THE ARTHUS PHENOMENON

Local Anaphylactic Inflammation in the Rabbit Brain

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Plate 12

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The brain as a functional unit in the production of generalized anaphylaxis has been extensively studied, notably by Besredka (1). As the seat of a local allergic reaction, however, it has apparently not yet been examined. Since the local anaphylactic reaction in the skin and in various organs (2) consists of edema, hemorrhage, and leucocytic infiltration, it appeared likely that the nervous tissue, which is so susceptible to the above mentioned pathological changes from a great variety of causes, would lend itself particularly well to the production of anaphylactic lesions.

In the present paper we have attempted to demonstrate the occurrence of local anaphylaxis in the brain of the rabbit.

EXPERIMENTAL DATA

Group I.—Seventeen rabbits received an intracerebral injection of 0.1 to 0.2 cc. of a foreign protein (red blood cells, serum, egg albumen), followed by a similar injection 1 to 5 days later. The trephinings were done with novocaine as anesthetic. They were then given a series of intravenous injections varying from 1 to 3 cc. of the particular antigen at intervals of approximately 5 days. After a free interval of 2 to 4 weeks 0.1 to 0.2 cc. of the specific antigen was again injected into the cerebrum through the original trephine hole. At the same time nine control rabbits which had not previously been sensitized were injected intracerebrally with the same antigens.

Ten of the seventeen sensitized animals died within 24 hours after the "shocking" injection with symptoms suggesting lesions of the

brain. Two rabbits died 7 days after the last injection of causes apparently unrelated to the experiment. Five were etherized at intervals of from 2 to 11 days. The brains were examined histologically. All but one animal, sacrificed at the 48 hour interval, showed changes characteristic of local allergic inflammation to be described presently.

None of the control animals died as a result of the experimentation. They were etherized and the brains were likewise studied histologically. While slight hemorrhages were present at the site of injection in one or two instances, none of the controls showed lesions comparable to those found in the sensitized series.

One factor in Group I appeared to us insufficiently controlled, namely that of trauma, adhesions, and mechanical rupture of large blood vessels as a result of repeated injections into the same area of the brain. We undertook, therefore, another experiment in which only one cerebral injection was to be done on each animal.

Group II.—This group consisted of ten sensitized animals and eight controls. The latter remained uninjected until the cerebral inoculation. The former were prepared by daily subcutaneous injections of 0.2 cc. of horse serum for 10 consecutive days. Most of the animals showed varying degrees of anaphylactic inflammation in the skin. 11 days after the last injection, the sensitized and control animals were given 0.2 cc. of horse serum into the left cerebrum.

Although no untoward effects were observed immediately, one sensitized animal was found dead and another dying 8 hours after the cerebral injection, the others survived symptomless. Examination of the brains of the two rabbits showed the typical sterile inflammatory changes characteristic of local anaphylactic reaction. The control group never showed any untoward symptoms as a result of this injection. On histological examination two of the control brains presented a slight hemorrhage along the needle tract. This was not associated with any of the other changes seen in the Arthus phenomenon and was due undoubtedly to mechanical trauma.

Group III.—The last group was treated similarly to Group II, except that a different antigen was used. Ten rabbits were sensitized with egg albumen, and 12 days after sensitization, they, together with seven normal controls, were each given 0.2 cc. of egg albumen into the left cerebrum.

Among the sensitized animals in this group three responded with tonic and clonic muscular contractions 1 minute after the cerebral injection, following which they kept rotating toward the right for 15 to 30 minutes. One of these animals died ½ hour after the attack. A fourth showed the rotary movements without preceding convulsions, a fifth one exhibited similar signs the next day to a slight degree. The four surviving rabbits which had shown clinical symptoms were etherized 3, 8, and 17 days later. As in the previous experiment, the controls showed no response whatsoever to the injection, but were etherized for histological comparison with the sensitized animals. Of the five experimental animals that had shown symptoms of cerebral disorder, four had histological changes characteristic of local anaphylactic inflammation in the brain. The fifth showed no pathological changes in the brain, but since the reaction in this case was mild, and the autopsy was not performed until 8 days after the injection, the signs of inflammation may conceivably have disappeared by this time.

The additional data obtained from these two groups made our conclusions certain that, while individual animals may differ in the degree of sensitivity, in most rabbits, given the proper experimental conditions, a localized anaphylactic inflammation of the brain can be made to develop.

Pathological Findings

In the gross the lesion seen in the brains of the sensitized animals is very striking (see Fig. 1). The side of the brain containing it is congested and enlarged and the midline structures are displaced toward the opposite side. On transverse section the entire center of the hemisphere is softened and hemorrhagic and the narrow margin of approximately normal tissue is edematous. The appearance suggests the results of a miniature explosion which had taken place in the middle of that hemisphere.

The histological picture (Fig. 2) of the Arthus reaction in the brain resembles very closely that described in the skin and subcutaneous tissue by Arthus and Breton, Gerlach, Doerr, and others, allowing for the differences in the fundamental structure of these tissues.

