FOCAL OR INSULAR NECROSIS PRODUCED BY THE
BACILLUS OF TUBERCULOSIS.

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PLATE LIV.

Since Virchow described the cellular tubercle, it has been adopted
as the anatomical basis for the lesions of tuberculosis; but the doctrine
that the effect of the bacillus of tuberculosis and its products upon
the tissues is invariably a specific one, having for its end the forma-
tion of a tubercle, is no longer believed. This was indicated when
Baumgarten (1) defined a tubercle as the "result of proliferative
and exudative changes," for the preponderance of exudative changes
on the one hand or of proliferative changes on the other leads to
lesions which differ morphologically and which cannot be considered
as having for their main constituent the presence of tubercles. The
researches of Orth (2) upon caseous pneumonia proved that in this
condition the effect upon the tissues of the bacillus of tuberculosis
is almost purely an inflammatory one, resulting in the formation of
fibrin without the formation of tubercles.

An analogous conclusion that a multiplicity of lesions which differ
morphologically one from another can occur as lesions of tuberculosis
may be drawn from the experiments which have been made with
dead tubercle bacilli. Although these experiments were made to
demonstrate that the dead bacilli contain within themselves substances
capable of instituting changes in the tissues, a most interesting feature
of the results obtained was afforded in the variety of the lesions
produced, and it is safe to assume that the differences that exist be-
tween the action of living and of dead tubercle bacilli upon the
tissues are chiefly quantitative differences. Thus when one sum-
marizes the results obtained by different investigators it is learned
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that in the hands of Koch (3), Wyssokowicz (4), and Prudden and Hodenpyl (5), subcutaneous injection of dead tubercle bacilli produced aseptic suppuration. By Vissman (6), Straus and Gamaleia (7), Prudden and Hodenpyl, and Masur (8), through intravenous injection, tubercles were produced in the lungs, but also an interstitial pneumonia with formation of fibrous tissue and endarteritis. Abel (9), by the injection of dead tubercle bacilli into the tracheas of rabbits, found, after twenty-four hours, white, isolated areas in the bronchi and alveoli made up of round cells among which were the bacilli. Twenty-four hours later these were necrotic and epithelial proliferation had begun. Thus we find, in marked contrast to one another, a liquefactive necrosis which we recognize under the more common term of suppuration, formation of fibrous tissue and a necrosis without liquefaction—three distinct processes differing from one another anatomically and histologically, and having for their etiological factor the poisonous substances present in the bodies of the dead tubercle bacilli.

That a multiplicity of lesions which differ in the amount of exudation and fibrin formation can result from the action of living tubercle bacilli, and that such lesions possess all transitional forms and stages from one to another, has been proven by the researches of Falk (10) under the guidance of Lubarsch. He found from many experiments upon animals and the examination of a large number of tissues from cases of human tuberculosis that the exudation and resulting formation of fibrin were dependent upon many factors, chief among which was the virulence of the bacillus. In support of this, fibrin was found to be absent both in the lesions produced by dead tubercle bacilli and those produced by bacilli of lessened virulence. That the tissue or animal resistance plays a part in the resulting phenomena of exudation was made manifest when it was learned that fibrin was generally absent in the tubercles produced in rabbits by pure cultures of living tubercle bacilli, and that it was constantly present in the tubercles produced in a similar manner in guinea-pigs, whose susceptibility to tuberculosis is universally known. The frequent presence of fibrin in genuine tubercle nodules in human beings
The possibility of a further variation in the lesions produced by the bacillus of tuberculosis dependent upon the amount of degeneration or necrosis effected has been recognized by very few observers. R. Kockel (11) in the experimental tuberculosis of guinea-pigs found insular necroses in the liver which showed the following features: Twelve hours after the injection, areas were found which showed necrotic, shrunken, glistening liver cells with small nuclei. They were located generally adjacent to the radicles of the portal vein, and these were filled with polymorphonuclear leucocytes among which the bacilli were present. Two days after inoculation the necrotic cells were still present adjacent to thrombi in the portal branches, in which proliferation of the endothelium of the vessel, as shown by the presence of karyokinetic figures, had resulted. These foci of necrosis the author believed to be due to plugging of the vessel, and in support of this view he gives the following reasons: 1. He cites the opinion of Schmorl (12) relative to the necroses observed in puerperal eclampsia, who believed such areas of cell death were produced in a similar manner. In this connection it must be noted that Leusden (13) takes exception to Schmorl's explanation of the genesis of the necroses observed in eclampsia, Leusden attributing the necroses to the action of some toxic substance in circulation in the blood. 2. Kockel mentions the experiments of Franeken (14), Naunyn (15) and Schmorl (16), with the injection of substances capable of producing coagulation of the blood, in which experiments similar areas of necrosis were observed. 3. As a control Kockel employed an indifferent substance, grits (Gries), and produced in the livers of guinea-pigs areas of necrosis which differed in no respect from those found following the injection of tubercle bacilli, those occurring in eclampsia, or those caused by the injection of substances which promote fibrin formation. The liver cells in the areas produced by these different methods were much shrunken, stained strongly with eosin and possessed nuclei smaller than normal which stained less intensely or not at all.

