

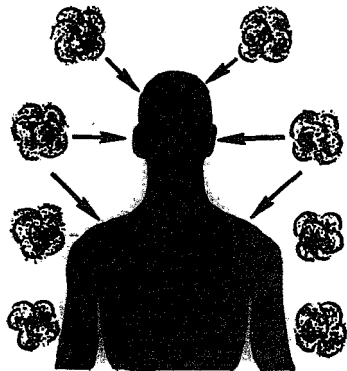
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ETHNIC WEAPONS

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A NEW generation of chemical weapons seems to be growing out of information collected and interpreted in research centers in both East and West. So far, chemical agents have been considered effective mainly against tactical targets of limited area. Even if this view may still be maintained, a new edge can be honed to an already formidable weapon. Forthcoming chemical agents with selective manstopping power will put into the hands of an assailant a weapon with which he cannot be attacked.

At the bottom of this new reasoning lies a careful exploration of the reaction of individual soldiers to chemical agents. Tactical consequences of the wide variation of such reactions involve both target analysis and the

selection of personnel for special missions.

With or without exposure to toxic products, most molecules of the human organism keep to their ordinary tasks of maintaining structure. A fairly great number of molecules are held in reserve against predicted needs, but a fatal chaos would result if too many molecules were ready to react with each other. Our energy requirements are satisfied by the transformation of molecules, capable of releasing energy, into other molecules with a less energy content. But every transformation, whether it takes place in a gun chamber or in a muscle, calls for the supply of activation energy.

High pressure and temperature are not compatible with vital functions. As in all other living organisms, our

molecules are kept arrayed until particular trigger mechanisms lower the activation energies of chemical reactions. These carefully safeguarded procedures for alerting molecules are extremely selective, and they depend on the activities of enzymes.

Such catalysts of living organisms have attracted an increasing interest, and new methods for the study of enzymes have accumulated some imposing, and mostly new, facts. One way to knowledge about the ladders of chemical reactions furthered at each step by a special enzyme is to study what happens when one enzymatic step is blocked. Material for such studies is provided by nature and by artificial inactivation of particular enzymes, intentional and accidental.

Catalase Activity

The immense laboratory of human natural variation provides many instances of sharp differences in the activities of well-defined enzymes. Catalase belongs to this category. Its task is to split hydrogen peroxide, H_2O_2 , setting free oxygen. Today, hydrogen peroxide may be better known as a rocket propellant than as a disinfectant. If used in the latter capacity, diluted peroxide foams when brought into contact with blood or a fresh scratch in the skin. Without catalase, there is no foam. We need the enzyme to inactivate hydrogen peroxide generated by bacteria trying to invade the gums through minute injuries.

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In the early fifties, several Japanese families were observed where some members lacked catalase activity. Their blood produced no gas when in contact with hydrogen peroxide, and they had more or less severe ulceration of the gums with loss of teeth. This enzyme defect is rare, and it follows a simple mode of inheritance, with the parents of patients having a normal or practically normal catalase activity. The changed gene responsible for lack of catalase is not confined to east Asian populations as was once suspected.

Scores of enzyme failures due to gene mutations have now become known. Many of them cause early death or severe mental retardation. Sometimes, a dietary adjustment suffices to overcome the consequences of enzymatic ineptitude. The study of such heritable disturbances has included their prevalence in different geographic regions.

Basic Pattern

Although some outstanding inequalities between widely separated ethnic groups have been registered, detrimental genes are, as a rule, rare all over. Significant is the basic pattern, repeating itself in scores of enzymatic failures, of a changed gene causing a distinct enzyme block. It does so alone or together with its similarly changed partner gene, carrying its false message unaltered from generation to generation.

Besides these experiments by nature, revealing the existence of an enzyme and its determining gene by replacing the gene with an inert imitation, information about enzymes has been obtained from the study of their inhibitors. Chains of vital processes in the human body, concerned with energy provision and material replace-

*Army News Features*

Enzyme inhibitors could turn these troops into a state of paralysis

ment, can be broken at will. For practical purposes, the effect of a specific enzyme inhibitor is a disturbed function that can be seen or measured with special methods. In effect, a supply point has been demolished.

For widely varying purposes, enzyme inhibitors have long been systematically studied. Their principal modes of operation have been traced, and their practical use includes agents with antibacterial and antitumor activity. The systematic search for enzyme inhibitors, useful as insecticides, began in Leverkusen in the Rhine Province in the thirties. Insects have solved their internal supply problems much in the same way as the gardener or farmer who tries to survive his bug fauna, but there are differences in susceptibility to enzyme inhibitors. In 1937, the Leverkusen lab-

oratories could, however, report a series of organophosphorous compounds that killed the gardener as well as his beetles.

