PERIVASCULAR REACTIONS IN LUNG AND LIVER FOLLOWING INTRAVENOUS INJECTION OF STREPTOCOCCI INTO PREVIOUSLY SENSITIZED ANIMALS

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Plates 19 and 20

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Certain reactions of rabbits to intradermal injection of living non-hemolytic streptococci have been studied in detail by Swift and his coworkers (1, 2), who demonstrated that such injections properly spaced induce a condition in all respects comparable to the sensitization of infection (tuberculin allergy).

Among the detectors of this condition is the lethal test, which consists of intravenous injections of living cultures in doses comparatively innocuous for normal animals, but which cause the death of about 50 per cent of sensitized rabbits in from 24 to 48 hours. Macroscopic postmortem findings in animals so dying include swelling and edema of lymph nodes and thymus, with gross hemorrhages into these organs, and also into the tricuspid ring, subperitoneal tissues, and elsewhere (1). Because lethal inocula regularly induce severe tissue damage, it has seemed of interest to determine what lesions, if any, might follow the administration of non-lethal doses.

EXPERIMENTAL

Method of Sensitization.—Sensitization of animals has been induced by repeated intradermal inoculation with appropriate doses of living 24 hour broth cultures of known sensitizing strains of non-hemolytic streptococci. In a few instances hemolytic streptococci, either living or as heat-killed vaccines, have been employed in addition. More frequently, however, indifferent Streptococcus Q 155 has been used, inasmuch as its sensitizing and shocking capacities have been thoroughly

tested (3). Sensitizing injections of non-hemolytic streptococci have been given over periods ranging from 3 to 10 weeks, with a total dosage of blood broth culture varying between 0.15 and 2.11 cc. (4). Living hemolytic streptococci have been used in such minute quantities that a total of 0.00022 cc. of living culture has not been exceeded; but as much as 4.44 cc. of vaccine made with this organism has been administered to one group. Vaccines of hemolytic streptococci have been prepared by heating at 56°C. for 1 hour the washed sediment from 24 hour infusion broth cultures, then resuspending the sediment in a volume of physiological salt solution equal to that of the original culture. Following the preliminary intradermal injections, the intravenous inoculum has consisted of doses varying from 1 to 5 cc., never exceeding a total of 6 cc. altogether, and this total has been divided variously into one, two, or three doses, given a day or two apart. As the 5 cc. quantity forms a large fraction of the shocking dose (1), it has been infrequently employed; more often divided doses of 1 or 2 cc. have been given. Indifferent Streptococcus Q 155 has uniformly been employed for the intravenous treatment.

Controls.—Several sets of controls were studied. One series of animals was sensitized by intracutaneous inoculation, then sacrificed without receiving any intravenous treatment. A second set was treated intravenously from the beginning, with the same amounts of culture as were given to a group simultaneously undergoing intracutaneous sensitization. Failure of hypersensitiveness to develop in this group confirms the observation of Schultz and Swift (5). Other animals received only an intravenous dosage similar to that administered to sensitive animals at the termination of an experiment. Finally, a small group was kept under laboratory conditions, without receiving any treatment whatever with bacteria.

The development and extent of sensitization was judged by means of the ophthalmic reaction (2). In addition, graded doses of bacteria were administered intradermally, and the size and course of the resulting lesions were observed daily for 72 hours (1). In the case of unsensitized controls, however, the intradermal inoculations were omitted, inasmuch as no increment of allergy, however slight, was considered desirable.

Preparation of Tissues.—Except for a small number which perished within 24 hours of the intravenous treatment, all animals were sacrificed on the day following the final injection unless otherwise noted. Some were chloroformed; others killed by a sharp suboccipital blow. Autopsies were performed at once, and small pieces of various organs—thymus, heart, lung, liver, spleen, adrenal, kidney, lymph node, and bone marrow—were fixed in Zenker-acetic acid mixture. Paraffin sections were prepared and stained with methylene blue and eosin, and with Weigert-Van Gieson for elastica and connective tissue. Sections were studied by

one of us (A. R. C.) who had no knowledge of the treatment previously administered to any animal.

