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The Inflammatory Response to Anaphylaxis and Intravenous Antibody or Antigen

M.L. Goodman, B.A. Way, and J.W. Irwin

Microcirculatory Laboratory and Mosher Laboratory of Pathology, Massachusetts Eye and Ear Infirmary, Boston, Massachusetts 02114, USA

Summary. The inflammatory process, as initiated by active or passive anaphylaxis or by the intravenous injection of antibody or antigen alone, was studied in the rabbit. Emphasis was placed on timing the events in inflammation. The inflammatory response was studied at three levels of experimentation: microscopic observation of the microvasculature and supporting tissue in the ear chamber, monitoring of the intravascular cellular elements during the reaction, and gross and microscopical study of ear chamber and visceral tissues secured just before death or sacrifice of the rabbit.

The first cell affected appeared to be the leukocyte. This was supported by observations in the ear chamber, white blood cells adhering to endothelial-lining cells of the microvessels, and a drop in the leukocyte count. Then the platelet count dropped quickly, and within 10 min emboli and thrombi were observed in the microvessels of the ear chamber. Later events in the inflammatory sequence included the swelling of endothelial cells, migration of leukocytes, and appearance of microhemorrhages in the ear chamber. Pathology was more marked in passive and active anaphylaxis than when either antibody or antigen alone was injected intravenously.

Histological examination of tissue from various visceral organs and the ear chamber secured just before the death or sacrifice of the rabbit, showed inflammatory changes consistent with those noted in the ear chamber during all phases of the response.

Key words: Inflammation – Anaphylaxis.

Introduction

When a living mammal, having antibodies to a specific antigen, is challenged with that antigen, anaphylaxis results. Accumulated data suggest that the union

Address offprint requests to: Dr. Max L. Goodman, Mosher Laboratory of Pathology, Massachusetts Eye and Ear Infirmary, 243 Charles Street, Boston, Massachusetts 02114, USA

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of antigen and antibody during anaphylaxis injures living tissue, resulting in inflammation. In this laboratory, inflammation is regarded as a reparative process, but not all investigators agree. Since the complex process of inflammation involves many reactions, it is unlikely that all responses occur simultaneously. The purpose of this paper is to report on several events which were monitored in rabbits at specific time intervals during active and passive anaphylaxis and following a single intravenous injection of antigen or antibody.

Methods and Materials

The experimental animal was the half-lop rabbit, whose large pinnae with intact cartilage are suitable for the insertion of chambers, into which a complete microvasculature grows. The ear chamber used was originally described by Sanders et al. (1954). The minor alterations made on this chamber and the methods used for its insertion into rabbit pinnae have been described in detail by Nims and Irwin (1973). Ear chambers were inserted under sterile conditions into the pinnae of 25 anesthetized rabbits two to four months prior to experimentation to insure complete microvascular growth and innervation.

Seven of these rabbits underwent active anaphylaxis. Into each of five toe pads of these seven rabbits, 0.5 ml of a mixture of bovine serum albumin (BSA) and Freund's adjuvant was injected. Two months later, the amount of circulating BSA antibody was determined for each rabbit. Serum, obtained from the blood of each rabbit, was run through gel diffusion columns. The final determination of antibody was made with precipitin and Biuret tests and a Beckman spectrophotometer. Irwin, Nims, and McGraw (1970) described in detail the methods used to sensitize rabbits to bovine serum albumin and to determine the antibody content of each rabbit. The seven rabbits which were actively sensitized had 4–12 mg of nitrogen antibody to BSA per 100 ml of serum. Following the determination of the level of circulating antibody, each of these seven rabbits was secured in a comfortable restraining holder. Into the central artery of the pinna without a chamber, a 23-gauge needle, part of a Butterfly-23 Infusion Set by Abbott, was inserted. The needle and tubing were filled with a heparin solution (1,000 units USP/ml). The ear chamber in the other pinna was inserted into a special stage of a light microscope. Prior to active anaphylaxis, arterial blood was secured for erythrocyte, leukocyte, and platelet counts, and the rectal temperature was taken. The microvasculature and circulation of the ear chamber were studied microscopically (objectives 10–90 ×, eyepieces 8 ×), and these observations were recorded on 16 mm motion picture film taken at 16 frames per second. Each rabbit then received an intravenous injection of BSA antigen, 4–20 mg/kg of body weight. The described observations were repeated after the challenging dose of BSA at 10 min and one, three, six, 24, 48, and 96 h, or until death seemed imminent. Prior to demise of the animal or conclusion of the experiment, the rabbit was anesthetized, and an incision was made along the ventral body midline. The liver, spleen, kidney, lung, and heart were observed grossly; then tissue samples were secured from these organs and the ear chamber for histological study. All tissue samples were fixed in 10% formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin.