Keeping quiet about these reports, the Wehrmacht began large-scale production in Dyhernfurth in Silesia of what was code-named Trilon. This was in April 1942. By 1945, some 12,000 tons had been produced of tabun or GA. Thus, began the mass production and stockpiling of the so-called nerve gases.

Such highly toxic enzyme inhibitors demonstrate quite convincingly the need for an orderly mobilization of molecules for a given mission—in this case, signal transmission. Too much or too little, too early or too late means chaotic performance by activated molecules.

When the brain orders a muscle to

shorten, the signal is dispatched via a nerve which triggers numerous muscle fibers. This is done through the transcription of the nerve signal to a chemical message, acetylcholine being released at the endings of nerve fibers. As long as the flow of impulses

mediate result is a persistent muscular contraction, a state of cramp, followed by paralysis. And this is exactly what happens when the critical esterase, called acetylcholinesterase, becomes inhibited by a G-type phosphorous compound. When the block



Army News Features

Face masks provide protection from a variety of agents, but a minute droplet of VE or VX passing rapidly through the skin can be fatal

travels through the nerve, acetylcholine is discharged and the muscle remains contracted. What happens when the muscle gets word to suspend action is not only that the transmitter substance, acetylcholine, stops being set free, but the chemical signal becomes muted, and acetylcholine is immediately broken up into inactive compounds. This vital task is fulfilled by an esterase, a specialized enzyme.

Without normal activity of this esterase, acetylcholine remains at the nerve fiber endings. The command to cease action does not arrive. The im-

mediate result is a persistent muscular contraction, the result is temporary inability of service. But muscles of respiration are also involved, with death following exposure to relatively small quantities. Thus, GA can kill in concentrations of 40 milligrams per cubic meter of air during 10 minutes of exposure through inhalation. However, GB and GD have a lethal concentration of only 10 milligrams under the same conditions.

A further development of the G series of chemical agents is represented by the V anticholinesterases

which are active after having passed the skin. The G agents are also absorbed through unprotected skin, but they evaporate too fast for full effect. A minute droplet of VE or VX passing rapidly through the skin, into the blood circulation, can kill a soldier.

Questions about the limitations of chemical warfare have been raised from time to time. The high toxicity of G and V-type enzyme inhibitors and the possibility of using strategic missiles with chemical warheads carrying well above four tons of payload have raised the discussion to animated altitudes. With existing ordnance employed on a modest scale, and with only a fraction of the GB now in stock, the inhabitants of Paris, Osaka, or Los Angeles could be asphyxiated. But this does not draw the whole picture.

Blocking Agents

By a peculiar coincidence, an inborn variability in the activity of cholinesterases has been observed. For various medicinal purposes, drugs are used to interrupt the transmission of the nerve impulse where it reaches the muscle. One objective is relaxation of the abdominal wall so that surgical manipulations can be carried out without resort to deep anesthesia.

Blocking agents of the same type are also used to decrease muscular spasms in tetanus and to prevent mishaps in the electroshock treatment of psychiatric disorders. One widely used blocking agent derives from curare, the South American arrow poison. Another is suxamethonium which cuts the nerve-muscle signal by interfering with the shifting of electrons at the critical junction.

The therapeutic effect aimed at should vanish with the need for relaxation, but in some patients suxa-

methonium caused unexpectedly long laming of muscles and dangerous standstill of respiration. While curare was, at an earlier stage of its medical use, the carefully guarded secret of tribal witch doctors, nothing in that way entered modern anesthesiology. The relaxant was right; the patient was unfit. The untoward reaction was brought about by a weak or absent cholinesterase activity.

Persons with this potentially fatal weakness are in excellent health as long as they are not exposed to suxamethonium. The deficient enzyme differs in some respects from the cholinesterase handling acetylcholine. It is produced by the directives of a changed gene and the fault appears in consecutive generations.

Human Variations

Such chance findings of heritable differences inevitably attract the attention of people who study the distribution of different genes in human populations. The esterase differences have been studied in detail with the aid of specific enzyme inhibitors. In essence, their inheritance follows well-known Mendelian patterns. A person who has the usual gene on both of two ordinary chromosomes is endowed with a 100-percent esterase activity; the atypical gene on the same site of both chromosomes renders only 50-percent enzyme activity. If two such persons start a family, their children will each have one usual and one atypical gene, and 75-percent enzyme activity.

Close to four percent of the normal people in Canada and Britain carry the atypical gene with the resulting reduced esterase activity. Similar proportions of 75 percenters have been observed in non-European populations. It is quite possible that the atypical

gene, and a third gene causing, in duplicate, zero esterase activity, will finally be found to have about the same distribution in geographically widely separated populations.