The Characteristic Lesions.—The most characteristic microscopic changes in positively reacting animals were found in the lung, liver, spleen, lymph nodes, and bone marrow. Scattered throughout the sections of the lungs were numerous, more or less uniform perivenous lesions consisting of definite collars six to ten cells in thickness (Figs. 1 and 4). The vessel wall at the site of the lesions was moderately edematous, and in some instances showed separation of the elastic fibers; in nearly all there were proliferation and swelling of the endothelial lining. The predominant cell in the perivascular lesion was large and irregularly shaped, about two and a half times the diameter of a mature lymphocyte (see Fig. 5). The cytoplasm was either homogeneous and deeply basophilic, or finely vacuolated and more faintly basophilic, with gradations between these two varieties. The rather large nucleus was pleomorphic—round, indented, horseshoe-shaped, club-shaped, or elongated. The nucleus was vacuolated, and contained dense chromatin packed at or near the center, apparently forming one to three nucleoli; masses of chromatin were also condensed at the periphery. Occasionally, delicate threads could be seen bridging the vacuolated gap between the central and peripheral masses of chromatin. Engulfed in the cytoplasm of the more faintly basophilic cells, which were considered as more mature forms of the cell under consideration, pyknotic nuclei of polymorphonuclear leukocytes were occasionally observed.

In addition to these basophilic cells, the perivascular lesions contained mature lymphocytes, a few eosinophiles, and other granulocytes. It is interesting to note that there was no evidence of local tissue destruction in the lesions and neither fibrin deposition nor attempt at reparative processes.

In the liver there were similar perivascular aggregates of large basophilic cells, lymphocytes, and granulocytes, particularly around the small branches of the hepatic artery at the periphery of the lobules (Figs. 2 and 3). The larger and more fully developed lesions also encircled the adjacent branch of the portal vein and the bile duct. In addition, the large basophilic cells were also found free in the liver sinusoids, where they could easily be differentiated from the

ordinary Kupffer cells normally occurring in this position. Among both controls and sensitized animals, were found a few cases of so called spontaneous cirrhosis of the liver, consisting of typical periportal fibrosis, lymphocytic infiltration, and regeneration of liver lobules. In view of the absence of fibrous tissue and other evidences of repair from the latter, and because of the distinct differences in cellular architecture, no difficulty was encountered in differentiating the spontaneously occurring lesion from that experimentally produced.

The large cell with basophilic cytoplasm predominating in the perivascular lesions is found normally in lymph nodes, spleen and other lymphoid tissue. In the hypersensitive animals marked hyperplasia and congestion were noted in lymphoid structures, and large basophilic cells were found in abundance in the sinuses of this hyperplastic lymphoid tissue and also in the pulp of the spleen. In the few specimens of bone marrow secured from such animals they were also present in increased numbers. In lymphoid tissue, where these cells were not gathered into definite aggregates, their cytologic features were more constant; the cytoplasm was more uniformly basophilic and the nucleus tended to be more constantly round.

The Experimental Animals.—For convenience, the experimental animals, exclusive of controls, were divided into four groups.

Group I consisted of six animals, each of which received on one day only intradermal inoculations of sedimented growth from 5 cc. of 24 hour blood broth culture of *Streptococcus viridans* V 92. 2 weeks later, when ophthalmic tests were performed, only two of the six showed marked sensitization. After the lapse of a further week, intravenous treatment with the homologous organism was begun; each animal received twice daily 1 cc. of culture per 2.5 kilos body weight. Three subgroups of two animals each were formed; one received 1 day of intravenous treatment, one 2 days, and one 3 days. One of the animals having ophthalmic hypersensitivity died following the 1st day's treatment, and the other after 2 days'. The survivors were chloroformed. Unfortunately the material available from these animals was limited, as these experiments were made before this study was planned; no lung tissue is at hand, and hepatic tissue from one only. Cardiac, renal, and adrenal tissues were uniformly free from the lesion described above; in three of the six, however, the characteristic cells were present in increased number in thymus, spleen, and bone marrow. Two of these three animals showed no ophthalmic hypersensitivity, yet the liver from one of these two revealed the perivascular aggregates in moderate degree. Tissues from one of the sensitive

rabbits showed no striking alteration. Of the three reacting animals, two had been treated intravenously for 3 days, one for 2 days. In this group, therefore, the tissue reactions were apparently more closely dependent upon the prolongation of the intravenous treatment than upon the preliminary sensitization. It appears, however, from a consideration of Groups III and IV that the omission of lung and liver from the tissues is probably responsible for this apparent relationship.