Ten of the rabbits were used for the experiments in passive anaphylaxis. Each rabbit received intravenously 5–20 mg of nitrogen antibody to BSA/kg. One to 26 h later, each rabbit was secured in the animal holder, and the observations and tests described under active anaphylaxis were made. The animal was then injected intravenously with 10–35 mg/kg of BSA. The tests and observations were repeated at time intervals of 3 min, 10 min, and one, three, six, 24, 48, and 96 h, and tissue samples were secured prior to the demise of each animal.

Three of the rabbits were injected intravenously with only antibody to BSA (25 mg or 100 mg of nitrogen antibody to BSA/kg). The experimental procedure was identical to that described for active anaphylaxis.

Five rabbits received only BSA intravenously (20–50 mg/kg). Again, the experimental procedure was the same.

Results

Active Anaphylaxis

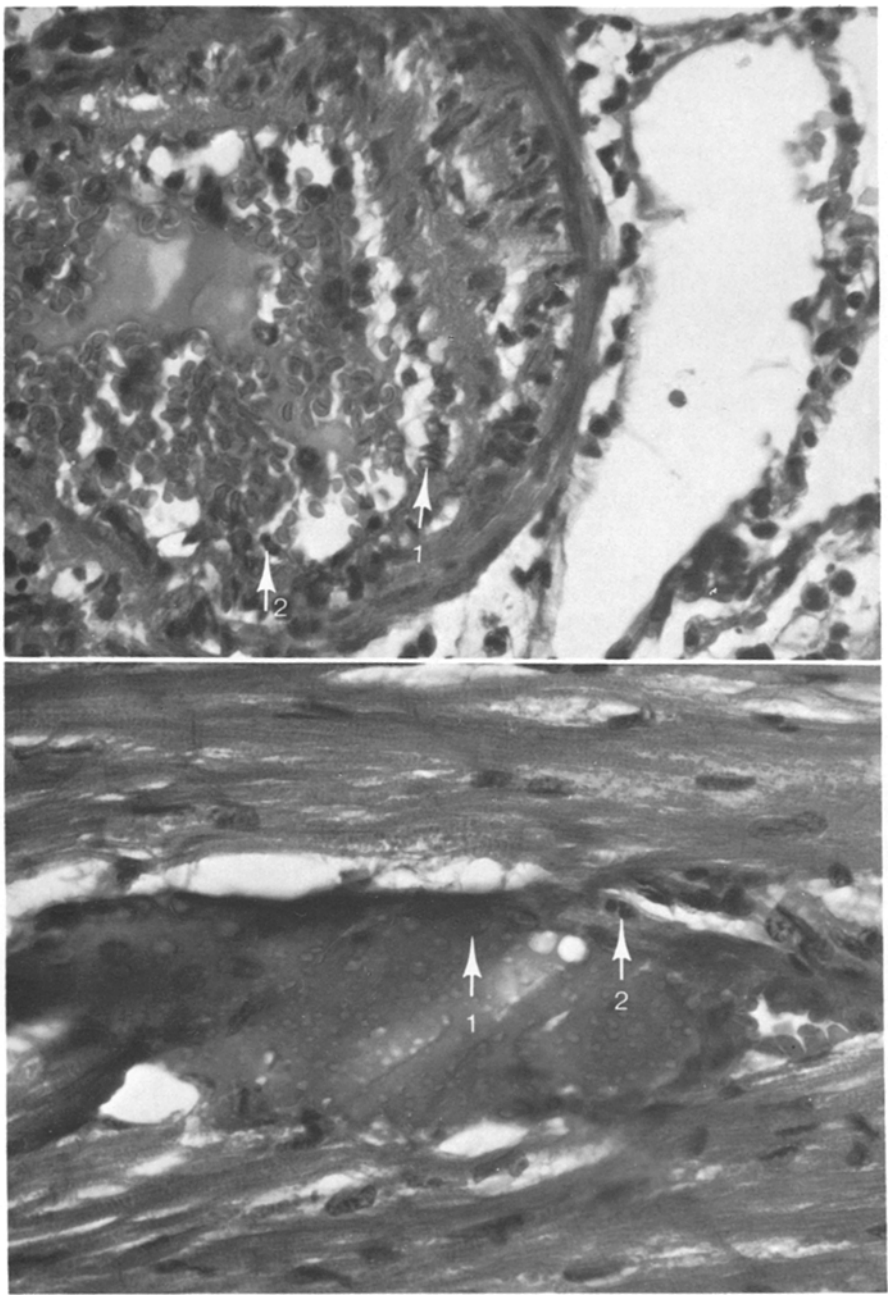
Of the seven rabbits used for active anaphylaxis, one died before one hour, two others died within 6 h, three other rabbits died within 48 h, and one animal was sacrificed at 72 h. Microscopic observations of the ear chamber tissue showed momentary sticking of white blood cells to the endothelial lining cells of venules within 1 min, even before the specific antigen was completely injected. At 10 min, white blood cells were seen sticking permanently to the endothelium of venules and capillaries, and small emboli were noted in all segments of the microvasculature. Although an occasional thrombus was noted in the venules at 10 min, thrombi were not numerous in all microvessels until 1 h following injection. Swelling of endothelial cells of the microvessels was apparent at one hour. Edema of connective tissue, microhemorrhages, and migration of leukocytes began at 1 h. Within 3 h the microvasculature of the ear chamber was non-functional and did not recover within 72 h.