But this is only a stray observation fitting into a repeatedly confirmed pattern of human variation. In brief, human populations can be characterized by frequencies of distinct genes. Sometimes, gene frequencies agree fairly well between widely dispersed populations, but more often there are great differences. This view differs from the concept of typification established in physical anthropology until mathematical models and the observation of simply inherited, normal traits made the study of gene frequencies meaningful.

Biochemical Differences

With World War I came the first impetus to the new approach, blood group frequencies in Allied armies being found to vary considerably among personnel of different geographic origin. Next, blood groups were used to map the world population. In central Asia, the B-gene frequency comes near 30 percent; in American Indians, this gene is originally absent. When new blood group systems were discovered, European, Asian, and African populations could be characterized by a number of independently varying gene frequencies.

Widely used in such studies of human populations is the ability to taste diluted solutions of phenylthiourea. Persons who carry a variant of the taster gene on both of the critical chromosomes are nontasters. If somebody were to dissolve a sufficient amount of phenylthiourea in the drinking water in Mahar, India, 54 percent of all water drinkers would complain of the bitter taste. Among

Brazilian Indians, an identical experiment would make little more than one percent aware of the admixture.

Several other biochemical differences between human beings have been studied with an increasing awareness that some of these differences may be adaptive. When a simply inherited variant of the red coloring matter of blood, practically absent in Europe, was observed to be common in a broad belt across central Africa, it was brought into relation with the high incidence of malaria in these regions.

Carriers of the changed gene have an increased chance of becoming grandparents in spite of the high mortality among their children where the abnormal gene in the duplex state is a merciless killer. The cause is the greater resistance to malaria granted by a single gene for the deviant pigment. In the Mediterranean region, similar situations include other variants of blood pigment and also an enzyme defect significantly common in old malaria regions.

Enzymatic Reactions

In the present decade, knowledge about enzyme polymorphisms has accumulated. If a deviant gene is too common in a given population to remain prevalent only through new mutations, it has a polymorphic distribution. More often than not, the selective forces balancing such relatively high frequencies of a substandard gene are completely unknown. The chance observation of a reaction to a certain drug is obviously just the shadow on the wall. The real item has to be searched for among entangled molecular supply lines in the living organism. Clearly a relative advantage in one environment granted carriers of a mutant gene can be

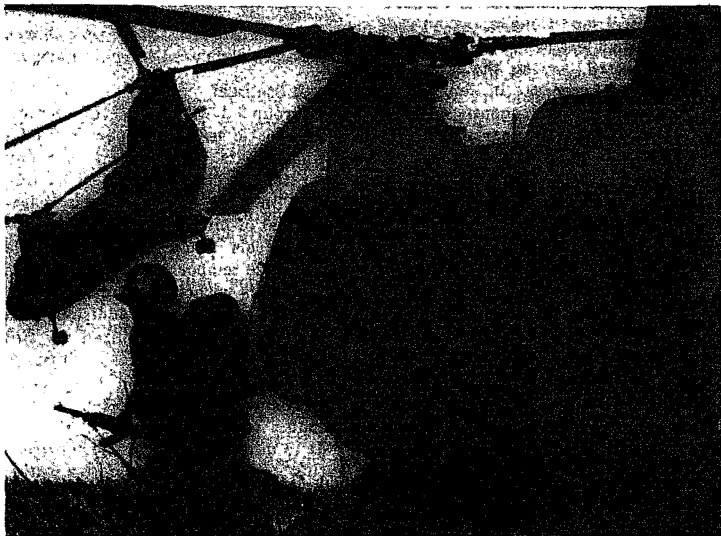
entirely void in another environment. But the decisive environmental factors of selection can hardly be suxamethonium drugs, sulfonamides, or BZ-type chemical agents.

Careful analyses of enzymatic reaction patterns to a series of drugs are underway, and we may soon have a grid where new observations of this kind can be pinpointed. One set of reference lines in this grid goes from genes necessary for enzyme production. Another set of lines marks substances turning on and off the making of active enzymes which can, but need not, be alerted.

Recently, a series of widely debated observations have revealed an enzyme deficiency in southeastern Asian populations, making them susceptible to

a poison to which Caucasoids are largely adapted. In such situations, the sketchy grid just mentioned is of some use. One looks for the possibility of the poison-provoking enzyme production, an individual adaptation observed in several instances.

The poison now at issue is milk. In Europeans, intolerance to lactose, or milk sugar, occurs as a rare recessive trait. Healthy parents, each carrying a single mutant gene, have children approximately one-fourth of whom react to milk ingestion with diarrhea, vomiting, malabsorption, and even death. When reports on milk intolerance in various groups of non-European began to accumulate, it was remembered that malnourished children in east Africa got diarrhea when



*Vertol Division
The Boeing Company*

Innate differences in vulnerability to chemical agents between different populations have led to the possible development of ethnic weapons

treated with dried skimmed milk. Then, the enzyme lactase was found to lose its activity in the intestinal mucosa of African infants over the first four years of life.

