related descriptive or abstract forms, which reflect a complex collection of space-time, principle-inquest and other relationships. Problems of this type are represented widely in different forms of work-oriented, educational and recreational activities which have the characteristics of foresight and creativity. Naturalists and philosophers, logicians and psychologists, engineers and writers concerned with analysis of the "technology" of thought, have confirmed the essential role of the mental experiment in the solution of theoretical and practical problems in science, technology and art [48, 56, 67, 85, 86, 116, 118, 182, 183, 247, 262, 282, 293, 318, 324, 328, 335, 344, 355].

We undertook an analysis of materials found in the psychological and scientific-methodologic literature to show that this mental process has not only cognitive but also didactic value as exhibited in the process of teaching and illustrative-demonstrative function [29-31, 128, 293, 301, 302]. Many empirically based methodological processes, utilized to develop thought are oriented in education to the use of mental experimentation. However, in view of the lack of in-depth study of recent theories of this process, its possibilities have not been realized in a complete or goal oriented fashion. Consequently, the practice

of mental experimentation occurs spontaneously but its formation is uncontrolled and undirected.

With increased attention to the scientific methodologic aspects of the mental experiment, theoretical studies related to logical-philosophic analysis of natural-scientific experiments and methods of building models have again been examined [86, 116, 139, 140, 181, 197, 262, 318, 338, 365]. Subjective-idealistic and neopositivistic treatises on the essence and gnosiologic role of a given mental process have been subjected to criticism [58, 86, 292, 318]. The basic structure of the mental experiment was recognized as the operation of ideal models, proceeding in terms of sensory and abstract-logical components of thought [86, 296, 297, 318].

Concepts of the mental experiment, constructed on the theory of relfection and on data compiled by psychologists and other scientists, is positive in many relationships: first of all, in general, its inherent nature is completely variable according to the content and level of complexity of the problems shaped by the type of activity. Thus, a component of the activity of the student and the operator, the builder and the artist , the writer and the scholar, is the ability to process information by assuming a structure for the ideal model and a mental operation for it. At the foundation of this process is a complicated structural-systematic nature of the mental experiment, recognized by scientists in many different functional terms. Moreover, a similar tendency is seen widely in the literature and appears even in terminology. Some authors prefer to use the term "hypothetical experiment", placing the accent on the leading role of fantasy; others use the expression "theoretical, idealized experiment", viewing the whole procedure as an abstract-theoretical one, infering mental activity with its logical apparatus; a third group speaks of the"ideal", "subjective experiment", focusing on its independence from the relationship to the experimental reality. The abundance of terms for designation of one and the same concept evidently is not accidental: it reflects a multitude of philosophical approaches to the interpretation of the existence, significance and gnosiologic role of the mental experiment. In fact, this is a consequence of the vagueness and indeterminancy of the term itself.

The dialectic-materialistic conception of the mental experiment has a potentially constructive program for examination of a whole series of related problems originating both in theory and in practice. It is particularly necessary to study the psychological mechanisms of the process for construction of various forms of ideal models which point to the study of the relationship of descriptive and abstract-logical components of

thought and the capacity to code information. Related to the model formation in mental processes and of particular timeliness is the study of operational structures of mental experimentation and formalization of the intellectual action which is its foundation. Of undoubted interest is the search for optimal conditions to formulate practices for effective use of a given intellectual process. This requires study of individual and age-related characteristics of mental experimentation. This is far from a complete inventory of the directions of possible approaches to the study of this heuristic process.

In this work, we attempt to correlate critically the theoretical materials related to this problem and to present results from our experimental studies in order to clarify the most general age-related and individual characteristics of mental experimentation. We also try to correlate the role of descriptive and abstract-logical components in mental experimentation and to uncover conditions which have an influence on the development of practices for use of this process.

This work, by no means claims to be an exhaustive resolution to all questions related to this concept.

The authors express deep gratitude to their scientific directors--to the late professor S.M. Vasileyskiy and to corresponding member of the USSR Academy of Science professor B.F. Lomov as well as to doctors of psychologic sciences Ya. A. Ponomarev, N.D. Zavalova, Yu.M. Zabrodin and candidate of medical sciences V.A. Popov for their valued critical comments.

Contents

[61-9139]

9139
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PSYCHIATRY

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PSYCHOPATHOLOGY OF POETRY COMPOSITION BY SCHIZOPHRENICS IN A DEFECT STATE

Moscow ZHURNAL NEVROPATOLOGII I PSIKHIATRII IMENI S. S. KORSAKOVA in Russian
Vol 81, No 1, Jan 81 pp 104-108

[Article by V. M. Milyavskiy, Poltavskaya Oblast Clinical Psychiatric Hospital (chief physician: A. G. Deneko), submitted 4 Sep 79]

[Text] There has been little study of the distinctions of composing poetry by schizophrenics in a "defective state". The few authors [1-7] who were concerned with this matter observed primarily distinctive features in the subjects handwriting: pretentiousness, appearance of superfluous florid elements, peculiar flourishes, curlicues, deformed letters, underlining words and syllables, profuse use of question and exclamation marks, quotation marks, etc.

P. I. Karpov [5] considered schizophrenics to be poor in literary creativity. Impoverishment of thinking, timelessness, monotony, lack of unity and completion, tendency toward paraphrasing, attraction toward abstract objects having no direct bearing on the writer, lack of logic, infantilism, invention of new words, tendency toward making rhymes that are often utterly meaningless have been found in the literary works of schizophrenics [5, 8-10].

Our objective was to make a psychopathological analysis of poetry composition by schizophrenics in a defect state, since we did not encounter such studies in the literature. We analyzed more than 300 poems written by 29 schizophrenics (25 men and 4 women) with progressive type of illness of over 15 years duration by the time the poetry was composed. The prevailing clinical sign was diminished mental activity in all of the patients. They were listless, showed little concern about being in the hospital; they were not interested in people around them and did not try to alter their mode of existence. In all cases, there was a marked personality change. Reduction of store of knowledge was demonstrated. There was prevalence of information gained in the premorbid period. Some patients had an impaired capacity for communication (disorganization, peculiar judgments, etc.). Most often the patients operated with concepts that were not clear or sufficiently formulated. Their speech was inexpressive, without graphic and colorful elements. Originality of thought, wit and resourcefulness were impaired.