Table 1 lists the mean leukocyte and platelet counts and the mean rectal temperatures of the actively sensitized rabbits before and after receiving the shocking dose of antigen. No change in the erythrocyte counts was noted during active anaphylaxis in any of these seven experimental animals. A marked drop in the leukocyte count occurred within 10 min and persisted for 6 h, despite the presence of a known reservoir of white blood cells. A leukocytosis was evident at 24 h, this elevation persisted for at least 72 h. The platelet count also fell within 10 min after the injection of BSA and continued for 72 h. The temperature of these seven rabbits dropped within 10 min of the antigen challenge and returned to normal levels within 3 h. These changes occurred in each rabbit without exception.

Histology of the major visceral organs of the seven rabbits in active anaphylaxis showed congestion of the microvasculature of all organs, swelling of the endothelial lining cells of the microvessels of these organs, and margination of leukocytes. The hepatic sinusoids and the splenic sinuses contained many neutrophils. Renal glomeruli were congested, and an occasional thrombus was noted. Emboli and thrombi were scarce in all sections of tissue from the internal organs of these animals.

Passive Anaphylaxis

Ten rabbits underwent passive anaphylaxis. Microscopic observation of the ear chamber revealed sticking of leukocytes to the endothelial walls of the microvessels even before completion of the injection of antigen. Multiple emboli and thrombi were noted within 10 min. Within 1 h, multiple microhemorrhages and edema were observed in the ear chamber tissue, and the microvessels appeared non-functional. Because of the short interval between the shocking dose of antigen and death in six animals and severity of symptoms in the other



Active anaphylaxis

Fig. 1. Lung of rabbit. Swollen endothelial cells (*arrow 1*). Margination of polymorphonuclear leukocyte (*arrow 2*). (×640)

Fig. 2. Rabbit myocardium. Swollen endothelial cells (*arrow 1*). Migration of polymorphonuclear leukocyte (*arrow 2*). (×640)

Table 1. Active anaphylaxis. White blood cell count, platelet count, and temperature before and during the response