In the rabbit's brain 24 hours after the injection, the lesion often involves the entire hemisphere on the side of the injection and may

extend to a slight degree over to the other side as well. It is limited usually by some natural barrier like the wall of a ventricle, the corpus callosum, etc. It is characterized chiefly by generalized edema, serous exudate, hemorrhage, and leucocytic infiltration. The extravasated red blood cells and sometimes even those within the lumina of the blood vessels appear to have been laked and the whole tissue within the lesion takes on a diffuse pink stain. The edema of the tissues extends frequently beyond the area of cellular infiltration and destruction. At the very periphery of the lesion edema is still recognizable as widening of the perivascular spaces.

Practically all the nervous elements within the central zone are wiped out except for occasional shadowy forms, especially where nerve cells are normally closely packed as in the Ammon's horn region. Everywhere, where tissue is still recognizable its hydropic appearance is striking. Cells which still show identifiable protoplasm appear to be filled with bubbles, many of which have apparently burst.

Only the larger blood vessels stand out as rings, with walls that are involved in the general amorphism, surrounded by leucocytes, both active and disintegrating. Some of the larger vessels show rupture of their walls at various points, thus probably accounting for the hemorrhages. The capillaries within the lesion usually show very edematous endothelial cells with the narrowed lumina often stuffed with white blood cells.

The leucocytic infiltration is confined chiefly to the periphery of the lesion and the neighborhood of the blood vessels or still within the lumina of the vessels. The type of these cells is for the most part that of polymorphonuclear leucocytes. Occasional clumps of eosinophiles are seen. Many of the cells are disintegrating, numerous others are loaded with granules of blood pigment. When the lesion involves the greater part of the hemisphere the leucocytes are concentrated mainly in the meninges and choroid plexuses giving the impression of a purulent meningitis or ventriculitis, although cultures from these areas are sterile. Recently Burn and Finley (3) have described such a picture in the meninges of tuberculous guinea pigs which were injected with tuberculin into the cisterna magna.

In animals that survive or are allowed to survive 5 or 6 days beyond the last injection, the central area of the lesion becomes considerably

shrunken and quite sharply demarcated from the rest of the brain. A moderate amount of necrotic, amorphous material with a large number of mononuclear phagocytic cells filled with blood pigment and fatty granules is still present. The polymorphonuclear leucocytes are still very much in evidence, now appearing nearer the center although still chiefly confined to the periphery of the lesion. The perivascular cells have by this time been replaced largely by lymphocytes. Surrounding the central area of the lesion for a considerable distance one sees a proliferation of glial cells and fibrils. The older the lesion grows, the more it shrinks in size, the necrotic tissue and scavenger cells gradually disappear, the glial cells become fewer in number, and the fibres increase until a residual scar remains.

In marked contrast to the changes in the brains of the sensitized animals is the paucity of abnormal findings in the brains of the controls (Fig. 3). With very few exceptions the control brains examined as early as ½ hour or as late as 2 weeks after the cerebral injections failed to give any indication of the location of the injection. In two of the brains from control animals in Group II examined 24 hours after injection, a little free blood was found along what was obviously the needle tract. This hemorrhage was very small, was immediately surrounded by normal, non-edematous brain tissue and showed no leucocytic infiltration.

Neurological Observations

The animals dying after cerebral injection die of symptoms referable to the brain. Sometimes convulsive seizures occur immediately after the injection. More usually the animals appear normal for ½ to 1½ hours and then begin to breath rapidly, hunch up, sometimes twitch locally or go into a generalized seizure. They may hold the head and eyes rotated to the side contralateral to the injection, or undergo actual rotary movements of the whole body toward the contralateral side. Often there is a paralysis of the contralateral half of the body, the animals lying in an enforced position on the contralateral side which they resume immediately when turned on the other side. Any given animal may show only a few of these symptoms and to a very mild extent, but in the severe cases they are progressive and usually end in death within 24 hours.

SUMMARY AND CONCLUSIONS

1. Sixteen out of seventeen rabbits actively sensitized to various antigens by repeated cerebral and intravenous injections showed upon intracerebral reinjection of the same antigen local anaphylactic inflammation of the brain at the site of inoculation.

2. Six out of twenty rabbits actively sensitized to either horse serum or egg albumen by extracerebral injections, showed, upon introduction of the homologous antigen into the cerebrum, local anaphylactic inflammation at the site of inoculation.

3. The pathological picture of the Arthus phenomenon in the brain of the rabbit resembled that seen in the skin, after allowing for differences in the fundamental structure of the tissues involved.

4. None of the control animals exhibited lesions comparable to those found in the experimental animals. A few controls showed slight hemorrhages due to mechanical injury of blood vessels.

5. Clinical symptoms of varying degrees of severity, often leading to the death of the rabbit were observed in the sensitized animals. These symptoms were referable to the site of injection.