Group II consisted of six animals treated intradermally over a period of 8 weeks with small doses of indifferent Streptococcus Q 155. The final injection was made intra-articularly (as part of another study). The total dosage of culture was 1.11 cc., distributed among eighteen inoculations. Ophthalmic sensitivity developed uniformly. 2 weeks after the intra-articular inoculation, each animal was given intravenously 1 cc. of 24 hour culture of Streptococcus Q 155. 2 days later three of the animals received a further intravenous injection of 5 cc. of similar culture. One animal from each subgroup died within 24 hours; two others were chloroformed after 24 hours, and two after 48 hours. Perivascular aggregates were uniformly present in the liver and lungs of all the animals except those dying spontaneously; and characteristic young cells were found in increased number in spleen and lymph nodes. Of the two rabbits which succumbed spontaneously, one showed marked aggregates about the vessels of the lung alone, without noteworthy increase of young cells in spleen or node; the other was quite free from perivascular reaction, and presented no unusual cellular picture in the lymphatic apparatus.

Serving in a measure as weakly sensitized controls upon this group, particularly with reference to the possible effect of intra-articular inoculation, were two rabbits, each of which was given on one day four intradermal injections of Streptococcus Q 155 aggregating 2.11 cc., and an intra-articular injection of 10^{-4} cc. in one case and 10^{-6} cc. in the other. Ophthalmic sensitivity failed to develop in one, and was very slight in the other. Following a 4 weeks' interval after the initial treatment, each animal received two doses of 2 cc. each of culture 24 hours apart. One animal was sacrificed after a further 24 hours, one after 48. No perivascular reactions were found, although in each case there was a slight increase in the number of basophilic cells in the spleen.

Group III consisted of five rabbits treated with hemolytic streptococci, Strain S 43 matt, avirulent for mice. Two animals were given intradermal inoculation of a total of 4.44 cc. of heat-killed vaccine over a period of 4 weeks. 2 weeks later a living culture of a hemolytic streptococcus strain, Q 33, was administered in dosage of 10^{-5} and 10^{-6} cc. intradermally; after 3 days living culture of Strain S 43 was similarly given. For eye tests, living hemolytic streptococci were inoculated with homologous immune rabbit serum. Such serum-treated organisms were found innocuous for normal rabbits' corneae, and were more satisfactory than vaccine for elicitation of the ophthalmic reaction. One animal showed marked sensitivity when such organisms were inoculated upon the scarified cornea; the other gave no reaction. 8 days following the last treatment with hemolytic

streptococci, each animal was tested with and found sensitive to indifferent Streptococcus Q 155; eye tests with this organism gave results comparable with those elicited with serum-treated hemolytic streptococci. 2 weeks after testing with Streptococcus Q 155, each animal received 1 cc. of culture of this organism intravenously, and after 48 hours was chloroformed. Marked perivascular reactions were present in liver and lung, and the spleens were found to be rich in basophilic cells. Two other rabbits of Group III received, from the beginning, living hemolytic streptococci (S 43) intradermally in doses of 10^{-5} and 10^{-6} cc.; a total of 0.000028 cc. of culture was administered over a period of 6 weeks. At the end of this period tests were carried out as above. Ophthalmic sensitivity to both Strains S 43 and Q 155, was intense; and cutaneous hypersensitivity to the latter was present. 2 weeks after testing with Streptococcus Q 155, 1 cc. of culture of this organism was administered intravenously, followed in 3 days by 5 cc. of similar culture. Both animals succumbed within 48 hours. No perivascular reactions were found in liver or lung, nor were the basophilic cells in the spleen increased in number. The final animal of this group received living hemolytic streptococci, one dose each of 10^{-5} and 10^{-6} cc. of culture intradermally, on two occasions 3 days apart. Strain Q 33 was employed for the first treatment, and S 43 for the second. 10 days after the second inoculation skin sensitivity to Strain Q 155 was already present. Eye tests were not done. 2 weeks later 1 cc. of culture of Strain Q 155 was given intravenously, followed in 3 days by 5 cc. 5 days after the second dose the animal was chloroformed. Perivascular reactions were present in both lung and liver, and there was a moderate increase in the number of basophilic cells in the spleen.