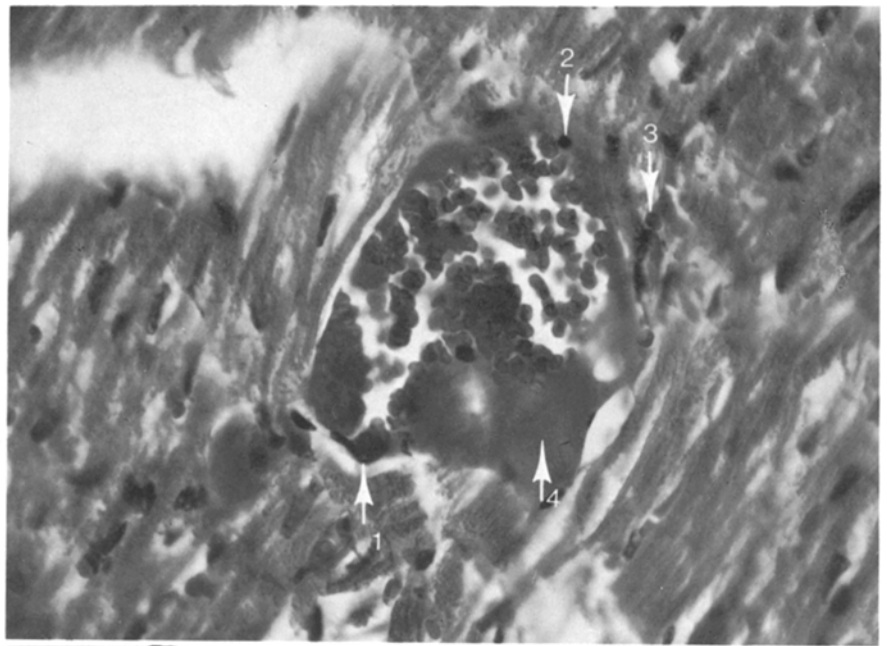
	Number of rabbits	Mean of WBC/mm^3	Mean of PLT/mm^3	Mean of rectal temperature (°C)
Normal	7	7,564	495,143	39.5
Shocking dose of BSA antigen				
10 min	7	1,904	136,000	38.6
1 h	6	4,862	264,333	38.5
3 h	6	5,787	282,500	39.5
6 h	4	4,562	194,500	40.0
24 h	4	12,006	135,000	39.4
48 h	1	18,050	191,000	38.8
72 h	1	35,300	156,000	38.3

Table 2. Passive anaphylaxis. White blood cell count, platelet count, and temperature before and during the response

	Number of rabbits	Mean of WBC/mm^3	Mean of PLT/mm^3	Mean of rectal temperature (°C)
Normal	10	10,382	529,800	39.3
Shocking dose of BSA antigen				
3 min	10	6,668	326,714	38.0
10 min	4	5,281	75,000	38.2
1 h	3	2,650	164,000	37.1
3 h	1	6,000	68,000	38.1
6 h	1	10,650	57,000	39.3
24 h	1	24,900	480,000	39.0
48 h	1	24,300	400,000	38.9
96 h	1	11,050	486,000	39.1

three rabbits, the microscopic observations of the ear chamber vessels during passive anaphylaxis were not optimal.

Table 2 shows the mean of the white blood cell counts, platelet counts, and rectal temperatures of these 10 rabbits before and at stated times during passive anaphylaxis. Within 3 min after the injection of antigen, a drop was evident in the white blood cells, platelets, and temperature. Six rabbits died within the first 10 min of passive anaphylaxis. The leukocyte counts, platelet counts, and temperature remained depressed in the four animals that survived for 10 min. The drop in the above counts and temperature persisted in the three rabbits that survived for one hour and in the one animal surviving for three hours. The leukocyte count and temperature rose by 6 h in the one surviving rabbit; the platelets in this animal remained low until 24 h. This rabbit was sacrificed at 96 h, when all microvessels and the data listed on Table 2 appeared normal.



