Inspection of the paleontologic history of many phyla shows that when certain members of a series of polyisomeres have been subjected to increasing stresses through long periods of geologic time, they have often become enlarged, strengthened or fused with their neighbors and have thereby passed into a state of anisomerism.

Thus taxonomy, paleontology, comparative anatomy, genetics, experimental biology, physiology and allied sciences may find new common grounds in tracing the history and behavior of polyisomeres, anisomeres and hyperpolyisomeres.

[1] Cope, E. D., "The Method of Creation of Organic Forms," *Proc. Amer. Phil. Soc.*, 238, 241, 242 (Dec. 15, 1871).

[2] Gregory, William K., "Fish Skulls: A Study of the Evolution of Natural Mechanisms," *Trans. Amer. Phil. Soc.*, **23**, Art. 2 (1933).

[3] Osborn, H. F., "The Titanotheres of Ancient Wyoming, Dakota and Nebraska," *Monograph* **55**, *U. S. Geol. Surv.*, *I*, 830 (1929).

ACTIVE AND PASSIVE IMMUNIZATION IN TYPHUS FEVER

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In preceding papers we have reported the successful production of a typhus vaccine made by obtaining concentrated suspensions of the Rickettsiae of the Mexican disease in the peritoneal cavities of rats in which the resistance has been reduced by radiation with x-rays. Since organisms of the Rickettsiae type cannot be cultivated, this method is so far the only one by which concentrated Rickettsiae suspensions can be obtained on a scale practically available for serological study and for extensive immunization. The Weigl method of producing similar suspensions for the same purpose by passing the European virus through lice and emulsifying the intestinal canals of the infected insects is excellent, but is hardly practicable on anything but a limited scale and is excessively dangerous, since the infected lice must be fed upon immunes for ten or more days after infection and must be handled under conditions of the greatest difficulty.

In the preceding papers alluded to we demonstrated that the vaccines now routinely prepared by us and by the Mexican Health authorities produce a satisfactory active immunization in guinea pigs infected with the Mexican virus and give about 30 to 50% immunization if the animals are sub-

sequently infected with the virus of the classical European disease. Serological work carried out by special methods of agglutination with these x-rayed rat vaccines indicated a close antigenic relationship between the two varieties of typhus virus mentioned, since human and animal convalescent sera from both types of the disease agglutinated both our Rickettsiae and the Weigl louse vaccines and since rabbits immunized with the two preparations, respectively, developed agglutinins for both Rickettsiae suspensions—the rabbit receiving our Mexican Rickettsiae powerfully agglutinating the Weigl vaccine, and vice versa. Additional proof of the specificity of our materials is furnished by the observation that the rabbits so treated developed Weil-Felix reactions.

In logical continuation of these results, we proceeded, two years ago, with the systematic treatment of a horse with our vaccines killed with 0.2% formaline, and we reported last year that the serum of this animal developed a Weil-Felix reaction and, although it had never received anything but the vaccine produced with the Mexican virus, it powerfully agglutinated the Weigl vaccines produced in lice with the European virus. At the same time, we showed that the serum of this horse, administered between twenty-four and seventy-two hours after infection with the virus, prevented the development of typhus in guinea pigs receiving heavy doses of the Mexican virus. These results are shown in a chart which has already been published[1] and which is important for the results which form the chief subject of our present report. The effect of this serum on typhus fever in man is being studied by a commission of Mexican physicians in their own country.

At the time that the last-mentioned experiments were done, we were unsuccessful in passively protecting guinea pigs with this serum against inoculations of the European virus. These results were anomalous and not easily explained in view of the close relationship between the two types of virus which the experiments outlined above had demonstrated. The most likely explanation seemed that our horse serum had not reached a sufficient potency to overcome the slight but definite antigenic difference between the two varieties of infectious agents. We continued, therefore, to treat the horse with increasing amounts of formalinized Mexican Rickettsiae, and resumed immunization experiments at the time when the horse's serum had attained an agglutinative potency of 1–640 against Bacillus Proteus X 19—about double the potency obtained in the bleedings used for the protection experiments just mentioned.

Also, we took into consideration in the experiments about to be presented the fact that when one inoculates European virus, the material is in the form of brain suspension and defibrinated blood of animals at the height of the disease. In such material the infectious agents are largely intracellular, and since the cells injected are species homologous, it is unlikely

that the virus enters the blood-stream of the inoculated animal in any considerable amounts until about four days after injection. Any serum given on the first day—as in previous experiments with the European material—is largely eliminated and is unavailable at the time when the infection seriously begins. We therefore altered our technique by allowing from two to three days to elapse between intraperitoneal inoculation of the virus and the subcutaneous administration of the horse serum. A preliminary experiment, in which four animals received a large intraperitoneal dose of European virus followed in two of them, after four days, by 2 cc. of the horse serum given subcutaneously and, on the fifth day, by an additional dose of 0.5 cc., gave us promising results in that the two controls developed typical and severe typhus fever and the untreated animals showed nothing more than temporary rises of temperature. Similar experiments are still going on.[1]

It is apparent from these simple tests that properly managed experiments in passive immunization—apart from the possible practical implications—corroborate our previous experience of the close immunological relationships existing between the classical European typhus fever and what is spoken of as the "New World" type.

Unlike many European observers, we are quite convinced that there is no fundamental difference between these two manifestations of Rickettsiae infection—that they belong essentially to the same group, with fractional antigenic differences probably brought about by passage through different animal and insect vectors.

That the European type of virus maintains itself for many years in America, largely in the immigrant population, was demonstrated by us recently by isolation from a case of Brill's disease occurring in Boston of a virus which has conformed through almost twenty guinea pig generations to the European type. Since the New World variety has been shown by ourselves and others to maintain itself in the interepidemic period in rats and rat fleas, and since the interepidemic reservoir of the classical European disease is not as yet known, there may be prospects by solving the reservoir of the European virus in American cities, of throwing light on the long mysterious question as to how the typhus virus maintains itself during long periods of quiescence in European communities where it breaks out so disastrously under conditions of famine, war and economic stress.

[1] The chart which illustrates the results of serum treatment in animals infected with Mexican virus was published in a paper by Zinsser and Castaneda in the *Journal of Experimental Medicine*, **57**, 395 (1933). The two charts illustrating the experiment here reported in a preliminary way will be published with the paper giving specific details of all the experimental work done on this subject.