Analysis of the data revealed that there were several typical features in most poems related primarily with manifestations of the schizophrenic defect. They included, first of all, signs of eccentricity (verschzobenheit) which, in the opinion of Bertse [11] are an expression of "secondary defect formation" and

consist of alteration of content of thoughts, tendencies and sets. The eccentricity of verses written by schizophrenics in a defect state is manifested by unexpected comparisons of seemingly incompatible concepts, unique interpretation of events described, unjustified emphasis on insignificant details. The excerpt quoted below, which was written by one of the patients in the group we studied, illustrates this.

To hypochondria we'll say--shut up
I have digested some of Medgiz.
To other hebephrenias we say--give up!
We give catatonia the prize.
The paranoid is silent, often stuporous...
Sometimes the heart is aching,
Speaking in angry pain,
All of these forms, brother, I gladly
Would endure without reward,
But arteriosclerosis
Will drive me to tears.*

Not infrequently, the eccentricity is manifested by a certain formal novelty related to play on words, peculiar arrangement of lines and rhymed endings (and a line could consist of a single word), grouping of words on the basis of some external feature, a tendency toward making various abbreviations, singling out some lines by writing them in larger letters or writing letters or whole words separately.

Eccentricity is not infrequently manifested by a "stilted" style, verbosity to the extent of the verbalization described by Jaspers [12], during which poetry is composed that can continue ad infinitum or be interrupted in the middle without appreciable difference to perception. The following poem can serve as an example:

On my grandfather Mishutka's side
I am a quartermaster--
Hail to Dante!
On my grandfather Gavrila's side,
It appears I am in control--
A true proletarian...
Give back the cigarette case...
With a low bow
I shall visit you in the summer.
I shall keep busy--
Swimming in the river all day.

In such verses the rhyme or meter are often more important than the content, which is arbitrarily changed to favor these factors. Bertse [11] stated, in this regard, that "what is said in a certain rhythm is correct" for schizophrenics.

Eccentricity is not the only sign of pathological ideation demonstrable in poems written by schizophrenics in a defective state. Amorphousness, absence of key points and inconsistency of plot were inherent in some of these verses. The placement of some lines and entire stanzas was not always determined by intrinsic necessity

*Translator's note: The author retained in the Russian version the patients' syntax and spelling, which cannot be reflected in the translation; this also applies to rhyme and meter.

and could be unintentionally altered without detriment to the contents. Some verses were not informative enough. In some cases, the paucity of content was combined with grandiloquent pathos, excessive pomposity, overt desire to achieve a rhyme by an overabundance of epithets that were not chosen because they were original and true, but in the sole desire to elevate the events described in the verses to the nth degree.

The schizophrenics in a defective state who compose verses readily indulge in hyperbolization. They try to impart solemnity to these verses, and this is sometimes achieved by altering the syntax of a sentence, reversing the places of subject and attribute, as can be seen from the following lines.

With a whip of lead-hetman the blow was inflicted.
In the head proletarian of the father, the earth spun.
He fell, to retain the balance of the planet trying....

Marked regression of graphic expression in the direction of infantilism and puerility is observed in verses written by schizophrenics in a defective state. They perceive reality in a simplistic way. Its poetic transformation is naive. There are elements of some sort of monotonous playfulness. An example:

The zebra is dashing on the savanna
in a striped pinafore
heading toward the watering hole over a reed-covered path.
Could there be a beast in ambush
crawling quietly from behind.
It [the zebra] will calm down after making sure it is alone.
Who will hurry to help,
if a predator runs up?
Will he then realize--
that it is not easy to catch it.

In some cases, the verses are overloaded with complicated associative elements. The comparisons are tenuous and wanting in definition. The thoughts are lost among the constructive conglomerations. This is illustrated in the following lines:

While the light as shimmering lava
hopped into the dark thicket
where in a consuming crowd
of teeth an oval was formed.
It is not as the night's hovering stronghold
with a fog woven of ice,
but as an overripe yellow melon
that the late moon rolled on.

Sometimes, as can be seen from the following lines, there are some lines that are unrelated to one another. There is impairment of grammatical structure. It is difficult to detect the main idea.

Where did you retreat and go?
And maybe you did not leave at all?
And maybe I shall never return?
You are coming, then come,
if not, then go....
Those who have returned depart,
And perhaps never....

Not infrequently the verses of this group of patients are removed from reality, wanting in subject matter and emotional expressiveness. They contain too many general words and not enough concrete concepts. As an example, we cite one of the numerous poems dedicated to a mysterious unknown woman, composed by one of the patients under our observation. We are impressed by the elements of paralogism and rationalization [argumentation], which are particularly noticeable in the epilogue accompanying the poem.

Second part of Chopin's concert
(to an unknown beloved woman).
When the moon casts silver
On the Chopin sound shed into the nigh,
Your smile is resurrected
In the beams of the moon and the foamy circle of
the moon's dew shed on the floor is
Merely the reflection bright of your tears,
Which to me in a stringed chalice
Chopin offered inebriating me.
Beyond the pure facet of the white keys [of piano]
Is hidden the world of my dream,
But if the facet could be struck through
To me you fly from the keys..
Brighter than springtime, forever imperishable
With a moonbeam enveloping my chest
Born of the love of Chopin
For my spectral love.

This poem was accompanied by the following epilogue:

"Epilogue to verses about music or manner of my thinking style. Beautiful reality or imagination, and a vivid idea about what is beautiful (i.e., 1st and 2d signaling systems) generate in the soul of a composer a rapturous resonance which, in all healthy people, if not infected by false pride, consistently expresses itself in joyous exclamations, and in a composer, in song. The conditioned reflex arc is formed in the composer's brain, where the music he composed is the conditioned stimulus of the beautiful. The idea of my verses was to be the conditioned stimulus of the musical joy experienced at some time by a person. Thus, my small abstract, even if its premises are flawed, demonstrates to all the ennobling influence of sulfozine on the logic of music lovers. I hope you will observe the order of my syllogisms and free me of accusations of being decadent and of the 17th sulfur injection. As for the other 16, placing my arm on my heart, they gave me as much pleasure as the ballads of Chopin."

In some of the verses by schizophrenics in a defective state, there is a tendency toward contamination, toward forming the "compact images" that E. Kretchmer [13] described, manifested by blending words into word combinations. The following lines can serve as an example.

> In the bright-fiery summer
> we shall plant clove-poppies in each aisle
> and having crossed out the series of "isms" with the letter "ya"
> we shall institute "communion" instead of religion.

There are many emotionally unreliable rational elements in the verses written by patients in the group we studied. The loftiest appeals, emphatically tender lines are not related to feelings [experiences] but, at best, to recollections about them. Most often, we are dealing with rehashing formed in connection with various manifestations of human feelings in literary standards.