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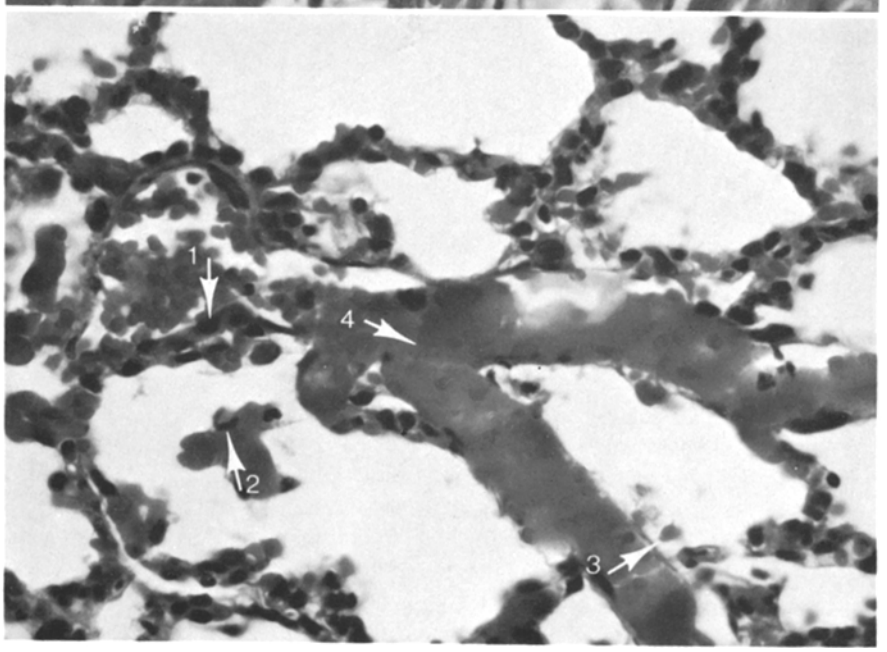

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Passive anaphylaxis

Fig. 3. Rabbit myocardium. Swollen endothelial cell (*arrow 1*). Margination of leukocyte (*arrow 2*). Extravasation of erythrocytes (*arrow 3*). Fibrin thrombus (*arrow 4*). (×640)

Fig. 4. Lung of rabbit. Swollen endothelial cell (*arrow 1*). Margination of polymorphonuclear leukocytes (*arrow 2*). Extravasation of erythrocytes (*arrow 3*). Fibrin thrombus (*arrow 4*). (×640)

Histological examination of tissue samples from rabbits which underwent passive anaphylaxis showed marked microvascular changes. Numerous fibrin thrombi were present in the microvasculature of the heart, lungs, liver, spleen, and kidney. The endothelial cells were swollen, and focal margination, migration, and extravasation of leukocytes and erythrocytes were seen. Numerous binucleated hepatocytes were present in the area of the liver's central veins. The fibrin thrombi of the liver and spleen were confined to the sinusoids and sinus spaces. Occasionally, fibrin deposits were found in the arterioles and glomeruli of the renal vasculature.

Intravenous Antibody

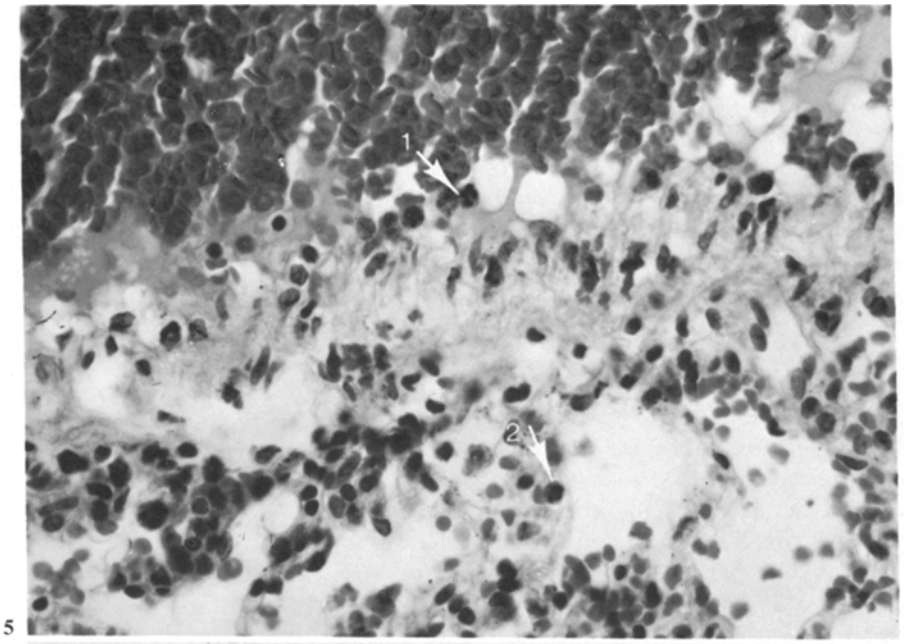
An increased rate of flow was noted within three minutes in the microvessels of the ear chambers of these three rabbits. At the same time, emboli were observed on both the arteriolar and venular sides of the circulation, and occasional sticking of white blood cells to the venular endothelium was noted. Within one hour, migration of leukocytes into surrounding connective tissue was seen, and edema was evident. Occasionally, a microvessel was thrombosed at six hours. Within 24 h, the microvasculature of the chamber vessels was normal, except for the vessels which had thrombosed.

