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Local Organ Hypersensitiveness: I. Experimental Production in the Rabbit Eye.

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Although there is a considerable and significant literature on the problems of general hypersensitiveness the known facts concerning local hypersensitiveness are few. The early work of Koch,[1] Calmette and Guerin,[2] and v. Pirquet[3] on the tuberculin reaction, the demonstration by Arthus[4] of skin necroses after repeated injection of foreign proteins, the work of Gay[5] on the typhoidin reaction and finally the work of Swift,[6] Dochez and Stevens,[7] and MacKenzie and Hanger,[8] and many others have helped our understanding of local changes in the reactivity of the skin. Furthermore, clinical observations have attested to the fact that apparently arrested areas of inflammation in various parts of the body have been relit by the introduction of the homologous noxious substance into distant sites. Experimental work along similar lines attempting to produce altered reactivity in other organs than the skin has not yielded uniformly positive results.

From a review of previous attempts to produce local hypersensitiveness it seemed that the critical requirement was the maintenance of a set of experimental conditions which would keep antigen in juxtaposition to body cells for a relatively long period of time. The structure of the anterior chamber of the eye presents a feature which probably allows this condition to be fulfilled. We had observed that heterologous erythrocytes when injected into the anterior chamber of the rabbit's eye would persist for several days. On this account the anterior chamber of the eye was the initial area chosen to test for the production of local hypersensitivity.

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[1] Koch, R., *D. M. W.*, 1891, xvii, 101 and 1189.

[2] Calmette, A., and Guerin, C., *Compt. rend. Soc. de Biol.*, 1908, lxiv, 722.

[3] v. Pirquet, C. E., *Ergb. d. inn. Med. u. Kinderheilk*, 1910, v.

[4] Arthus, M. M., *Compt. rend. Soc. de Biol.*, 1903, lv, 817.

[5] Gay, F. P., and Force, J. N., *Arch. Int. Med.*, 1914, xiii, 471.

[6] Swift, H. F., Derick, C. L., and Hitchcock, C. H., *J. Am. Med. Assn.*, 1928, xc, 906.

[7] Dochez, A. R., and Stevens, F. A., *J. Exp. Med.*, 1927, xlvi, 487.

[8] MacKenzie, G. M., and Hanger, F. M., Jr., *J. Immunol.*, 1927, xiii, 41.

A number of workers in ophthalmology have attempted to explain certain types of conjunctivitis and keratitis on the basis of "ocular anaphylaxis". Schieck,[9] Lemoine,[10] Tooker,[11] and Pasteur Vallery-Radot[12] among others have contributed clinical observations in this regard. Kodama[13] found that in sensitized guinea pigs the introduction of the shocking agent "into the orbit" produced stimulation of plain muscle, circulatory disturbances, and hypersecretion of eye glands. In attempting to explain the manifestations of sympathetic ophthalmia on the basis of "anaphylactic phenomena", Elschnig,[14] Kummel,[15] Wissman,[16] Fuchs and Meller,[17] von Szily,[18] and Woods,[19] have made certain contributions regarding the question of whether the injured uveal tract of one eye may act as a sensitizing and subsequent shocking antigen to the other eye. Wessely[20] found that the injection of horse serum into the cornea resulted in a local reaction which subsided in 48 hours. Two weeks later a spontaneous relighting of the same cornea appeared. If just prior to this response the cornea of the opposite eye was injected with horse serum, a violent reaction ensued in the injected eye. Stanculeanu and Nita[21] have demonstrated the Arthus phenomenon in the conjunctiva by the use of horse serum, and Kirchner[22] has sensitized the cornea of the rabbit to *S. scarlatinae* toxin, demonstrating sensitization by repeated injections into the cornea. Attempts to reactivate a locally sensitized eye by intravenous injection of the homologous antigen have been few and only successfully accomplished by Von Szily[18] and Riehm[23] in their studies on sympathetic ophthalmia. Schoenberg[24] injected human serum into the anterior chamber of 2 rabbits and tuberculin into the anterior chamber of 2 other rabbits.

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[9] Schieck, *Zeitschr. f. Augenheilk.*, 1914, xxxii, 95.

[10] Lemoine, *Arch. Ophth.*, 1929, i, 706.

[11] Tooker, C. W., *Arch. Ophth.*, 1929, ii, 540.

[12] Pasteur Vallery-Radot, *Presse Med.*, 1929, xxxvii, 529.

[13] Kodama, R., *J. Inf. Dis.*, 1921, xxviii, 48.

[14] Elschnig, A., *Arch. f. Ophth.*, 1911, lxxix, 428.

[15] Kummel, R., *Arch. f. Ophth.*, 1912, lxxxi, 486.

[16] Wissman, R., *Arch. f. Ophth.*, 1911, lxxx, 399.