Unlike the poetry composed by schizophrenics in the acute stage of the disease, in the defective state such patients do not usually write about the experiences caused by their illness. There is no sense of the catastrophe, which often permeates their early poems. Moreover, as can be seen from the following lines, there is a certain bravado in some cases, defense of some advantages that schizophrenics presumably have over other people.

> If you wish, the schizophrenic
> is more honest than others in the world.
> He will not cheat by even a penny
> living in friendship with everyone.

We are impressed by the fact that the above-described distinctions in the poetry composed by schizophrenics were usually noted when there was moderate manifestation of the defect. With increase in defective symptoms the verses became wanting in such specific features inherent in all schizophrenic poetry as eccentricity, bizarreness, tendency toward slipping and contamination, etc. Paucity of content and simplicity of creative devices became prominent.

We believe that our results indicate that there are pathological signs in poems wirtten by schizophrenics in a defect state, which are due to disturbances in ideation, which lend a specific flavor to all their poetic compositions, and in a number of cases it could serve as one of the differential diagnostic criteria aiding in distinguishing between defective states.

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10,657
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DEPRIVATION OF FREEDOM AND SOCIOPSYCHOLOGICAL PREMISES FOR ITS EFFECTIVENESS

Kazan' LISHENIYE SVOBODY I SOTSIAL'NO PSIKHOLOGICHESKIYE PREDPOSYLKI YEGO EFFEKTIVNOSTI in Russian 1980 (signed to press 30 May 80) pp 2-5, 216

[Annotation, introduction and table of contents from book "Deprivation of Freedom and Sociopsychological Premises for Its Effectiveness", by Fedor Romanovich Sundurov, Izdatel'stvo Kazanskogo universiteta, 6100 copies, 216 pages]

[Text] Based on the investigation of the practices of correctional institutions and the current achievements in law, philosophy and social psychology, this monograph analyzes relevant theoretical and practical problems of loss of freedom, discloses the essence of confinement, its preventive and educational significance, and examines the methodological aspects of the effectiveness of incarceration. The main emphasis is on the studies of sociopsychological factors that insure effectiveness of confinement in case of repeat-offenders.

This book is intended for field workers, scientists and students of juristic institutions. It will also interest a wide circle of readers.

INTRODUCTION

An increase in the role of ideo-educational activity is one of the typical features of a mature socialist society. As pointed out at the 25th CPSU Congress, "the party considers the teaching of communist conscientiousness, readiness, will and ability to build communism as its permanent responsibility" [1]. The basic direction of improving and strengthening ideological work is a "complex approach to the whole educational system, i. e. it insures a close unity of ideo-political, labor and moral education taking into consideration the characteristics of different groups of workers" [2]. Confirming the wide range of rights and freedoms of soviet citizens, the const tution of the USSR declares that the country plans to expand the real potential of citizens for developing creative activities, abilities and talent, and an all around personal growth (p. 20).

The complex educational approach points out particularly the necessity to overcome encountered breaches of morals and the law. Confirming the indivisibility of the rights and obligations of citizens, the Constitution of the USSR devised a legal base to eliminate violations of the standards of law and morality. The fundamental law of our country is based on the incompatibility of amoral and illegal acts of behavior with socialist law and order (p. 4).

The behavior of individuals who--inspite of education, and in some cases, punishment--inflict dangerous acts on society, is in deep conflict with socialist principles. The elimination and prevention of recidivist crimes is an important part of a historic task--the liquidation of crime in our society.

The problems associated with the battle against recidivism have been investigated by Soviet scientists-jurists from a penal-legal, criminological and the traditional penitentiary aspects. Meanwhile the necessity to search for more effective measures to prevent relapses and reeducate the repeating offenders condemned to prison, requires a comprehensive evaluation of the above range of problems from the standpoint of law, social psychology and socialist educational theory.

The author continues to examine the legal and sociopsychological problems of the effectiveness of reeducation of repeating offenders condemned to prison. In a previously published book by Kazan' University entitled "Legal and sociopsychological aspects of the correction and reeducation of law-breakers", the main emphasis was placed on theoretical aspects of the study of the prisoner's personality, the identification of the typical and individual traits of the personality of the repeating offender. One of the chapters of the collective monograph, "Personality of the offender and the use of punishment", examines the philosophical aspects of the theory of reeducation of prisoners.

In addition to discussions of the above problems, this book focuses primarily on the determination of the sociopsychological factors that ensure positive results from punishment, and on devising measures of correctional labor for repeating offenders. The book concentrates on those problems that have not been fully explored in Soviet literature. Attitudes that were subjects of investigation are mentioned by the author only if they concern the more important aspects of the present studies.

The experimental research is based on a complex investigation of practices in correctional labor colonies with strict conditions and the results of selective sociological investigations of a relatively representative group of sentenced repeaters; a group of prisoners serving in colonies with stricter conditions served as control.

The author sincerely thanks the scientific editor Professor B. C. Volkov, Professor V. P. Malkov, other scholars of the Faculty of Law of the Kazan' University, K. Sh. Sadreyev, public prosecutor of Kazan', and Docent R. M. Valeyev for the help rendered during the preparation of this book for publication; he also expresses his gratitude to S. P. Khabibullina G. M. Safikhanova and other collaborators of the criminological laboratory of the university, who participated in concrete sociological studies associated with the problems discussed in this book.

TABLE OF CONTENTS

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FIRST EXPERIENCE WITH USE OF DATA BANK TO OPTIMIZE MANAGEMENT IN THE TERRITORIAL PSYCHIATRIC SERVICE AS RELATED TO REHABILITATION OF MENTAL PATIENTS

Moscow ZHURNAL NEVROPATOLOGII I PSIKHIATRII IMENI S. S. KORSAKOVA in Russian
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[Article by M. A. Mazur, Problem Laboratory (headed by M. A. Mazur) of the Automated Control System of the Kuznetsk Basin Scientific Research Institute of Traumatology and Rehabilitation, Kemerovskaya Oblast Psychiatric Hospital (chief physician M. A. Mazur), submitted 21 Apr 78]

[Text] In modern psychiatry, rehabilitation of mental patients is very important [1, 2]. Thanks to the broad adoption of modern methods of treatment, rehabilitation regimens vocational and social therapy, some success has been achieved in implementing some rehabilitation programs in many psychiatric organizations [3-11]. However, as we know, these advances did not lead to a radical change in the situation: absence of a standard [single] rehabilitation system that would make it possible for a considerable number of chronic patients to adjust [integrate] into the public and prevent them from settling in a hospital, led to an increase in readmissions within short periods after prior discharges from institutions, and the need for psychiatric beds has not diminished appreciably.