Group IV contained four rabbits sensitized by the intradermal route with green Streptococcus V 110 A and indifferent Streptococcus Q 155. During a period of 2 months each animal received a total of 0.22 cc. of culture of the former, and from 0.56 to 0.9 cc. of the latter. All developed ophthalmic reactivity to Strain Q 155. At the end of the period of sensitization, each animal received intravenously 1 cc. of culture of Strain Q 155, followed 24 hours later by a second dose of the same size. 24 hours thereafter the rabbits were killed by suboccipital blows. In each case perivascular reactions were found in liver and lung, with distinctly increased numbers of basophilic cells in spleen and lymph nodes.

The Control Animals.—Control Group A contained fifteen rabbits which received a total of 0.15 cc. of Strain Q 155 intradermally over a period of 6 weeks. No intravenous treatment was administered at any time. Seven developed satisfactory ophthalmic sensitivity. At the end of the period of sensitization the animals were killed by suboccipital blows. No perivascular reactions were found in the liver. In four animals slight perivascular aggregates were noted in the lung; these aggregates, however, were only two to three cells thick, contained fewer of the characteristic cells, and were found about only a few of the vessels in the section. In three, slight to moderate increases in the number of basophilic cells were noted in spleen, and in lymph node in four. Three of these four had shown satisfactory ophthalmic tests.

Control Group B consisted of seven rabbits treated intravenously with Strain Q 155, at the same time and in the same dosage as administered to the animals in Group A. No eye sensitivity developed. They were sacrificed at the same time and in the same manner as the animals of Group A. In one case slight perivascular aggregates were found in the lung; none was present in the liver. In two instances there were slight or moderate increases in the immature cells of spleen and lymph node.

Control Group C was composed of eight animals kept under laboratory conditions with Groups A and B, but uninoculated. They were similarly sacrificed, and at the same time. There was no ophthalmic sensitivity. In one animal there were slight perivascular pulmonary changes; in a second the spleen was rich in basophilic cells, while in a third these were present in considerable numbers in a lymph node.

Control Group D contained four rabbits sensitized over a period of 11 weeks with total doses of Strains Q 155 varying from 0.22 to 0.9 cc. All developed satisfactory ophthalmic reactions. No intravenous treatment was administered. None of these animals presented pulmonary or hepatic reactions, nor did spleen or lymph node contain increased numbers of immature cells.

In control Group E were three rabbits, each of which received intravenously 1 cc. of Culture Q 155 on each of 2 successive days. There was no preliminary sensitization. They were killed by suboccipital blows 24 hours following the second inoculation. One animal revealed slight pulmonary and hepatic perivascular reactions, together with a moderate increase in immature cells in the spleen.

DISCUSSION

Perivascular aggregates of basophilic cells, occasionally containing granulocytes, have been described by numerous authors in immunized or infected animals.

In previously vaccinated mice Tsuda (6) noted an acceleration of marked vascular endothelial swelling and perivascular accumulations of cells in foci induced by intracutaneous injection with streptococci or pneumococci. Domagk (7) described phagocytosis of staphylococci by swollen vascular endothelium of mice inoculated intravenously with these microorganisms; and this was followed later by focal accumulations of cells in several organs. Comparable perivascular alterations were noted by Louros and Scheyer (8) in mice that received streptococci intraperitoneally; and both they and Domagk observed that the number and intensity of reactions increased with repeated inoculations. Jacob (9), on the other hand, while recognizing the reactions in mice treated intravenously with staphylococci or green streptococci, failed to note this parallelism.

The evolution of vascular responses in guinea pigs was followed in more detail by Oeller (10) who described endothelial phagocytosis of avian erythrocytes 30 minutes after they were injected intravenously, and perivascular accumulations

of mononuclear cells after 60 minutes. He attributed the response to a toxic action of the foreign hemoglobin; but this opinion was controverted by Gerlach and his coworkers (11–13), who observed similar lesions in the lungs of supposedly normal animals. Epstein (14) noted particularly collections of "basophilic round cells" not phagocytic for carmine in the hepatic capillaries and periportal tissue of rabbits treated intravenously with sheep erythrocytes, swine serum, or lipoid serum mixtures. Pentimalli (15) observed similar accumulations of cells in various tissues of rabbits after repeated injections of foreign protein; most numerous in the liver, fairly frequent in spleen and lymph nodes, and least marked in the kidney and lung. These observations were confirmed by Vaubel (16) who also described fibrinoid swelling of the ground substance as often preceding the accumulations of mononuclear cells. He observed that the intensity of response was conditioned by the amount of foreign protein previously injected, or in other words, by the degree of hypersensitivity. Klinge (17) described a similar evolution of the focal lesions in rheumatic fever, and for this reason ascribed a common pathogenesis to the two conditions.

