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Remarks on past and future

Theatrum Vacunae

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In the days of yore people died from infectious diseases simply because there were no therapeutic or preventive agents. As far as viral infections are concerned the last two hundred years saw the emergence of vaccines preventing certain infections.

The prototype vaccines designed by Jenner and Pasteur effectively protect against infections persons who were vaccinated. The two vaccines are based on viruses devoid of virulence but preserving the ability to stimulate the immune reaction.

Massive vaccinations against smallpox using vaccinia virus had eradicated the disease worldwide [1]. In the case of Pasteur vaccine the problem is more complicated since the "fixed" strain of rabies virus had not been attenuated as much as Pasteur thought. It was only after a tragic accident involving a case of rabies among children, "immunized with Pasteur vaccine containing viral particles that were not inactivated by formalin treatment", that the danger of using the "fixed" virus in its "live" form for human immunization was realized [2].

In contrast to a sizeable number of viral vaccines prepared within the last couple of decades there are very few drugs active against viral diseases. The reason for this may be due to the fact that, with the exception of poliomyelitis destroying infected cells as a result of virus multiplication, the majority of viruses do not affect the host in such a way. They rather trigger infiltration by macrophages or lymphocytes and secretion of substances destroying infected cells. Three or four existing antiviral drugs are not active against such infections and huge funds spent on searching effective antiviral drugs have been besides the purpose. Complete elimination of a virus from an infected cell by using a biochemical substance may not be feasible at all. More attention needs to be devoted therefore to control postviral infiltrations and toxic substances produced by infiltrated cells.

One of these substances is nitric oxide, NO, the smallest biologically active molecule. Nitrogen oxide, produced by iNOS (the inducted NO synthase) is toxic to cells. iNOS is produced by infiltrate-present monocytes and perhaps by microglia and astrocytes. NO is detectable in the central nervous system in cases of viral infections of the brain and allergic palsy related to the autoimmune reaction [3]. iNOS induction is also detected in the plaque areas in the brain of people affected with multiple sclerosis [4]. We have at our disposal substances blocking the induction of NO-synthesizing enzyme or inhibiting NO action directly [5]. Such approach to viral infections makes more sense than the attempts to find new drugs directly affecting viruses in the host.

Anti-virus vaccines pose some serious problems; they pertain mostly to their price and mode of administration. In the U.S., a single administration of a "new" anti-rabies vaccine prepared in tissue culture costs $90 and individuals at risk of rabies need four such administrations of the vaccine. Since the greatest demand for an anti-rabies vaccine exists in India it is obvious that the most endangered people cannot afford such expense.

The second problem is in the mechanism of vaccine administration. In countries where population is most at risk of rabies' infection public health services do not have enough personnel to effectively administer the vaccine in the injectable form. An alternative needs to be found.

Between 1957 and 1958, Courtois and myself organized the first worldwide massive vaccination against polio using an oral preparation [6]. During six weeks we were able to vaccinate 250 thousand children. It made us think that the future of vaccinal campaigns depends on the availability of oral vaccines. To lower the cost of vaccine one needs to resort to the cheapest methods available for their preparation, i.e., the ones that utilize plants.

"Edible" vaccines will be within reach of any society on the planet. Preparation of transgenic plants has been known for long enough, mainly in the context of eliciting resistance of a given plant species against plant parasites [7]. Only recently transgenic plants containing genes from animal microorganisms or even their antibodies became available, however. Examples include tomatoes with rabies virus glycoprotein [8], potatoes with hepatitis virus and tobacco with antibody from *Streptococcus elegans*. They illustrate the progress made towards creating vaccines attainable to everybody [9]. Even if the administration of "edible" vaccines may stretch out in time the culturing of animal microorganisms in plants is so cheap that extracts from nonedible plants such as tobacco may be used in production of cheap vaccines.

The "Brave New World" by A. Huxley was pure fantasy at the time of writing. Today, some of Huxley's prophecies have been fulfilled, for example culturing (for a limited time) human embryos in a test tube. "Edible" vaccines may be regarded as fantasy by today's skeptics but the time shall come when their use will help us to fight or maybe even eliminate harmful microorganisms from human environment.

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