For the last 10 years, in Kemerovskaya Oblast there has been development, on the basis of the systems approach, of a management system, which is being adopted in the psychiatric service, and which is oriented toward optimizing the structure of psychiatric institutions and functional relations in their work, combining the efforts of medical workers at all stages of rehabilitation, with redistribution of flow of patients in order to improve the effectiveness of rehabilitation programs and fully meet the needs of the public with regard to all forms of psychiatric care without increasing the number of hospital beds [12].

This oblast was divided into territorial zones in order to optimize the structure of psychiatric organization; in each of these zones all forms of care are available by means of a rehabilitation complex that is part of a psychiatric hospital with a dispensary department and intermediate sections (see Diagram). Psychiatric offices were opened in remoted populated centers.

The dispensary department is the main structural section of the complex that implements contact with the public. The district psychiatrist, who implements measures for early detection and dynamic observation of patients, coordinates implementation of programs for rehabilitation therapy at all its stages. Hospitalization, discharge from a hospital and referral to intermediate units can occur only with the permission of the district psychiatrist.

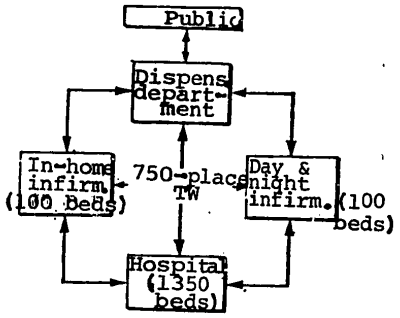

Diagram of rehabilitation complex

The hospital's psychiatric department services mixed groups of patients, regardless of severity of symptoms and duration of illness. Differentiated rehabilitation regimens have been adopted, and active biological therapy is combined with social and vocational therapy. At first, the patient is admitted to a department where there is a vacancy, but when readmitted he is always put in his own department.

The in-home infirmary that has been attached to the dispensary department since 1960 makes it possible to discharge serious cases from the hospital, who would otherwise have remained there for an indefinite time. The patients in this infirmary are unable to attend a day infirmary or therapeutic workshops because of their somatic condition, for family reasons or because of the distinctions of their mental illness [13].

Redistribution of the flow of patients and the objective of early discharge from hospitals made it necessary to concentrate the work of the day infirmary chiefly on rehabilitation of patients with protracted course of illness who cannot be referred to the therapeutic workshops (TW), since they require extensive biological therapy and a more sparing regimen. The night infirmary is intended for patients who continue to work, or else it can be used when they start on a job to facilitate adjustment to industrial conditions.

The TW acquire particular importance in the structure of the complex, and those working together there consist of patients who are in the hospital, day infirmary and others referred from the district. As a patient advances over the phases of rehabilitation he remains in the same workshop.

Optimization of the structure of the psychiatric service is directed toward bringing closer the different links of the rehabilitation chain and providing for the organic unity of intra- and extra-mural care. It is possible for such a complicated complex to operate effectively only if there is optimum management so that each section is governed by the needs of the rehabilitation program as a whole.

The automated systems presently existing in psychiatry [14-20] are informative, and they serve to automate statistical and book-keeping calculations, or else to process laboratory and other data in order to make computer diagnoses. We have developed and introduced an automated system for the control of rehabilitation of mental patients, which is based on the use of a so-called intellectual data [information] bank [21]. This progressive conception, used for the first time in public health, makes it possible to apply the systems approach by analyzing information about each patient that is updated constantly. The bank makes it possible to obtain the information that is necessary for management by accumulating and processing large data arrays [22].

Instructions have been worked out, numbering over 900 descriptors combined in 50 sections, to code the data. This information is inputted in the computer by means of compact, intermediate data carriers. When a patient is put on the rolls, the

dispnesary physician fills out the form, "Record of initial information about mental patient placed on the rolls," which contains the minimum information that can be obtained at the first meeting with the patient. In addition to the diagnosis, prime syndrome, data about heredity, concomitant diseases, domestic and marital conditions, a note is made of the priority rehabilitation measures that the patient requires.

Subsequently, all of the data obtained as a result of in-depth examination of the patient are inputted in the computer using the "Card with additional information." It is filled out by the physicians of medical institutions, regardless of their departmental subordination, each time there is a patient visit, hospitalization, discharge, change in condition, treatment or rehabilitation measures, etc. This card ["coupon, check"] can also be used to correct previously inputted erroneous data.

The medical information accumulates in chronological order from the time the patient is put on the rolls, and it constitutes the computer analog of an individual case history containing information about the dynamics of the patient's clinical and social status, hospitalizations, administered therapy and its efficacy, results of rehabilitation programs used, as well as measures required for the patient and reasons preventing performance thereof. There is also accumulation of data pertaining to living conditions, bad habits, tendencies toward socially dangerous acts, temporary and prolonged disability, microsocial environment and the patient's attitude toward his illness and treatment. Data characterizing the patient's condition at the present time are reflected in the "status units" that are constantly formed in the computer.

The set of models for optimization of performance by institutions and their departments, as well as the entire psychiatric service, which makes it easier to select a management decision and provides for feedback in order to monitor its effectiveness, is one of the main strucutral elements of the data bank. The method we propose for modeling makes use of the heuristic method of trial and error. As models of optimization, we use sets of interrelated systems parameters, systems standards and rating scales, which reflect the quality of performance of rehabilitation programs, and these sets were selected by means of expert evaluations. In a certain sense, this method is arbitrary; however, the objectivity of the evaluation is increased by the equal operating conditions in similar departments.

Systems parameters are the most important features of performance by the psychiatric service, and by controlling them one can have it function in accordance with the set goal. They are divided into two types: stimulating ones, which reflect important aspects of the work of each institution and limiting ones, which demonstrate flaws in implementation of programs and rule out the possibility of reaching high parameters to the detriment of continuity requirements. As an example, we are listing the set of systems parameters of performance by a territorial psychiatric service, which reflects the degree of implementation of a rehabilitation program. In this case, the list is limited to stimulating parameters:

1. Groups of mental patients on the rolls, including those with psychoses.

2. Number of patients who returned to work, who had previously not worked because of a mental illness for a year or longer, including the percentage of overall medical and occupational rehabilitation.

3. Number of patients who restored or preserved their families.

4. Number of patients who have been in the hospital for over 2 years.

5. Number of days patients spent in a hospital, as the total for all hospitalizations over the period of a year (average per patient), including schizophrenics.