It is important to remember, and we are reminded of the fact by
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Leusden, that according to Ziegler (17) ischemic necrosis does not occur in the liver unless radicles of both hepatic artery and portal vein are obstructed.

Previous to Kockel, necroses in the liver in connection with tuberculosis had been described by Pilliet (18), who found and described necroses in the livers of guinea-pigs, but believed that they had no specific relation to the bacillus of tuberculosis. In the human being Leredde (19) has described multiple visceral necroses in acute and subacute phthisis. Tubercle bacilli, however, were not found in the areas, the areas were located invariably around the central veins of the lobules, and from the description given and the accompanying illustrations it is difficult to assume that the lesions could be explained as the effect of chronic passive hyperemia.

While we agree with Baumgarten that the usual effect of the tubercle bacillus upon the tissue is to produce a tubercle with a combination of exudative and proliferative changes, it seems evident from the lesions about to be described that the primary effect may be, at least in exceptional instances, one of necrosis combined with exudation and resulting fibrin formation; in other words, a coagulation necrosis. As instances of this, the following cases are presented.

Case I. Abstract of clinical history. G. S., a woman, colored, aged 60 years, was admitted to the Cook County Hospital, March 21, 1894. She complained of a cold and cough which had lasted for four weeks. Bronchophony and bronchial breathing, with marked dulness over both lower lobes posteriorly, were obtained upon examination of the chest.

Death took place April 19. The autopsy, made two days later, the body having been kept at about freezing temperature in the meantime, showed chronic vegetative endocarditis, chronic tuberculosis of both lungs with cavity formation and passive hyperemia of the liver and kidneys. The spleen was small and hard, and showed no lesions of tuberculosis to the naked eye.

The lesions found microscopically in the spleen in this case serve as a type for those present in each of three cases, and are therefore described first.

Under a low power * attention immediately became directed to areas

* Obj. 16.0 mm., apr. 0.30, tube length 160 mm., ocular 4, diam. 62. Zeiss.
in which the nuclear staining was imperfect (Plate LI, Fig. 1). These were so numerous that scarcely a field could be obtained which did not contain one such area, and many fields were found which contained two or three. In size the largest equaled in width one-third the breadth of the field under this power; an area of average size approximated closely the size of the normal renal glomerulus of an adult.* In serial sections, cut in paraffin and from 4 to 6 μ thick, the same area was found present on an average in twenty sections. As seen with this amplification in sections stained with haematoxylin and eosin, the eosin stain predominated and, upon this as a background, dust-like granules, darkly stained with haematoxylin, were distributed.

No round cell infiltration existed about any of these areas, nor could any fixed position of the areas be made out as regards either the bloodvessels (small arterioles) or the Malpighian corpuscles. Occasional areas were found situated close to one of the more minute of the radicles of the splenic artery, but at no time could the invasion of a Malpighian corpuscle or the presence of an area directly within such a corpuscle be found.

Under a higher power,† the dust-like granules seen before became more distinct as intensely staining, oval or round bodies of varying sizes, occupying mainly the central part of the area. The larger ones appeared highly refractile. All were smaller than cell nuclei. Their position, size and staining reactions left no doubt that they were the remains of nuclei, chromatin granules, resulting from nuclear fragmentation. Among these granules many distorted and shrunken nuclei, long drawn out, wedge-shaped, curved, or with dumb-bell-like enlarged ends, were found. These, although most numerous at the periphery, were also found here and there throughout the area. They exhibited all degrees of intensity of staining, but generally stained darkly. No cell bodies could be made out for these nuclei. Here and there in the areas were found cells with oval or round nuclei, which stained faintly or not at all with the nuclear dye.

