6891

Effect of Sensitization with Tuberculin Protein upon Development and Course of Experimental Tuberculosis.

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The relation of tuberculin hypersensitiveness and resistance to tuberculosis has long been in dispute. Austrian[1] concluded that the state of hypersensitiveness to tuberculin protein afforded no protection against subsequent tuberculous infection and was even harmful. Krause and Willis[2] observed some lowered resistance to infection in animals sensitized to tuberculo-protein and more definitely in animals inoculated while suffering with anaphylactic shock. Their animals showed no cutaneous sensitivity. Nevertheless, they[3] attributed the usual state of resistance to reinfection in tuberculous animals directly to the effect of the allergic inflammatory reaction. Rich and McCordock[4] opposed this view on the basis of observations on experimental animals and human beings. Sabin, Smithburn and Geiger[5] noted no beneficial effect of the hypersensitive state on the course of experimental tuberculosis. Myers[6] and Stewart[7] have recently emphasized the predisposing effect of allergy for the development of adult type of tuberculosis. It has been shown[8] that upon repeated injections of sufficient quantity of highly antigenic preparations of tuberculin protein guinea pigs and rabbits will react cutaneously not only to this protein fraction, but also to the active material isolated from Old Tuberculin. It seemed desirable, therefore, to study the effect of this high degree of hypersensitiveness upon the tuberculous process.

Seventeen guinea pigs were sensitized with a tuberculin protein fraction, TPT,[8] by weekly intracutaneous injections of 10 mg. Six

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1 Austrian, C. R., *Bull. Johns Hopkins Hosp.*, 1913, **24**, 11.

2 Krause, A. K., *J. Med. Res.*, 1911, **24**, 361; 1916, **35**, 25. Krause, A. K., and Willis, H. S., *Am. Rev. Tuberc.*, 1919, **3**, 153.

3 Krause, A. K., *Am. Rev. Tuberc.*, 1925, **11**, 343. Krause, A. K., and Willis, H. S., *Ibid.*, 1925, **11**, 439.

4 Rich, A., and McCordock, H. A., *Bull. Johns Hopkins Hosp.*, 1929, **44**, 273.

5 Sabin, F. R., Smithburn, K. C., and Geiger, J. T., *Trans. Nat. Tuberc. Assoc.*, 1933.

6 Meyers, J. A., *Am. Rev. Tuberc.*, 1933, **27**, 121.

7 Stewart, C. A., *J. Am. Med. Assn.*, 1933, **100**, 1077.

8 Seibert, F. B., *J. Inf. Dis.*, 1932, **51**, 383.

TABLE I.
Course of Tuberculosis in Tuberculin Protein Sensitized and Non-sensitized Guinea Pigs.

	Sensitized						Non-sensitized					
Route of inoculation	Time of death after inoculation	days	Wt. of Spleen gms.	Extent of lesion in Spleen	Liver	Lungs	Time of death after inoculation	days	Wt. of Spleen gms.	Extent of lesion in Spleen	Liver	Lungs
Subcutaneously	Died	93	Large	+++	+++	+++	Killed	93	Med.	++	+	+
	"	94	12.6	+++	+++	++	"	94	2.4	+++	+	+
	"	101	10.0	+++	+	+	"	101	2.0	++	+	+
	"	125	21.6	+++	+++	+++	"	125	3.2	+	+	++
	Killed	185	5.9	+++	±	+++	Died	146	6.0	+	++	+
							Killed	185	4.5	++	+	+++
							"	193	6.6	+++	+	+
							"	193	9.5	+++	+++	+++
Intracutaneously	Died	91	5.2	+++	+++	+++	"	91	2.2	+++	+	+
	"	151	4.1	++	++	+++	Died	139	1.6	+	+	+++
	"	152	7.6	+++	+	+++	Killed	151	4.9	+++	+	+++
	"	159	13.9	+++	+++	+++	"	159	2.4	++	+	++
	Killed	193	5.3	+++	+	++	"	193	4.9	++	+	+++
	"	193	4.4	++	+	+++	"	193	4.1	+++	++	+++
							"	193	3.4	+++	++	—

of these died from intercurrent infection before significant tuberculous changes developed, and are omitted from the accompanying table. The first injection elicited very little, if any, cutaneous reaction; the next few injections were followed first by small and finally by large pale edematous reactions. After the seventh to the tenth injection, most of the animals gave reactions that were red and localized, intensely indurated and necrotic in the center, thus resembling very closely the severe reactions obtained with tuberculin in tuberculous animals. At no time did the animals display evidence of anaphylactic intoxication following the injections and, on the whole, they constantly gained weight. One week following the twelfth injection, 17 untreated and the 17 hypersensitive guinea pigs were inoculated with 0.001 mg. of a live virulent human-type tubercle bacillus, strain H 37, half of them subcutaneously and the other half intracutaneously. Following this whenever a sensitized animal died a control animal of approximately the same weight was killed, and finally, 6 months from the time of inoculation all surviving animals were killed.

In general those animals that had been sensitized and then inoculated subcutaneously, died sooner than the others. The most conspicuous change was great involvement of the spleen, as can be seen from the weights of this organ recorded in the table. The extensive distension of the splenic tissue by edema and hemorrhage and the diffuse caseation and necrosis with almost complete disappearance of normal tissue in the sensitized animals was in marked contrast to the predominating, discreet, raised and fibroplastic lesions found in the control spleens. Next in order of splenic involvement and in time of death were the sensitized guinea pigs that had been inoculated intracutaneously. After 6 months the lesions in the few surviving sensitized and in the non-sensitized control animals more nearly resembled each other and were in both groups of the chronic type.

These results, therefore, lead to the conclusion that a high degree of hypersensitiveness to tuberculin protein confers no immunity or increased resistance to subsequent tuberculous infection. On the contrary, it seems to hasten and extend the lesion and to be associated with much more extensive necrosis and caseation than is found in unsensitized animals. The experiment is being repeated and greatly extended.