6. Number of socially dangerous actions.

Standard values are given to the systems parameters, and they depend on the level of development of the psychiatric service in a given region, as well as the actually achieved indicators. Rating scales were developed in an analogous manner, with consideration of the rank of each parameter, and they make it possible to express as a grade [in points] the deviations of achieved indicators from the standards. Grading makes it possible to compare the performance of different institutions and their departments. When the institutions care for identical patient groups, their performance can be evaluated by means of one optimization model.

Table 1. Dynamics of indicators of psychiatric hospital performance

Parameter	All psychiat. hosp.			Oblast psych. hosp.		
	1970	1974	1977	1970	1974	1977
Hospitalizations per 10,000 population	47.9	56.5	66.0	50.7	66.8	76.6
Hospitalizations per 100 beds	431.3	468.9	526.0	443.5	555.7	600.1
Patients admitted for the first time in their life, % of all admissions	49.0	57.6	61.0	58.6	65.1	71.2
Patients readmitted within 1 year after discharge, % of all admissions	26.1	14.2	12.7	19.9	10.1	9.1
Mean bed-days	72.3	66.2	60.8	67.6	60.1	50.9
Patients who spent more than 2 years in hospital: absolute number	1038	666	430	281	140	89
% of those in hospital at end of year	29.4	18.7	11.6	21.4	10.3	6.3

Information tables are formed by processing the computer analogs of case histories; these tables list the indicators of performance of psychiatric institutions and their departments that are required for operational control by means of optimization models. The performance indicators are compared to the optimization model and deviations from standard parameters; failure to meet system requirements is rated by the rating scales. The overall grade for stimulating parameters minus the overall grade for limiting parameters yields the general grade reflecting the degree of implementation of a program. The systems indicators of different departments are so combined that it is possible to obtain a high grade only if their is complete continuity in the performance of different departments, while analysis of the grades for each parameter is the basis for decision making by the administrator, and the quality ["optimality"] of the decision is checked by subsequent change in the overall grade. All of the departments receive the rating tables once a month. The completeness and objectivity of information obtained makes it possible to implement management on all levels with a minimal risk of making an incompetent decision.

The control system changes to the level of making tactical decisions when higher indicators are achieved than provided by the systems standards, as well as when

flaws are detected in the optimization model. At this stage, analysis is made of deviations of achieved indicators from standard values, and if these deviations are persistent, the system is able to propose variants for correcting the optimization models, with consideration of accumulated information, and from these the administrator will choose the optimum one.

Table 2. Dynamics of indicators of performance of intermediate departments

Indicator	Entire oblast			Oblast psych.hosp.		
	1970	1974	1977	1970	1974	1977
Patients treated at in-home infirmary	355	825	1069	355	807	866
Schizophrenics among the above	175	409	830	175	394	656
Patients treated in day infirmary	211	1018	1915	211	610	910
Schizophrenics among the above	156	922	1458	156	575	869
Patients treated in TW	97	434	598	97	374	458
Schizophrenics among the above	92	271	481	92	224	384
Patients treated in all intermediate departments	663	2277	3582	663	1791	2234
Schizophrenics among the above	423	1604	2769	423	1193	1912
Placed in industrial jobs	20	124	147	30	101	112
Schizophrenics among the above	15	92	103	15	82	99
Readmitted to hospital, % of all who made use of intermediate departments	19.0	13.6	9.4	19.0	7.2	7.0

We cannot rule out a situation where a change in the model could, in spite of a higher grade, have an adverse effect on implementation of the rehabilitation programs for some category of patients. To check how a decision affects the health of the group being cared for, there are provisions for feedback which occurs by means of constant monitoring of the dynamics of the "health indicator." This indicator is calculated when analyzing the status units, in which a numerical value is given to each of the factors with consideration of its rank. The aggregate of these values is an evaluation of the patient's condition at a given time, while the sum of such ratings is the "health indicator" for different groups or the entire set of patients. The administrator's decision can be considered correct if there is not only normalization of the grade, but elevation of the "health indicator." Otherwise, the search for an optimum decision must be continued.

It is possible to correct the optimization model only within the limits of the restrictions set into the system, and this determines the range of tactical management, upon reaching which the system moves to the next level, the level of strategic control.

The presence of a large amount of data makes it possible to construct a computer simulator model, which permits a "replay" of the situation by simulating the patient flows through the departments of medical institutions. This makes it possible to provide prognostic evaluation of the results of reorganization of psychiatric institutions.

Operation of this system for several years proved it to be effective. The possibility of shortening patient hospitalization time was demonstrated on the basis of extensive data.

Table 1 lists the dynamics of indicators of performance of oblast psychiatric institutions. We took 1970 as the base year. As can be seen in Table 1, there was 2.4-fold reduction in number of chronic patients in hospitals with concurrent reduction to less than 50% of readmissions within a year after discharge. As a result, there was a 1.5-fold increase in hospital admitting capacity. In these years, over 15,000 patients, mainly with severe and progressive diseases, received qualified care in intermediate departments, while 748 patients who had not worked for a long time were placed on jobs (Table 2). There was a 36% decrease in number of socially dangerous acts committed by patients.

Our results are indicative of the productivity of the systems approach to improving the effectiveness of management of the territorial psychiatric service as related to rehabilitation of mental patients.

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EFFICACY OF TREATMENT OF PROCESS SCHIZOPHRENIA WITH EARLY ONSET USING VARIOUS PSYCHOTROPIC AGENTS AND COMBINATIONS THEREOF

Moscow ZHURNAL NEVROPATOLOGII I PSIKHIATRII IMENI S. S. KORSAKOVA in Russian
Vol 81, No 1, Jan 81 pp 114-121

[Article by Ye. S. Sobolev and S. G. Zaytsev, Department of Therapy and Rehabilitation of Mental Diseases (headed by Prof G. Ya. Avrutskiy), Moscow Scientific Research Institute of Psychiatry (director: Prof V. V. Kovalev), RSFSR Ministry of Health, submitted 4 Sep 79]

[Text] In spite of the wide use of psychotropic drugs, treatment of patients with adverse chronic course of a schizophrenic process, in particular, in the case of "nuclear" [?] schizophrenia, is still one of the pressing problems of clinical psychiatry. Differentiated indications for the use of different drugs and methods of therapy still require more comprehensive development and definition.