A few cells with characteristic nuclei marking them as polymorphonuclear leucocytes were frequently observed in the peripheral zones, but in some areas these were entirely wanting. The transition between necrosis and the surrounding normal tissue was quite gradual. In the immediately surrounding tissue there were occasional cells possessing nuclei which stained poorly or not at all, surrounded by cells all of which

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* Eckardt gives the diameter of a normal glomerulus in an eighteen-year-old girl, as 189.88 μ. Virchow's Archiv, cxiv (1888), 227.
† Obj. 2.0 mm., apr. 1.30, tube length 160 mm., eyepiece 8, diam. 1000. Zeiss.
stained in the usual manner. With the Weigert fibrin stain, fibrin was always found in these areas as a fine network, not only at the periphery but pervading the area throughout. In the central part the bands were often heavier; in the periphery the fine threads extended out among the unchanged cells. No evidences of thrombosis were found in adjacent capillaries or larger blood-vessels. To demonstrate the presence of the bacillus of tuberculosis, sections were cut in celloidin, which was then removed with clove oil. The sections were then fixed upon a slide by means of Mayers' albumin fixative or Schallibaum's collodion and clove oil mixture, stained with the ordinary carbol-fuchsin solution by heating for five or ten minutes, decolorized with 30 per cent sulphuric acid, followed by alcohol until a pinkish hue was obtained, and finally counter-stained with methylene blue. By this method tubercle bacilli were invariably found—not in large numbers, but always a few in an area, and most numerous in the peripheral parts of the necrosis.

A careful examination by means of serial sections was made for multinuclear giant cells, but these were invariably wanting, nor were any areas found which presented for a part or the whole of their circumference cells with the vesicular nuclei commonly described in connection with the lesions of tuberculosis as "epithelioid cells."

A careful search for other bacteria was made by the following method. The sections fixed upon the slide were stained with methylene blue, washed slightly in water, cautiously allowed to dry, dehydrated with ether and clarified with xylol. This was found peculiarly applicable in that none of the blue was removed in dehydrating or clarifying. Results were negative. In the sections stained by the fibrin method also, no micrococci or other bacteria were found.

In the liver were found microscopically the following lesions: Situated within or occupying to a large extent the interlobular connective tissue, areas similar to those in the spleen were found. These differed from those in the spleen in that a slight zone of round cells, mainly polymorphonuclear leucocytes, were present around the periphery. The invasion of the area of necrosis by these leucocytes was generally slight and seldom extended throughout the area. The necrotic liver cells and fibrin made up the main part of the area (Plate LIV, Fig. 2). Giant cells were not found, but tubercle bacilli were easily demonstrated.

Case II. Abstract of clinical history. R. C., male, colored, aged 25 years; was admitted to the Cook County Hospital, February 21, 1894, with a history of illness which began with cough, fever and general weakness. At the date of entrance a painful cough, with considerable expectoration, loss of appetite and occasional vomiting were the main symp-
toms. A few rales were present over the whole chest; the abdomen was tender to pressure, and the spleen palpable. Death resulted March 7.

At the autopsy there were found a tubercular peritonitis with serofibrinous exudate; tuberculosis of the mesenteric, anterior mediastinal and bronchial glands; chronic tuberculosis with marked thickening of the right pleura; miliary tuberculosis of the upper lobe of the left lung, and a large and soft spleen adherent to the diaphragm at a point opposite to which the bronchial glands were adherent on its upper surface. The liver and kidneys on section showed nothing remarkable. Microscopical examination of the spleen showed areas similar to those in Case I, but they were not so numerous; in all other respects they were identical. In the liver, on the other hand, typical microscopic tubercles were present.

Case III. Abstract of clinical history. M. O'D., a woman, white, 48 years of age and single; was admitted to the Cook County Hospital, October 27, 1894, complaining of vomiting, dizziness, excessive perspiration, insomnia and occasional cough. On examination the relative cardiac dullness was found slightly increased, and a systolic murmur was heard over the lower part of the sternum. Liver dullness was increased, and some edema of both lower extremities was present. Death occurred March 14.

The autopsy record has interest only in so far as it concerns the retroperitoneal lymph glands. There was present an unbroken chain of enlarged glands, extending from the aortic arch to opposite the sacrum. They were largest below; above they were pigmented. The largest was the size of a pigeon's egg. No marked adhesions existed between adjacent glands or the surrounding tissue. On section they all with one exception presented a smooth surface, of an even pale flesh tint throughout. The one exception was found in a small gland near the head of the pancreas, which contained calcified areas. No eroded bone was found in an examination of the vertebrae, sacrum and innominate bones.

