STUDIES IN INFARCTION: *

II. EXPERIMENTAL BLAND INFARCTION OF THE LUNG.

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OUTLINE.

In a previous publication [1] a brief review of the literature of infarction in general was presented, little being said, however, about pulmonary infarction, a subject which in the present communication is discussed more fully because of the large number of clinical, pathological, and experimental investigations that have appeared.

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A most important topic, one that has received much attention (in spite of which there remains much to be learned) is that of the normal circulation of the lungs. One of the earliest careful investigations was that of Küttner,[2] who showed that in the frog's lung the capillaries come off directly from relatively large vessels, that they are capable of taking over the function of anastomoses between two arteries or systems of arteries, that they can enlarge so as to resemble arterial anastomoses and further that veins with the aid of capillary streams can functionate as anastomoses between two arteries. These views were strongly supported by Stadelmann[3] from his pathological anatomical studies. Such free anastomosis had been denied by Rindfleisch,[4] but the free anastomosis between bronchial and pulmonary circulation had been supported by Haller,[5] Hyrtl,[6] Henle,[7] Luschka,[8] and Virchow.[9] Cohnheim and Litten[10] published their first study shortly after the appearance of Küttner's communication and claimed to have demonstrated by injection methods the interdependence of and lack of anastomosis between the bronchial and pulmonary systems. These findings, however, soon were contradicted by Küttner,[11] who applied the methods of his earlier work to the study of mammalian lungs, reaching practically the same conclusions to which his work on the frog's lung had led The validity of Küttner's work was acknowledged later by Litten,[12] who stated that the earlier conclusions of Cohnheim and himself were faulty because of imperfect technic. On the publication of his "Vorlesungen" two years later, Cohnheim[13] gracefully accepted Küttner's conclusions. Küttner's work, however, is not without minor faults and the later work of Miller[14] would indicate that the intercommunication of the two systems is not so free as Küttner believed.

Nevertheless, there is sufficient reason adduced from these studies for the belief that simple occlusion of a pulmonary arterial trunk does not cause true infarction and many of the earlier workers accordingly declined to accept the view that pulmonary infarction was in any way related to embolism. It seems that Laennec failed to recognize the embolus as a

cause of infarction, Rokitansky [15] was not clear on the subject and Pannum [16] stated that the pulmonary embolus produced no effect on the lung and was soon encapsulated. The experimental demonstration of embolism as the cause of pulmonary infarction came with the appearance of Cohnheim and Litten's [10] article and since then has been confirmed repeatedly, although not without some dissension, for as late as 1891 Grawitz [17] absolutely denied the embolic origin of lung infarcts and went so far as to state that if an embolus were present the infarct occurred in spite of it rather than because of it. This was in the face of the work of Klebs,[18] who, by producing lateral conglutination thrombi in addition to the embolism, almost constantly obtained well marked infarcts. The later work of Fujinami,[19] of Orth,[20] and of Zahn [21] completely refuted Grawitz's conclusions and there could no longer be any doubt as to the causative relation of the embolus. Fujinami obtained results by injecting into the jugular vein paraffin of such consistence that the plugs would lodge not only in a large branch of the pulmonary artery, but also in several smaller branches, so as to shut off collateral circulation. Orth mixed various chemical irritants with the emboli and obtained fairly constant results. Although Küttner had noted that ligation of the pulmonary vein tended to make the infarcts more distinct, Zahn was the first to apply, what had been noted clinically, namely, that passive congestion increased the likelihood of pulmonary infarction and accordingly by tightly binding the rabbit's thorax, two days after the emboli had lodged, was able to produce typical infarcts in the lungs. If, however, he produced constriction earlier, the infarcts did not appear. It is generally known that the emboli in the vast majority of cases must lodge near the margin of the lungs in order to produce infarction. As far as can be learned the frequency with which the various lobes are affected has been reported chiefly by Tiedemann,[22] who states that nearly fifty per cent of all infarcts of the lung occur on the right side at the base. In an analysis of thirty-three cases he found the right lower lobe involved in fifteen, the right upper in seven, the left

lower in five, the left upper in four, and the right middle in two.