Table 3 lists the mean leukocyte and platelet counts and the mean of the temperature readings before and at stated intervals after the injection of intravenous antibody into normal rabbits. One rabbit was sacrificed at 3 h; another was sacrificed at 24 h; and the third rabbit was sacrificed at 96 h. A significant drop in the white blood cells, platelets, and temperature occurred within 10 min and persisted for 1 h. Within 3 h a leukocytosis was present, and the temperature had returned to a normal range. The platelet count remained depressed until 6 h following the injection of antibody.

Histological study of the microvasculature in sections of tissue obtained from the internal organs and ear chamber of rabbits which had received only

Table 3. Intravenous antibody. White blood cell count, platelet count, and temperature before and during the response

	Number of rabbits	Mean of WBC/mm^3	Mean of PLT/mm^3	Mean of rectal temperature (°C)
Normal	3	7,792	451,000	39.2
Antibody to BSA				
10 min	3	4,942	276,000	38.5
1 h	3	4,725	284,000	38.4
3 h	3	9,167	395,000	39.0
6 h	2	7,600	454,000	39.4
24 h	2	6,300	334,000	39.2
48 h	1	4,425	229,000	39.1
96 h	1	5,250	310,000	39.1



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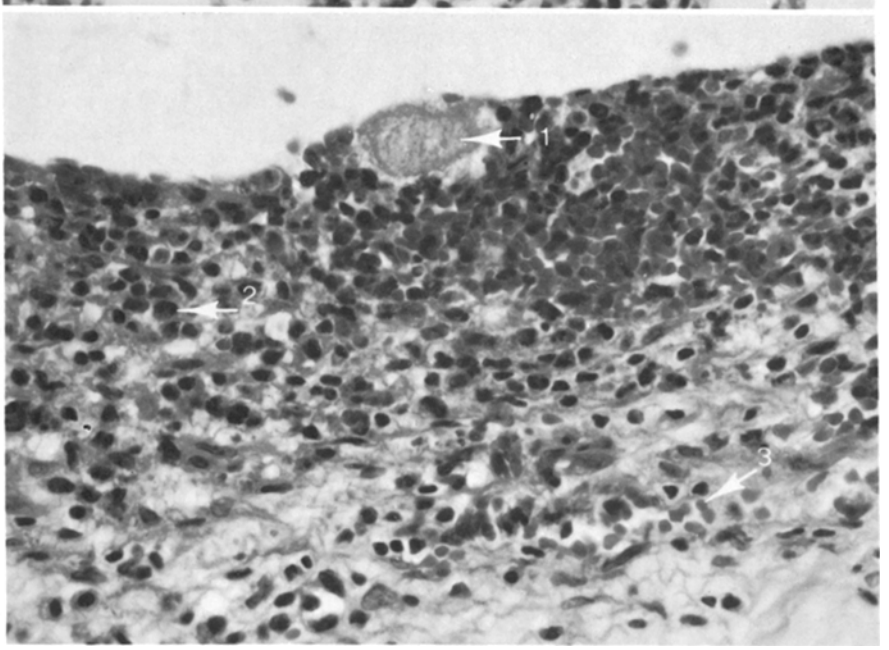

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Intravenous antibody

Fig. 5. Lung of rabbit. Margination of polymorphonuclear leukocytes (*arrow 1*). Migration of polymorphonuclear leukocyte (*arrow 2*). (×640)

Fig. 6. Ear chamber connective tissue. Luminal surface of microvessel with fibrin deposit (*arrow 1*). Migration of polymorphonuclear leukocytes (*arrow 2*). Extravasation of erythrocytes (*arrow 3*). (×640)

intravenous antibody to BSA showed swollen endothelial cells. In addition, the pulmonary and myocardial microvessels revealed focal margination and migration of leukocytes and non-occlusive fibrin deposits.