In studies dealing with nuclear schizophrenia attention was usually focused on clinical systematics, course, some distinctions of pathomorphosis and form production [1-5], rather than therapy. In the studies of A. A. Yezhkov [6], who dealt specially with psychopharmacotherapy for this group of patients, emphasis was placed only on the study of only two potent neuroleptic agents, majeptil and trisedyl, in his discussion of a differentiated approach to therapeutic tactics. The summarizing textbooks and monographs [7, 8] discuss indications for treatment of nuclear schizophrenia with due consideration of a number of clinical signs of the disease and spectrum of psychotropic action of drugs, but the instructions contained in these books have not yet been submitted to statistical verification.

There are definite qualities and advantages in studies that compared the clinical and statistical ratings of efficacy of a number of products referable to one of the classes of psychotropic agents: antidepressants, tranquilizers and neuroleptics [9-12]. The data obtained from such comparison are absolutely necessary to substantiate the choice of drugs and optimum therapeutic tactics. At the same time, the authors of these works did not deal with the efficacy of combinations of psychotropic agents which are used so extensively in modern therapy.

We studied the efficacy of different forms of therapy (the concept of "form of therapy" included both the separate and combined use of drugs) as related to the clinical variant of nuclear schizophrenia.

In accordance with our objective, we analyzed the clinical efficacy of 1211 courses of treatment for 96 patients with nuclear schizophrenia, who were screened and grouped according to variants on the basis of criteria in the literature [1-4]. The diagnosis was based essentially on retrospective study of early stages of development of the disease, initial stage and the one of early manifestations, since the clinical findings at the time of our study often had elements of drug pathomorphosis, which could have led to diagnostic errors. A number of observations, where the course of illness had been previously qualified in different ways (depending on efficacy of therapy), either in the direction of milder forms or of "nuclear" schizophrenia, confirmed the desirability of such an approach.

We made a distinction between four clinical variants of the disease: 1) unproductive with prevalence of negative disorders in the presence of obliterated, undeveloped and rudimentary productive symptoms (16 patients); 2) with a shizoaffective component, presence of circular and schizoaffective disorders throughout the illness (18 cases); 3) paranoid, with prevalence of paranoid or hallucinatory and paranoid disorders (42 cases); 4) catatonic-hebephrenic, with prevalence of catatonic and catatonic-hebephrenic disturbances at the stage of early manifestation of the disease (20 patients).

In essence, the second variant consisted of two variants of hebephrenia according to Yu. I. Polishchuk [3] with circularity and sporadic course, and this was deemed feasible in view of the rather frequent alternation in the same patients of both the circular and schizoaffective (depressive-paranoid, oneiroid, acute paranoid) syndromes. Otherwise, we retained all of the diagnostic criteria for "nuclear" schizophrenia and its clinical variants indicated by the cited authors.

Course of therapy was construed as a segment of illness lasting at least 2 weeks, during wich only one of the forms of therapy was administered to the patient from the forms provided in a predeveloped statistical program of study, within the range of one of the three differentiated dose levels. Maximum duration of a course was 32 months, with prevalence of courses lasting 3 to 10 months.

There were some methodological difficulties related to differentiation of "forms of therapy." Grouping of different drugs was found to be unsuitable, since use thereof was often not as the only drug or mutually exclusive; the products were prescribed in the most varied combinations, the diversity of which was considerable. Ultimately, our search for the most adequate grouping enabled us to decide on 10 qualitative variants of factor T ("therapy"), which are listed in Table 1.

The grouping principle we applied enabled us to differentiate between use of a single neuroleptic ("mononeurolepsy") and combinations. Thus, therapy forms T_1-T_3 can be considered as "mononeurolepsy," T_5-T_7 as "bineurolepsy" (combination of only two neuroleptic agents) and T_8-T_{10} as "polypharmacotherapy," since these combinations included at least two psychotropic drugs referable to different classes, in addition to the main drug.

Antidepressants, which were not included in variants T_1-T_7, were used not only in T_8, but in T_9-T_{10}. Similarly so-called new neuroleptics could be used in combination with other drugs, in T_9 and T_{10}, while deponeuroleptics could be used only in T_{10}. The T_8-T_{10} combinations could include

all prior forms of therapy, with the exception of insulin. The polypharmacotherapy group was based on the most important elements of drug combinations (for example, antidepressants) without considering some secondary ones (in particular, corrective agents).

We used the overall ("global") rating of efficacy of therapy, which is similar in its main features to other forms of evaluation of severity of mental states and depth of remissions that are used extensively in psychiatry [13-17] as the resultant indicator reflecting the degree of response to therapeutic measures. It should be noted that we did not record the depth of remission, which characterizes a certain stability in time, in our studies, but the immediate efficacy of a course of therapy at the time it was terminated because of change to another form of therapy or at the time of discharge from the hospital.

We made a distinction between three levels of efficacy of therapy (Ef). The first type, EF_2, refers to cases when there was considerable reduction of psychopathological symptoms (in particular, encapsulation of hallucinatory-delusional disorders, regression of catatonic ones to the level of individual "stigmas" and disturbances referable to flexibility of movements) with their negligible or sporadic influence on the patient's behavior. The patients' behavior was characterized in such cases by conformity with work and collaboration, with some extraneous inducement, and the possibility of some adjustment to work.

The second type, Ef_1, refers to cases when there was some negligible reduction of psychopathological symptoms, mainly in the form of calming down. The reality [importance?] of pathological experiences remained variable. The patients often presented pathological behavior, which made it difficult for them to communicate and collaborate with others. At the same time, they regained elementary skill in self-care, it was possible to have the patients perform simple errands.

The third type, Ef_0, refers to cases when there were no positive changes in the mental status of the patients, or else it worsened.

It is apparent from the foregoing that the levels of efficacy of therapy that we singled out did not coincide with the scale indicators for evaluation of efficacy of treatment of schizophrenia as a whole. They reflect the specifics of expressly nuclear schizophrenia: even Ef_2, which is the maximum level of efficacy, signifies essentially a rather moderate degree of improvement.

The primary data were submitted to statistical processing by the method of multifactor analysis of variance, adjusted for use in biological studies [18, 19] and paired comparisons of shares with calculation of significance according to Fisher (ϕ method). We used two-factor analysis of dispersion for nonuniform sets with qualitative tags. We used the percentage of improvement of the Ef_2 type as the resultant indicator.

According to the data in Table 2, which lists the results of variance analysis, factor T (form of therapy), V (variant of disease), as well as the effect of their interaction (VT) have a statistically reliable influence on the results of

therapy: the efficacy of the latter differs appreciably and consistently as a function of form of therapy and variant of disease considered separately. The reliability of the interaction effect indicates that with the constellation of a specific variant of the disease with a specific form of therapy there are often effects that cannot be explained by simple addition of the influence of each factor separately: the results of therapy either exceed the summation effect, or else they are substantially lower. At the same time, the overall force of all these influences (η^2) explains only a small share (13%) of all variations in efficacy of therapy, which indicates that there are a number of factors that we did not take into considerations, which determine efficacy.