Siegmund (18) traced systematically the reactions in blood vessels following the introduction of a variety of substances, and found that certain dyes, colloidal metals, foreign proteins, or bacteria stimulated the active mesenchyme and induced focal myelopoiesis or lymphopoiesis in different degrees depending upon the nature of the stimulant. Following the intravenous injection of certain bacteria (19) there was marked endothelial activation, which was accelerated in highly immune animals and took the form of interstitial collections of lymphoid and plasma cells. Subsequently (20) he described the formation of "intimal nodes" in the blood vessels of rabbits and guinea pigs that received multiple intravenous injections of bacteria. Such nodes might heal completely or lead to atheroma-like lesions. Similar pictures were seen in the blood vessels of patients dying of typhoid fever or staphylococcal sepsis. In the veins and endocardium of subjects dying 6 to 8 weeks after the onset of scarlet fever there were subendothelial nodes, and in other structures areas of cellular proliferation closely resembling those of rheumatic fever (21). Scheyer (22) earlier had correlated the amount of proliferation of reticulo-endothelial elements in various sites with the clinical course in puerperal sepsis, and found that the presence of focal reaction indicated a certain degree of resistance to the infection. Intense mononuclear cellular proliferation was observed by Ehrich (23) and by Nye and Parker (24) in animals following prolonged intravenous injection of bacteria; and the latter described similar lesions after the injection of certain colloids.

It is obvious that lesions resembling those described by us have been elicited with a variety of antigenic reagents, introduced through different routes, and in several species of animal. Despite the inclusive use of the term "immune" in the German literature and also the description of "hyperergic inflammation" by numerous authors, there

has been little distinction drawn between conditions of immunity (*i.e.* lessened reaction with increased resistance to toxic agents) and sensitization (*i.e.* increased reaction to toxic agents either with or without increased resistance to those agents). Even when these factors are considered the probable differences in cytological reactions between "anaphylactic sensitivity" and the hypersensitivity of infection have often been ignored, particularly by most histopathologists. Dienes and Mallory (25), however, have described the differences between these two conditions, and their criteria will doubtless be more carefully applied in the future.

Böhmig and Swift (26) studied the cutaneous response to focal injection in "immune" and "hypersensitive" rabbits, and found in the former relatively less tissue destruction and granulocytic infiltration than in the latter. In all lesions there was a marked perivascular "monohistiocytic reaction." Böhmig (27) subsequently demonstrated a stage of "hypersensitive type of response" to focal inoculation during the early period of intravenous immunization, later an "immune type of response," and finally as the immunity passed off a return to the first phase. His further demonstration that an animal may show the "immune type of response" to the bacteria with which it has been immunized, but a "hypersensitive type" to heterologous bacteria suggests that it may be hypersensitive to one immunochemical component of a microorganism and immune to another, and that the final focal evidence of infection of a previously treated animal may be the algebraic sum of the various modes of response.

In view of the fact that various degrees and types of reaction may be elicited in different animal species by the same antigenic substance, and also that different antigens induce different responses in the same species, it would seem probable that among the numerous investigators most of the histologic permutations and combinations of allergy and immunity have been described. In spite of differences, however, in most instances there have appeared very similar perivascular aggregates. The production of this reaction may, then, be regarded as not dependent upon the presence exclusively of any particular allergic condition of the animal, but rather as a function of chronicity of treatment with antigenic material and also of dosage. In most of the papers cited, the doses, when mentioned, have been fairly large.

No claim is made, therefore, that the preliminary sensitization is a *sine qua non* for the elicitation of these peculiar perivascular aggregates. It becomes obvious, however, from a consideration of the

experimental data, that there are *quantitative* differences between the sensitive and normal animal. In other words, the rabbit, after preliminary sensitization by the intradermal route, developed this lesion following subsequent intravenous treatment with a dose that seldom induced a comparable lesion in a non-sensitized control. Furthermore, under the condition of the experiments, rabbits inoculated intravenously from the beginning usually failed to display the lesion. Because at certain periods this route of inoculation induces tissue "immunity" (hypoergy) rather than hyperergy (2, 27), the experiments here presented show that the development of perivascular collars is conditioned by tissue reactivity, in addition to being a function of dosage of antigen.