REFERENCES

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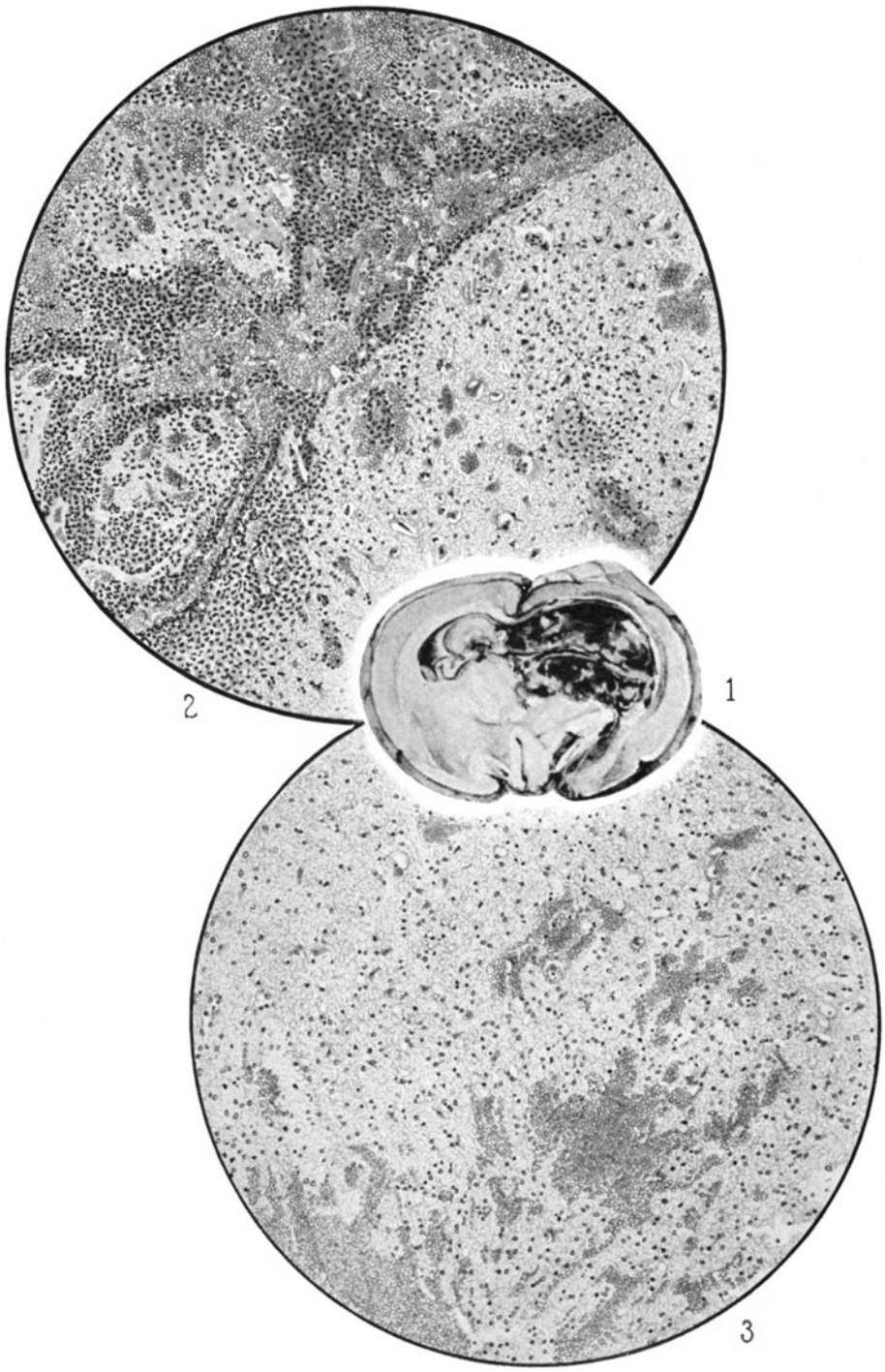
2. Seegal, D., Seegal, B. C., and Jost, E. L., *J. Exp. Med.*, 1932, **55**, 155.
3. Burn, C. G., and Finley, K. H., *Proc. Soc. Exp. Biol. and Med.*, 1931, **28**, 795.

EXPLANATION OF PLATE 12

FIG. 1. A cross-section of the brain of a sensitized rabbit 24 hours after the intracerebral injection of the specific antigen, horse serum. Note the extensive hemorrhage and edema pushing the structures of the midline over to the opposite side. Drawing ×2 natural size.

FIG. 2. An area from the brain of a sensitized rabbit 24 hours after the intracerebral injection of the specific antigen, horse serum. Note the marked hemorrhage, extravasation of leucocytes, and edema of the cerebral tissue. Hematoxylin-eosin stain. Magnification ×300.

FIG. 3. An area from the brain of a control rabbit 24 hours after the injection of horse serum. Note the slight hemorrhage incident to mechanical trauma to a small blood vessel. Extravasation of leucocytes and edema are absent. Hematoxylin-eosin stain. Magnification ×300.



(Davidoff *et al.*: Arthus phenomenon)