Microscopic Examination. Situated beneath the capsule of the gland, and never extending to any great depth into the glandular substance, are many areas similar to those described in the spleen of Case I. They differ in that they are more irregular in outline and frequently confluent (Plate LIV, Fig. 3). These areas showed similar bizarre forms of cells and nuclei, similar nuclear fragments, absence of any peripheral round cell infiltration as well as absence of giant cells. Located here and there in the surrounding glandular substance, and without any fixed relation to the areas of necrosis, were found what appeared with a low power to be large cells, or possibly giant cells. Under a higher power these resolved
themselves into closely approximated nuclei surrounded by a homoge-
neous, highly refractile membrane. The nuclei were always few in
number, never showed any central necrosis, and often no peripheral ar-
rangement. For these reasons they were regarded as phenomena resulting
from proliferation of the endothelium of lymph channels. This proba-
bility was further increased by finding, after considerable search, occa-
sional leucocytes in the centre of some of the groups. Occasional large
lymph cells were seen and some of these possessed a nucleus with a star-
shaped mitotic arrangement of the chromatin elements. Tubercle bacilli
were found in these areas, but they were not numerous. Other bacteria
were not found.

That such areas of focal necrosis as we have seen to occur in the
spleen in the most typical form are rare as a lesion of tuberculosis is
to a slight extent substantiated by the researches of Manicatide (20).
This writer examined the spleen in twelve cases of tuberculosis in
children. In most of the cases the tuberculosis was visible to the
naked eye; in two instances the tubercles were small, and in one of
these no bacilli were found. In all of the other ten instances, typical
tubercles possessing epithelioid cells and giant cells are spoken of.

That the areas in our three cases are areas of genuine focal necrosis
is further substantiated by comparing these lesions with other observed
forms of focal necrosis from various causes.

The substances ricin and abrin, products isolated respectively from the
castor bean and the jequirity bean, studied by Warden and Waddell (21),
Kobert and Stillmark (22), S. Martin (23), Hellin (24), Ehrlich (25),
Kobert (26), S. Flexner (27), and Werhovsky (28), were found by
Flexner to produce marked focal necroses in the lymphatic tissues with
fragmentation of nuclei, also coagulation necrosis of liver cells and capil-
lary endothelium in the liver and necrosis of the intestinal epithelium.
Liver cells were found devoid of nuclei or the nuclei appeared in frag-
ments. The cells sometimes were broken up into a reticulated mass,
which reacted to Weigert's fibrin stain. More frequently the cells re-
tained their shape but failed to stain with nuclear dyes. Ehrlich found
marked necrosis produced by abrin at the point of inoculation with loss
of hair from the surrounding skin, and came to the conclusion that abrin
has a peculiar specific action upon the skin in this respect. Werhovsky
in his experiments upon rabbits with abrin concluded that the greatest
changes were produced in the cardiac muscle and the lining of the ali-
mentary canal. In the heart, swelling and fatty metamorphosis of the muscle fibres were observed; isolated foci of necrosis in the liver were not noted, and such changes as were found in the liver were attributed by him to the passive hyperemia resulting from cardiac weakness.

Foci of necrosis in connection with diphtheria were first noticed by Bizzozero (29) in the spleen, mesenteric glands, and Peyer’s patches. We are indebted to Oertel (30) for the first complete description of the histological changes which take place in these foci in human diphtheria, and to Welch and Flexner (31) and Babès (32) for concise accounts of similar changes produced in experimental diphtheria. By these authors focal necroses were described in the liver, spleen, lymph glands, heart, muscle, kidney and intestines. Bulloch and Schmorl (33) have described areas of degeneration in the submaxillary gland in diphtheria in which fibrin was demonstrated; Dubief and Bruhl (34) produced necroses in the livers of guinea-pigs with experimental diphtheria; Courmont, Doyen and Paviot (35), necroses in the livers of dogs, produced by the diphtheria toxins. The necroses described by these various authors consist of minute areas of nuclear fragmentation, with entire or partial dissolution and disappearance or great distortion of the fixed cells of the part. The nuclear remains stain darkly and give a dust-like appearance to the area. There were also found areas in which the cells retained their shape but stained imperfectly. In addition to these changes Barbacci (36) in a recent article has described edema, hemorrhage and hyaline degeneration of the follicles of the spleen, and only the occasional presence of fibrin; in the lymph glands a predisposition for the necroses to occur in the peripheral parts of the gland and in the germinal areas, also hyaline degeneration of the vessels, cell elements and stroma; in the liver, changes were described in the nuclei of the liver cells, but no actual foci of necrosis.

Foci of necrosis have been found in the liver in cases of puerperal eclampsia by Pilliet (37), Gerdes (38), Lubarsch (39), Schmorl (16), and Leusden (13). The liver cells were necrotic and stained more intensely with eosin than the surrounding liver cells; in places they showed irregular, indefinite outlines with shrunken nuclei.