The failure of the lesion to develop in all rabbits showing positive ophthalmic reactions, as well as its occasional appearance in untreated animals, illustrates the variability of host susceptibility in this species. Rabbits become sensitized unequally; and ophthalmic hypersensitivity is no guarantee that the usually lethal test dose will be fatal. Many rabbits contract spontaneous streptococcal infections from which they recover, doubtless with altered tissue reactivity to subsequent infection. It is not surprising, therefore, that sensitization should not be equally effective in the individuals of any given group. Likewise, the occasional appearance of a perivascular collar in previously untreated rabbits may indicate either abnormal spontaneous hypersensitivity or previous infection. These host variations, in either direction, are quite familiar to immunologists.

It is noteworthy that in the four animals that succumbed to the intravenous injection of 6 cc. of culture no cellular multiplication was found, except for a moderate reaction in the lung of one; but microscopic congestion and hemorrhage occurred. Probably in these rabbits the condition of shock, due to excessive dosage of antigen, was sufficient to inhibit any proliferative response. In other words, although sensitized tissues are easily stimulated by small inocula to a rather typical cellular reaction, larger amounts of the same material may lead to cell death.

Spontaneously occurring lesions must be differentiated from those experimentally induced. In the rabbit periportal aggregates of small round cells mixed with a few fibroblasts are not uncommon, at times

associated with true portal cirrhosis; but the lymphocytes in such lesions are obviously mature, and the large deeply basophilic cells are not found. On the other hand, these last mentioned cells do occur normally in spleen and lymph nodes, so that the extent to which reactions have been induced in these organs depends upon quantitative alterations in their cellular content, together with variations in cellular distribution. Normally occurring peribronchial and perivascular nodules of lymphoid tissue are readily identified, from the architecture of the aggregate and the type of cell.

We have preferred describing rather than naming the large basophilic cell which predominates in the perivascular lesion, for with the data at hand attempts at classification would be futile. The pleomorphism of its nucleus, the character and distribution of the nuclear chromatin, the nuclear vacuolations, the fine reticulation in the cytoplasm of the more faintly basophilic cells, and, finally, the occasional evidences of phagocytosis, all indicate the reticulo-endothelial system as its probable source. Further study with vital staining methods and observation of its behavior towards parenterally introduced India ink should furnish more conclusive evidence as to its identity. Whether it is produced directly by the presence of the bacteria or secondarily to the destruction of some other cells or tissue is also a problem for the future to unfold.

SUMMARY AND CONCLUSIONS

Intravenous inoculation of small doses of non-hemolytic streptococci into previously sensitized rabbits is usually followed by the appearance of perivascular cellular aggregates in lung and liver.

The characteristic cell in these aggregates is moderately large, with vesicular nucleus, prominent nucleoli, clumped chromatin, and basophilic cytoplasm. In addition, the lesions contain small lymphocytes and granulocytes.

This lesion is easily differentiated by architecture and cell content from normally occurring lymphoid aggregates, and from spontaneous rabbit hepatic cirrhosis.

This mononuclear response does not occur when the intravenous dose is large enough to cause death of the animal within 24 hours.

In spleen and lymph nodes the characteristic basophilic cells, which normally occur in these organs, are present in increased numbers.

Following intravenous treatment alone, or sensitization without intravenous treatment, the lesions occur much less frequently, and when present are smaller and more sparsely found.

Inasmuch as in the present series of experiments this lesion was not found in normal animals, and infrequently in those treated by the intravenous route alone, it is suggested that the preliminary sensitization serves to enhance the animal's reactivity to the antigen. In this way a small dose of bacteria is capable of eliciting the cellular phenomenon, which in unsensitized animals appears only when larger doses of antigen are administered over longer periods of time. Too large a dose of antigen, however, results in shock and cell death rather than proliferation.

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EXPLANATION OF PLATES

All tissues used in illustrations were stained with eosin and methylene blue.

PLATE 19

FIG. 1. Lung. Low power photomicrograph showing three perivascular aggregates in lung. × 100.