Table 1. Main forms of administered therapy as related to different variants of process schizophrenia with early onset

Conventional design. of form of therapy	Characteristics of therapy	Courses as related to variants				Total courses
		nonproductive (V_1)	with schizoaffect. compon. (V_2)	paranoid (V_3)	cataton.-hebephren. (V_4)	
T_1	Sedative neuroleptics: aminazin, tisercin, chlorprothixine (mononeurolepsy)	12	12	57	28	109
T_2	"Antidelusional" neuroleptics: triftazin, haloperidol, etaperazine (mononeurolepsy)	13	17	36	17	83
T_3	"Potent" neuroleptics: majeptil or trisedyl (mononeurolepsy)	6	2	15	11	34
T_4	Insulin therapy: alone or with neuroleptics	16	27	65	43	151
T_5	"Antidelusion" or "potent" neuroleptics combined with sedative	25	40	130	85	280
T_6	"Antidelusion" or "potent" neuroleptics combined with "minor" ones: frenolon, mellaril, neuleptil or teralene	8	6	20	8	42
T_7	"Antidelusion" neuroleptics combined with "potent" ones	2	15	72	44	133
T_8	Antidepressants combined with psychotropic agents	29	35	66	20	150
T_9	"New" neuroleptics: leponex, eglonil, piportil, randolectil, combined with other psychotropic agents	24	26	60	42	152
T_{10}	Deponeuroleptics: moditen [fluphenazine] and pipothiazine-depo with other psychotropic agents	14	10	28	25	77
	Total courses	149	190	549	323	1211

While variance analysis does offer a quantitative description of reliability and force of influences of different factors, it does not yield information about the direction of these influences. The obtained data are submitted in the form of two-dimensional tables (Tables 3 and 4) for more detailed description of the effects of the factors under study.

Table 2. Results of two-factor variance analysis for factors V and T and their interactions

Parameters	V	T	VT	x	z	y
$\eta_i = C_i/C_y$	0.015	0.051	0.066	0.13	0.87	1.0
ν	3	9	16	39	1171	1210
$F_i = \sigma_i^2/\sigma_x^2$	6.85	7.8	5.6	4.6	--	--
P	<0.001	<0.001	<0.001	<0.001	--	--

Note: V, T are the factors studied, whose value is given in text; VT is the interaction between these factors; x is ordered variation; y is total variation; z is random (residual) variation; η^2 is the indicator of force of influence; ν is the number of degrees of freedom; F is the criterion of reliability of force of influence; C is the sum of the squares adjusted to nonuniformity of the complex.

The indicators of effectiveness of using ten forms of therapy, regardless of variant of the disease, are listed in the last column of Table 3, ranked from minimum to maximum. The efficacy of therapy was found to be maximal with the use of combinations that included depo-neuroleptics, antidepressants, "antidelusion" or "potent" neuroleptics, together with "minor," "new" neuroleptics (leponex, piportil, randolectil, eglonil); "antidelusion" neuroleptics used separately. Noncombined therapy with "potent" neuroleptics, insulin therapy, the combination of "antidelusion" or "potent" neuroleptics with sedative ones were less effective. Least effective was the combination of "antidelusion" neuroleptics with "potent" and sedative neuroleptics.

A comparison of the efficacy of the three broad forms of therapy--"mononeurolepsy," "bineurolepsy" and "polypharmacotherapy" (see Table 4) revealed that, on the whole, the last was much more effective. The existing differences are demonstrable with all four variants of the disease.

Analysis of efficacy of therapy as a function of clinical variant of the disease (bottom line in Table 3) revealed that efficacy was at a maximum with the nonproductive variant of schizophrenia and at a minimum with the catatonic-hebephrenic one. Treatment was also substantially more effective ($P<0.01$) with the variant that had a schizoaffective component than the catatonic-hebephrenic.

The interaction between factors V and T, which turned out to be statistically reliable, was manifested, in particular, by the fact that the correlation between efficacy of specific forms of therapy was not the same with different variants of schizophrenia. In this respect, there was a particular distinction inherent in the catatonic-hebephrenic variant. Combinations including antidepressants (T_8), as well as "minor" neuroleptics (T_6) were inferior to most other forms of therapy for

this variant, occupying only 8th and 10th places in the ranking, respectively, whereas with other variants their relative efficacy was much higher, particularly that of antidepressants. Conversely, the separate use of "potent" neuroleptics (T_3) demonstrated an advantage for this variant, which was not present for the third variant. The same applies to combinations containing "new" neuroleptics (T_5) (as compared to second and third variants). The "new" neuroleptics also demonstrated maximum efficacy (along with depo-neuroleptics) for the nonproductive variant of nuclear schizophrenia. Insulin therapy (T_4) and "antidelusion" neuroleptics (T_2) were somewhat more effective for the second variant; this applied to the "antidelusion" neuroleptics for the third variant. Sedative neuroleptics (T_1) had the lowest efficacy with the second variant.

In interpreting the obtained data, it must be noted that some of them are quite consistent with conceptions that ensue from routine therapeutic practice. We refer, for example, to the relatively high efficacy of depo-neuroleptics in the case of paranoid and catatonic-hebephrenic variants of schizophrenia, "antidelusion" neuroleptics for the paranoid variant, "potent" neuroleptics for the catatonic-hebephrenic, some positive effect of sedative neuroleptics on the paranoid variant and low efficacy of the latter (as well as insulin therapy) with the other variants. The maximum efficacy of antidepressants and minimum efficacy of sedative neuroleptics (aminazin) in the case of the variant with a schizoaffective component are also quite understandable, if we consider the special place that this variant of depression occupies in the structure of syndromes.

Statistical analysis revealed that the mixed group of "new" neuroleptics (leponex, eglonil, piportil, randolectil) plays a special role in the treatment of nuclear schizophrenia. They have indeed been highly rated by clinicians who tested them. Evidently, their advantage can be attributed in part to the fact that patients become habituated to products taken over long periods of time. On the other hand, eglonil and leponex have a unique spectrum of psychotropic and neurotropic activity (minimal extrapyramidal action, eglonil's effect on sluggish and apathetic symptoms, that of leponex on catatonic ones). From this point of view, it is interesting that these drugs play a relatively more important role in the treatment of two extreme clinical variants, the first and fourth, with which apathoadynamic and catatonic-hebephrenic disorders are the most marked.