Flexner (27) found necroses in the viscera of rabbits into which intravenous injection of the blood serum of dogs had been made. They were present in the liver, spleen and kidney; in the spleen marked nuclear fragmentation resulted, in the liver areas of coagulation necrosis.

The so-called lymphoid nodules occurring in the liver in typhoid fever, described by Friedreich, E. Wagner and others, have been shown by Reed (40) to be areas of necrosis into which the polymorphonuclear
leucocytes have wandered, and were produced experimentally by the last
named author by injecting pure cultures of the typhoid bacillus into the
mesenteric veins of rabbits. The areas of necrosis, according to Reed,
are frequently oval or irregular in outline, occupying a space equivalent
to a few liver cells or the larger part of a lobule, are situated in any part
of the lobule, and show various signs of cell death or degeneration. In
places the shape of the cell and cell rows is well preserved, but nuclear
fragmentation and deficient stain absorption are present. In other areas
the liver cells have lost their shape, show pale and swollen nuclei and
may contain polynuclear leucocytes. In still other areas the liver cells
have entirely disappeared.

Areas of necrosis have been noted in the liver as the result of hog
cholera infection by Welch in 1889 and by other observers (41), but a
detailed account of the minute changes taking place is apparently want-
ing.

Foci of necrosis have also been noted in the liver in cases of acute
lobar pneumonia and in experimental pneumococcus infection by Welch
(42). In these, the nuclei of the liver cells were in large part absent or
fragmented, the cell body opaque or more refractive than normal or con-
taining fat globules. Polynuclear leucocytes had invaded the areas from
the edges.

Wright (43) has recently given us an account of the earlier histological
changes which take place in the nodules of experimental glanders in
guinea-pigs, in which the changes noted are very similar to those already
described in other forms of focal necrosis. The foci were observed in the
liver, spleen, lymph glands, testicle, peritoneum and adrenals as minute
greyish points, or larger, somewhat yellowish areas, and in all localities
showed microscopically essentially the same changes. Marked necrosis
or degeneration of the fixed cell elements, as shown by the various de-
gres of cell dissolution, deficient staining, and a considerable quantity of
nuclear remains in the shape of darkly staining chromatin granules or
balls, was found, with a slight infiltration of polynuclear leucocytes which
likewise had undergone necrosis or degeneration. From these findings
he takes exception with Tedeschi to the heretofore accepted views of
Baumgarten concerning the histogenesis of the nodules of glanders, in
that nothing was found which would indicate that a primary cell prolifera-
tion had occurred, and he comes to the conclusion that the first effect of
the bacillus of glanders upon the tissues is to produce, not cell prolifera-
tion, but cell death.
CONCLUSIONS.

1. It must be accepted from a comparison between the histological changes described in the focal necroses due to abrin and ricin, diphtheria, eclampsia, blood-serum intoxication, typhoid fever, lobar pneumonia and glanders, and those described here in three cases of tuberculosis, that the last are also instances of focal necrosis.

2. It may be claimed that the areas of necrosis in the three cases of tuberculosis had their origin in ischæmia, for the reason that they were numerous in the spleen and were not found in the kidney. Against such an explanation of their causation are the facts: that other forms of necrosis affect frequently the spleen and seldom the kidney; that thrombosis of vessels or any fixed relation of the areas in the spleen to blood-vessels could not be established; that the tubercle bacilli were invariably present; and lastly and of no slight importance, that these necroses were all present in cases of marked marasmus.

3. That the areas of necrosis in these three cases might be phenomena resulting from a mixed infection with pyogenic bacteria is possible, but no groups, colonies or even single bodies could be found which answered to the requirements in shape or staining properties for such bacteria. Even were it the case that the focal necroses here presented are the histological lesions of a septicemia occurring as a complication of tuberculosis, the presence of the bacillus of tuberculosis in the areas of necrosis would still require explanation.

4. Lastly, it is not unreasonable to suppose that a diminished resistance on the part of the tissues incidental to marasmus is an important factor in the production of these necrotic lesions.

DESCRIPTION OF PLATE LV.

Fig. 1. Area of necrosis in the spleen. Case I. × 62.
Fig. 2. Area of necrosis in the liver. Case I. Weigert’s fibrin stain. 1, heavy bands of fibrin. 2, finer bands of fibrin. 3, degenerate liver cell nucleus. 4, leucocyte. × 1000, reduced one-third.
Fig. 3. Necroses in lymph gland. Case III. × 62.

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