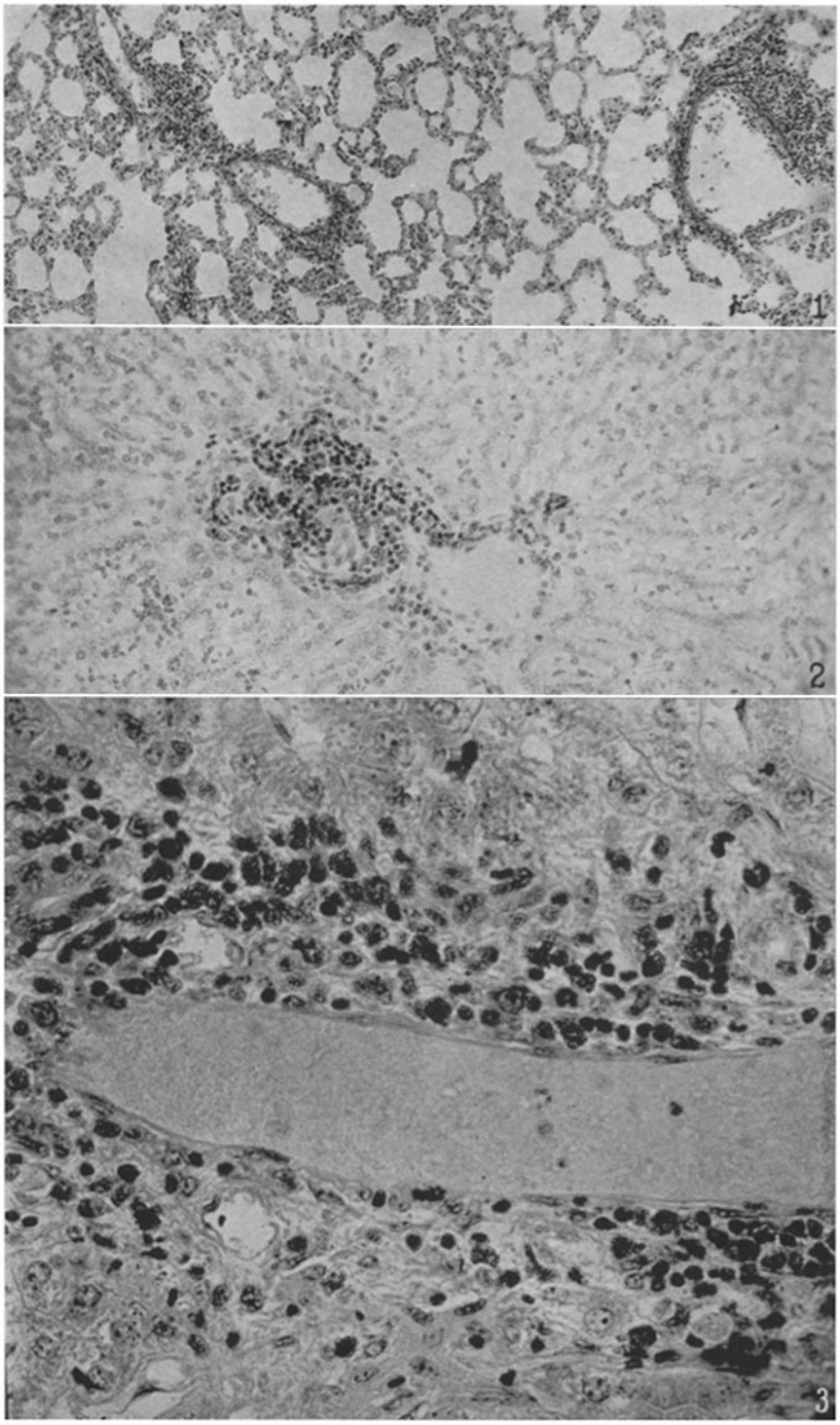
FIG. 2. Liver. Showing aggregate in portal area. × 200.

FIG. 3. Liver. Higher magnification, showing marked cellular aggregation around a portal vein. Numerous granulocytes are present. × 480.