Intravenous Antigen

The effect of a single intravenous injection of antigen into five normal rabbits was studied. Momentary sticking of white blood cells to the endothelial-lining cells of capillaries and venules in the ear chamber was observed within 10 min after the injection. Edema of supporting connective tissue and swollen endothelial cells lining the venules and capillaries were evident within 6 h. Small hemorrhages and cessation of flow were seen in many vessels of the ear chamber by 24 h.

Table 4 shows the change in white blood cell and platelet counts and temperature at various time intervals after the injection of the antigen. Four rabbits were sacrificed at 24 h, and one animal was sacrificed at 96 h. The leukocyte count dropped within 10 min after the injection of BSA antigen and dropped even further at 1 h. A leukocytosis was evident at 3 h and persisted until 48 h. The platelets also dropped within 1 h, but they returned to normal levels within 3 h. The temperature dropped within 10 min after injection and returned to normal or elevated levels within 3 h. Normal temperatures were recorded within 24 h.

Histological preparations of tissue samples from these five rabbits again showed focal vascular changes similar to those in animals which had undergone active or passive anaphylaxis. The endothelial-lining cells of the microvasculature of all tissue sections from the internal organs were swollen, and focal margination and migration of neutrophils, as well as occasional non-occlusive fibrin deposits, were present. The hepatic alterations were minimal, but increased numbers of neutrophils were present in the sinuses, and the renal glomeruli were congested. Sections of tissue from the ear chamber showed margination and migration of neutrophils and extravasation of red blood cells.

Table 4. Intravenous antigen. White blood cell count, platelet count, and temperature before and during the response

	Number of rabbits	Mean of WBC/mm^3	Mean of PLT/mm^3	Mean of rectal temperature (°C)
Normal	5	8,390	300,200	39.3
BSA Antigen				
10 min	5	6,035	284,200	38.5
1 h	5	4,840	199,600	38.5
3 h	5	11,170	375,600	39.6
6 h	5	11,812	317,750	39.7
24 h	5	11,905	343,600	39.1
48 h	1	8,325	227,000	39.1
96 h	1	6,375	257,000	38.9

Discussion

The word anaphylaxis was coined early in the twentieth century by Portier and Richet (1902). They described the severe reaction of dogs, which had survived the initial dose of an extract made from the tentacles of *Actineria*, to a small second dose administered one week later. Theobald Smith noted that guinea pigs often died after a second injection of a mixture of diphtheria toxin and antitoxic serum. He did not publish but told Ehrlich of his observations. Otto (1906), a student of Ehrlich, described the anaphylactic reaction of animals injected with a second dose of normal horse serum. In the intervening years, extensive work has led to a better unterstanding of anaphylaxis. Rocha e Silva (1950) summarized this work under four general headings: physiological, chemical, immunological, and hematological.

Rössle (1914) was the first to describe the inflammatory process initiated by the antigen-antibody reaction. He also noted that an inflammatory response occurred after the injection of a foreign protein into non-sensitized animals. Using guinea pigs and rabbits, Rössle studied allergic reactions in tissue sections secured from the injection sites and also the anaphylactic reaction in the living mesenteric microcirculation and surrounding tissue. He inserted abdominal windows into rabbits and then observed peritonitis initiated by an antigen-antibody reaction. Rössle emphasized that an increased number of eosinophils was involved in the inflammatory process due to anaphylaxis.

Abell and Schenck (1938) studied the microvasculature in rabbit ear chambers during anaphylaxis and reported momentary arteriolar constriction, sticking of leukocytes to the vascular endothelium, leukocytic migration, and edema of connective tissue. Burrage and Irwin (1953a, b) noted similar changes in the pulmonary and hepatic microcirculation during anaphylaxis.

Biedl and Kraus (1909) were the first to report a leukopenia during experimental anaphylaxis. Dean and Webb (1924) confirmed these observations, reporting that an initial drop in the leukocyte count occurred within one minute and was followed by a leukocytosis in three hours. Kinsell et al. (1941) reported an initial drop in the platelet counts of monkeys undergoing anaphylaxis, and Rocha e Silva (1950) showed that intravenous peptones decreased the leukocyte and platelet counts in unsensitized mammals.