The lowest efficacy of treatment as a whole in the case of the fourth variant and higher efficacy with the second and third variants also conform with the generally held views. However, the fact that the first variant turned out to be the most curable does not conform with conceptions, according to which "simple nuclear"--"shizokarnaya" [?] according to Mauz [20]--schizophrenia is manifested chiefly by defective and, consequently, irreversible states. As shown by our clinical observations, with this variant of the disease, adequate psychopharmacotherapy discloses an entire range of undeveloped, diffuse productive disorders, including affective ones, beyond which one often detects a personality with adequate compensatory possibilities. There are interesting data concerning the particularly beneficial effect if moditen-depo on this variant, and this can be related both to the stimulating and general behavioral components of psychotropic activity of this product.

Table 3. Efficacy of different forms of therapy (% EF_2 type improvement) of patients with process schizophrenia with early onset, as a whole and for different clinical variants

Conventional designation of form of therapy	Variants of schizophrenia				Aggregate of courses
	V_1	V_2	V_3	V_4	
T_1	33±14	0±3	12±4	7±5	12±3{a
T_7	-	27±12	10±4	18±6	14±3{b
T_5	48±10	25±7	32±4	20±4	29±3{aa bb d
T_4	44±12	37±9	28±6	28±7	31±4{aa bb c
T_3	-	-	27±12	36±15	32±8{aa bb e
T_2	54±14	47±12	47±8	29±11	44±6{aa bb
T_9	71±9	39±10	42±6	48±8{kkk	47±4{aa bb cc dd
T_6	-	-	40±11{ii	0±12{i k	48±8{aa bb cc
T_8	62±9	54±8	48±6{jjj	15±8{l j	48±4{aa bb cc dd
T_{10}	71±12	50±16	54±10	44±10{11	53±6{aa bb dd ee
Entire set of courses	57±4 {ffff gggg hhh	39±3{ggg h	38±6{f	26±2{g	34±4

Note: There are blanks (dashes) where there were too few cases (these cases are included in the summary columns). The same letters are used here and in Table 4 to mark values that differed reliably from one another when compared in pairs. The lower of the two is designated with one letter (a, b, etc.) and the higher by two when P<0.05, three with P<0.01 and four letters with P<0.001; the values of T and V are the same here and in Table 4 as in Table 1.

Table 4. Comparative efficacy (% of Ef_2 type improvement) of mononeurolepsy, bineurolepsy and polypharmacotherapy

Type of therapy	Variant of schizophrenia				Aggregate of courses
	V_1	V_2	V_3	V_4	
Mononeurolepsy (T_1–T_3)	45±9{a	26±8{b	24±4{c	20±5{d	27±3{e
Bineurolepsy (T_5–T_7)	51±9	33±6	26±3{f	18±3{g	26±2{h
Polypharmacotherapy (T_8–T_{10})	67±6{aa	48±6{bb	47±4{ccc fff	39±5{dd ggg	48.8±3{eeee hhhh

The demonstration of rather high efficacy of combinations containing antidepressants and "minor" neuroleptics for the paranoid variant is relatively new and, apparently, clinically very important. We could try to interpret this in the light of drug pathomorphosis which was manifested, in particular, by enhancement of depressive disorders and partial move of symptoms to the neurosis-like category in the course of long-term therapy [21-25]. Conversely, the fourth variant, in which drug pathomorphosis was the least marked, was minimally responsive to the above-mentioned forms of therapy. In particular, frenolon is, as we know, a product whose "target" is mainly the syndrome of catatonic stupor. However, when predicting its efficacy one must take into consideration the clinical variant of the disease, in addition to the syndrome. While it reduces substuporose phenomena satisfactorily in the presence of the first three variants, according to our clinical observations it had a therapeutic effect on the fourth variant only in the presence of sluggishly apathetic stupor and when patients refused to take food, and even then not in all cases. Majeptil had the best effect on such states.

In addition to facts that are already known, as well as relatively new ones but those that are easy to interpret, we also obtained some data that were difficult to interpret. They include the relatively low efficacy of "potent" neuroleptics in pure form in the third variant, and in combination with "antidelusion" drugs in the second and third variants, as well as the combination of "potent" and sedative neuroleptics for all variants. Yet it is believed that the use of "potent" neuroleptics is indicated primarily for the treatment of "nuclear" schizophrenia. But, according to our data, their efficacy, when used alone, was ranked rather high only in the case of the catatonic-hebephrenic variant. Of course, with the other variants there were individual cases of rather beneficial effects of majeptil and trisedyl, but often they were inadequate, as indicated by the averaged statistical rating.

When we analyzed the different cases, we were able to note that, in a number of cases, the use of these products not only led to appearance of marked extrapyramidal disturbances, but concurrent arrest of the therapeutic effect or even enhancement of stimulation, chiefly of the catatonic-hebephrenic type, with change thereof to the amentia-like form with severe worsening of mental state. Evidently, the onset of such states is not so much inherent in nuclear schizophrenia itself as in patients with latent organic deficiency of the central nervous system when there is early onset of process schizophrenia. But it only partially explains the obtained findings. On the other hand, if we exclude the

depo products, antidepressants and "new" neuroleptics, the use of which for treatment of such patients began only recently, from our comparison, the efficacy of the "potent" [probably "major"] neuroleptics will turn out to be rather high. This explains the high rating they were given in the past.

Thus, the statistical data we obtained essentially have a satisfactory interpretation from the clinical point of view. When there is a comprehensive follow-up on patients for whom different types of therapy were prescribed successively, the same correlations were demonstrable quite often. At the same time, it is unquestionable that numerous factors other than the ones we studied, which require analysis, also affect the efficacy of therapy. Bearing this in mind, it may be assumed that our study warrants the following preliminary conclusions, which could become the starting point for future research: 1) the efficacy of treating nuclear schizophrenia under modern conditions, using a number of products and combinations thereof, depends appreciably on the type of therapy, clinical variant of schizophrenia and interaction of these conditions; 2) among patients suffering from all clinical variants of nuclear schizophrenia there are groups (which have not yet been clearly delineated clinically or by other criteria) that respond better to polypharmacotherapy with concurrent use of products with different spectra of action than to intake of a single, even potent, neuroleptic. For this reason, refinement of therapy of nuclear schizophrenia should apparently proceed in the direction of a wider diversity of drugs used and development of methods of clinically substantiated combined therapy.

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