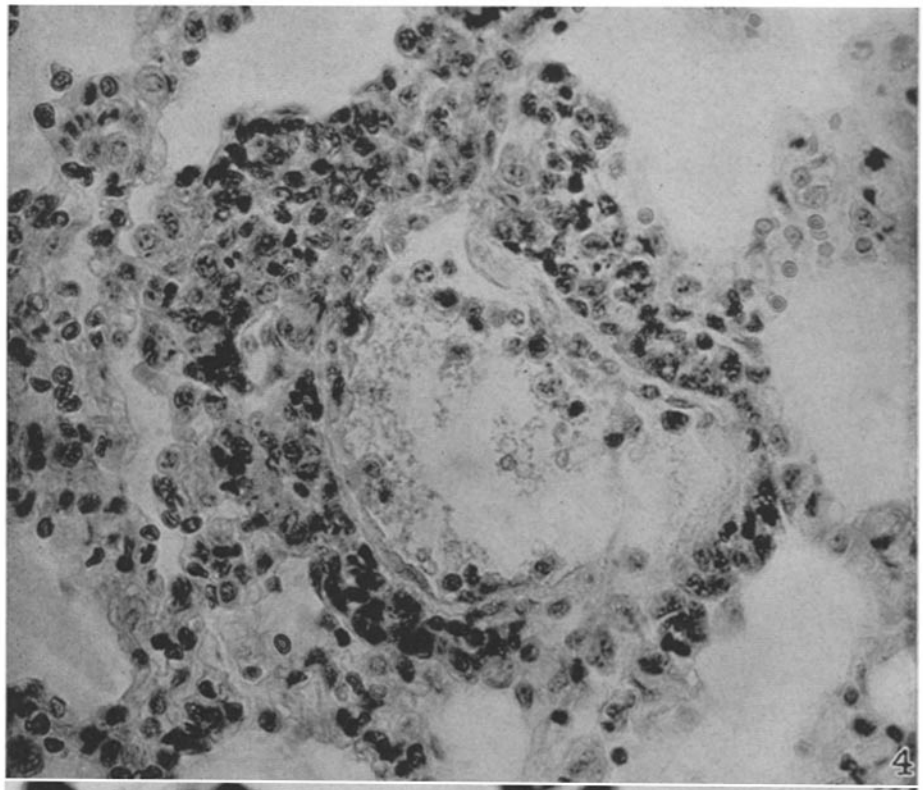
PLATE 20

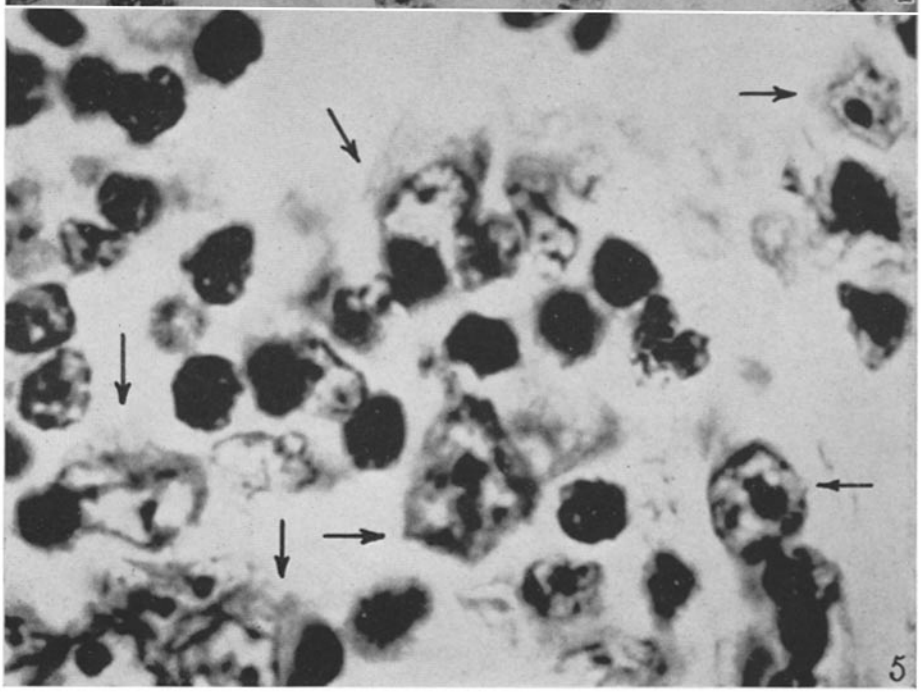
FIG. 4. Lung. Higher magnification. Endothelial reaction accompanying marked perivenous aggregation. × 480.

FIG. 5. Liver. A small portion of Fig. 3, showing pleomorphism of the characteristic cells (indicated by arrows). × 1,900.



(Hitchcock *et al.*: Perivascular reactions to streptococci)





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