Pfeiffer (1909) reported a drop in temperature in animals undergoing anaphylaxis, but he did not repeat these readings at multiple time intervals. The experiments reported here vary from previous experiments because in each rabbit observations on the microvasculature and changes in the blood cellular elements and temperature were made and recorded simultaneously at specific time intervals throughout each experiment. Tissue from the liver, spleen, kidney, lung, heart, and ear chamber were secured for histological study prior to demise or sacrifice. These studies clearly indicate that anaphylaxis injures living tissue and evokes the inflammatory response. Damaged tissue does recover if the injury is not too severe. Furthermore, the intravenous injection of a single foreign protein, either antigen or antibody, also elicits the inflammatory process.

In any series of experiments, the laboratory materials used must be checked for possible contamination. The bovine serum albumin and antibody to BSA

used in the reported experiments tested positively for pyrogenic contamination by the Limulus Amebocyte Lysate test. (The BSA used tested positively for pyrogens in dilutions of 1 to 10^{-3} mg BSA/ml, and the antibody tested positively in dilutions of 1 to 10^{-4} mg/ml.) The proteins used, therefore, contained some pyrogenic material which may have contributed to the reported inflammatory responses.

It is unlikely that any commercially prepared BSA or antibody to BSA would be free of pyrogens. In fact, BSA and antibody to BSA obtained from one commercial source tested positively to Limulus. To separate these proteins in the laboratory would require large quantities of serum, and to keep the proteins free of pyrogenic contamination, while separating them in a column of Sephadex, would be a major task. Chicken egg white was selected for study of a pyrogen-free antigen, since this protein contains no detectable pyrogens. The egg white used for the experiments was secured from a whole egg under sterile conditions and consistently gave a negative response to the Limulus test. Each rabbit in a group of five animals was injected intravenously with a dilution of pyrogen-free egg white; two to six weeks later, when sufficient time had elapsed for the formation of antibodies, a second intravenous injection of egg white resulted in active anaphylaxis. To date, experiments with this antigen indicate that a typical inflammatory response does occur. Results of the experiments using pyrogen-free egg white, therefore, indicate that pyrogenic contamination of the antigen and antibody used in the described experiments did not contribute significantly to the inflammatory responses reported here.

The first changes noted in all experiments were the sticking of leukocytes to the endothelial walls and a drop in the leukocyte and platelet counts. Spors (1969), using electronmicroscopic techniques to study the lung during anaphylaxis, showed that neutrophils phagocytize antigen-antibody complexes. The sticking of leukocytes to the endothelium and the drop in the leukocyte count suggest that many leukocytes were disrupted in their attempt to rid the tissue of antigen-antibody complexes. Perhaps the platelets also play a defensive role.

Later in time during anaphylaxis, swelling of the endothelial-lining cells of the microvasculature was seen. Histamine and other substances such as a Slow Reacting Substance, described by Kellaway and Trethewie (1940), may be released from leukocytes; such substances could then damage the endothelium. Brocklehurst (1960) reported that Slow Reacting Substance and histamine, released during anaphylaxis, were found primarily in pulmonary and vascular tissue. Our histological data showed damage to the endothelial cells of the microvessels in all tissue samples of the organs studied.

After damage to endothelial cells occurred, emboli and thrombi became prominent. Histological study of tissue samples from rabbits in active or passive anaphylaxis revealed strands of fibrin in the microvessels. These emboli may contain antigen-antibody complexes, which may initiate the complement system. Friedemann (1909) believed that "anaphylatoxin" was produced by the action of the antigen-antibody union. Spear and Kihara (1970) shocked guinea pigs by injecting Forssman antiserum intravenously; they found that the animals, when depleted of complement, were more resistant to this form of shock.

Edema and the escape of intravascular cells into the surrounding tissue was seen as a later event during inflammation. The microcirculation, as observed in the ear chamber, ceased shortly thereafter.

Anaphylaxis and the intravenous injection of foreign proteins resulted in an inflammatory response similar to that resulting from physical or other forms of injury. The leukocytes and platelets play an early and prominent role in inflammation.

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