[17] Fuchs and Meller, *J. Arch. f. Ophth.*, 1914, lxxxviii, 280.

[18] v. Szily, A., *Die Anaphylaxie in der Augenheilkunde*, Stuttgart, 1914. *Klinische Monatsb. f. Augenheilk.*, 1916, lvi, 79.

[19] Woods, A. C., *Arch. Ophth.*, 1917, xlvi, 8.

[20] Wessely, K., *M. M. W.*, 1911, lviii, 1712.

[21] Stanculeanu and Nita, *Compt. rend. Soc. de Biol.*, 1909, lxvi, 1112.

[22] Kirchner, O., *Z. f. Immunitatsfsch.*, 1928, lv, 157.

[23] Riehm, *D. M. W.*, 1929, lv, 907.

[24] Schoenberg, M. J., *N. Y. S. J. M.*, 1914, xiv, 493.

Intravenous injection of the homologous anigen 2 weeks later produced no significant eye reaction. Brown and Dummer[25] injected increasing doses of hemolytic streptococcus vaccine into the conjunctiva of 2 rabbits for 4 days and then injected a suspension of the living organisms intravenously on the following day. No eye reactions were noted.

A preliminary experiment to produce local hypersensitivity in the eye was carried out as follows: Two-tenths of a cubic centimeter of the anterior chamber fluid from the right eye of 5 rabbits was removed under cocaine anesthesia and replaced by 3 separate substances. Each of 2 animals received 0.15 cc. of a 40% saline suspension of guinea pig red blood cells, 2 received a similar quantity of a 40% saline solution of fresh egg white and the remaining animal 0.15 cc. of physiological saline solution. There was a very slight injection of the conjunctival vessels for 24 hours in the saline treated animal. In the other 4 animals the anterior chamber appeared cloudy and definite injection of the iris and conjunctiva occurred, which cleared up completely in from 3 to 6 days. The eyes of all animals remained normal in appearance until the thirteenth day after injection, when a test for the local sensitivity of the eye was attempted. Rabbit 1, sensitized with guinea pig red blood cells, was injected intravenously with 1.0 cc. of 30% saline solution of fresh egg white, while Rabbit 2, similarly sensitized, was injected intravenously with 1.0 cc. of a 40% suspension of guinea pig red blood cells. In a similar manner, of the 2 animals prepared by an

TABLE I.
Reactivation of Locally Sensitized Eyes.

Rabbit No.	Right eye sensitized with	13 days later injected intravenously with	Maximum reaction in eye 5 hours later
1	Guinea pig red blood cells	Egg albumen	None
2	Guinea pig red blood cells	Guinea pig red blood cells	Hyperaemia of conjunctiva and iris. Chemosis, lacrimation
3	Egg albumen	Guinea pig red blood cells	None
4	Egg albumen	Egg albumen	Hyperaemia of conjunctiva and iris. Chemosis, lacrimation
5	Physiological saline	Guinea pig red blood cells	None
		24 hours later Egg albumen	None

[25] Brown, A. L., and Dummer, C., *Arch. Ophth.*, 1929, ii, 573.

injection of egg white into their anterior chambers, one was given egg white and the other guinea pig red blood cells intravenously. The saline control animal was injected with 1.0 cc. of guinea pig red blood cells and 24 hours later with 1.0 cc. of egg white. The animals injected with their homologous antigens reacted positively while the remaining animals failed to show any change in the eye.

The positive reaction in the eye was characterized by a moderate to deep injection of the conjunctival vessels, a similar though slight hyperaemia of the iris, slight chemosis and moderate lacrimation. This reaction tended to reach a maximum in about 5 hours and faded in the course of about 24 hours. The results of this experiment, shown in Table I, signify that specific local hypersensitiveness can be produced in the rabbit eye. Subsequent intravenous injections of the homologous antigens resulted in a much decreased local reaction. This we interpreted as a desensitization phenomenon. This desensitization could be completely accomplished by repeated injection of the usual doses of the homologous antigen.

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Local Organ Hypersensitiveness: II. Repeated Response in the Rabbit Eye.

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The demonstration of the availability of the rabbit's eye for local sensitization by a single antigen[1] suggested the possibility of the production of repeated eye response under appropriate experimental conditions. In order to avoid the phenomenon of desensitization and to work with an eye which might be kept more or less constantly in a condition of sterile inflammation, a "multiple" antigen was used to sensitize the eyes of a new series of rabbits. This was prepared by mixing together the citrated or defibrinated blood of a number of animals along with some other foreign proteins. The first multiple antigen consisted of citrated guinea pig, sheep and pigeon blood, horse serum, 5% casein, 5% egg white, and an anhemolytic streptococcus vaccine. Considering each blood as com-

[1] Seegal, D., and Seegal, B. C., PROC. SOC. EXP. BIOL. AND MED., 1930, xxvii,