New reports on milk intolerance in Chinese, Filipinos, and Indians were met with skepticism in that the groups studied might not be representative of their peoples. A study reported from the Chiangmai University in Thailand has, however, revealed a widespread lactose intolerance in adults in northern Thailand, the lactase activity getting lost between the first and fourth years of life. By inference, it has been found likely that Southeast Asians, in general, are deficient in lactase production.

Rapid and Slow Inactivators

Similar observations of geographically distinct enzyme differences are to be expected. Among the obviously inherited differences in enzymatic response to chemical agents, acetylation is marked by a clear separation of people in two groups. Originally, one group was characterized as composed of rapid inactivators of isoniazid, a drug used against tuberculosis. The other group of slow inactivators carries an alternative gene less efficient in converting isoniazid to acetylisoniazid. Europeans, as well as Americans of African descent, have among their numbers about 50 percent slow inactivators. Eskimos and Japanese have approximately 10 percent slow inactivators.

The method of acetylation to inactivate a molecule is not confined to isoniazid. People belonging to the two acetylator classes reveal differences in handling a number of other drugs, including enzyme inhibitors acting upon the central nervous system. Although the study of drug metabolizing

enzymes is only beginning, observed variations in drug response have pointed to the possibility of great innate differences in vulnerability to chemical agents between different populations.

A series of enzyme inhibitors and chemically active substances interfering with signal transmission in the brain and spinal cord have been intensely studied since the early fifties. Many of these substances have a colorful prehistory saturated with tribal sorcery.

The incapacitant known as BZ derives from a drug which before its present renaissance as lysergic acid diethylamide (LSD) caused epidemic outbursts of Saint Anthony's fire in the Dark Ages. With ditran-like compounds, BZ shares the capacity to produce transient toxic psychosis, sometimes compared to schizophrenia.

Search Continues

Surrounded with clouds of secrecy, a systematic search for new incapacitating agents is going on in many laboratories. The general idea, as discussed in open literature, was originally that of minimal destruction. Psychochemicals would make it possible to paralyze temporarily entire population centers without damage to homes and other structures. In addition, with the small quantities required for full effect of modern incapacitating agents, logistics problems would be minute. The effective dose of BZ-type agents amounts to micrograms.

It is quite possible to use incapacitating agents over the entire range of offensive operations, from covert activities to mass destruction. One fairly obvious offensive preparation is protection of the country's own personnel by tolerance-building. This is where enzymatic response to psycho-

chemicals enters the scene. Exposure to drugs or to molecules of almost identical composition is known to produce, with varying degrees of accuracy, resistance to the toxic effect at repeated exposure. As this is a known and thoroughly discussed procedure, concealment of large-scale preparations of this type probably would be difficult if not wholly impossible.

Another prospect may tempt an aggressor who knows he can recruit from a population largely tolerant against an incapacitating agent to which the target population is susceptible. An innate immunity would offer concealment of preparations and obvious advantages in many tactical situations. When the proper chemical agent is used against intermingled friendly and enemy units, casualties may occur in proportions one to 10.

Such inferences are barely extrapolations of observed genetic differences between major human populations and of research programs known to be in progress. Widely different opinions have been ventured as to the type of chemical operations likely to be directed against military personnel and the civilian population in a future war. There have been some recent tendencies to stress the wide latitude between incapacitating and the lethal action of BZ-type agents. Friendly troops could use them to dampen belligerence. They effectively slow down physical and mental activity, make the poisoned personnel giddy, disoriented, and more or less unable or unwilling to carry out commands.

Friendly forces would discriminately use incapacitants in entangled situations to give friend and foe a short period of enforced rest to sort them out. By gentle persuasion, aided by psychochemicals, civilians in enemy cities could be reeducated. The adversary would use incapacitants to spare those whom he could use for slaves. There is little that human biology can contribute to prognoses of that type.

The factual basis of abundant enzyme inhibitors of widely different types can be neglected as little as modern methods for their distribution. They need not be gases in a true sense. Well-studied enzymes represent a small proportion of the total number of catalysts necessary for our vital processes. When new enzyme varieties are discovered, some of them are likely to overstep the prevalence limits so far observed, both high and low, in different populations.

But the production of enzymes in the living cell could not be selectively quenched until details of early signal transmission from the gene became known in 1969. During the first half of that year, several laboratories reported factors engaged in passing over the genic message from DNA, the primary command post, to RNA which relays the chemical signal. The enzymatic process for RNA production has been known for some years, but now the factors have been revealed which regulate the initiation and specificity of enzyme production. Not only the factors have been found, but their inhibitors. Thus, the functions of life lie bare to attack.