The circulatory disturbance produced by the embolus has been found to be variable with the size of the ambolus or more literally with the size of the vascular trunk occluded and also with the number of vessels occluded (work of both Fujinami [17] and of Klebs [18]).

Most workers have shown that the lodgment, if productive of any change, shows as a consequence the development of a generally conical area (affected in shape by the outer contour of the lung) of congestion, interstitial and alveolar edema and sometimes small foci of hemorrhage. Hemorrhage involving the entire area and subsequent tissue necrosis, however, is found but rarely unless some complicating condition is present.

The infarct of the lung is so typically hemorrhagic that the white or so-called anemic infarct is believed by many not to occur. In the experience of the writers, however, three such infarcts have been observed at the post-mortem table. There was marked pleural effusion and on histological examination the infarcts were found to be markedly necrosed and probably represented decolorized hemorrhagic infarcts. The possibility of such decolorization is discussed by Orth [23] and the occurrence of pallid infarcts has been noted by Welch,[24] by Parson and O'Sullivan,[25] and others.

The most noticeable feature of the infarct is the hemorrhage, which has received as much if not more attention than the infarct itself. Laennec, as is evidenced by the earlier name of the condition, apoplexia pulmonalis, considered it the most important feature and it is almost certain that Rokitansky [15] and others of even later times shared this view. That it is a secondary process, however, cannot be doubted, and the chief question is as to its origin. The general phases of the problem were discussed in an earlier paper,[1] but certain special features in connection with the lung have received considerable attention. From the investigations of Virchow,[9] Cohnheim,[13] von Zielonko,[26] and others, it is certain that lysis of the vessel walls in the area is associated with the

hemorrhage, but as to its causative relation there is some question. There is unquestionably capillary dilatation, which according to the views of von Zielonko,[26] Brown-Sequard,[27] Bier,[28] and others believe that in general the hemorrhage is the result of increased vasomotor pressure. Much doubt, however, has existed as to the presence of vasomotor nerves in the pulmonary arteries, but anatomically non-medullated nerves have been found in the dog's pulmonary artery,[29] and the physiological work of Wood[30] and others can leave little doubt that vasomotor function exists. That increased capillary pressure plays an important part in the etiology of the hemorrhage might be inferred from the fact that it is almost impossible to produce hemorrhage in the lung infarcts unless passive congestion or some other circulatory interference is present, a fact well recognized both pathologically and clinically.

Necrosis is secondary to the marked circulatory disturbance produced by the embolism and hemorrhage, but is rarely seen at the autopsy table probably because of the fact that the patients usually are seriously ill at the time of the infarction and die before extensive necrosis occurs (see Welch[24]). This statement must hold true also in regard to decolorization of the infarct, because as Orth and Welch point out, and as is confirmed by our experience, although the condition is rare, it has been observed in human cases.

Conglutination of red corpuscles in the blood vessels and in the hemorrhage is an almost constant finding and was believed by Klebs to be important etiologically. Increased viscosity of the blood has been suggested by Funke[31] as being important from certain clinical studies, but no experimental work has been brought forward to confirm or contradict this view.

No studies on the healing of pulmonary infarcts have been made, but it is well known that completely organized conical areas, presumably healed infarcts, often have been found (Welch).

The purpose of the present work is to study the effects of experimental bland embolism and the consequent changes in

the lungs, to investigate the effects of limiting the lung circulation, to devise a method for the constant production of infarction, and to study the changes found in the infarcts.

The alterations in general circulation were produced as follows: (1) For interruption of the bronchial artery supply a ligature was thrown around all the branches of the aorta below the left subclavian and including the second pair of intercostals. According to the general anatomists this includes all sources of bronchial arteries. Küttner claimed that branches might come from the internal mammaries and other arteries, but if such is the case the amount of blood so supplied would be inconsiderable because of the ramifications in the mediastinal ligaments. (2) For interruption of the pulmonary venous drainage, the branch coming from one lobe, in which a seed could be found by palpation, was tightly ligated. The venous drainage, in small degree, probably occurred through the bronchial veins. (3) Lesser degrees of congestion, as well as marked compression of the lungs, was produced by filling the thorax with sterile olive oil.

METHODS.

For the introduction of seeds into the pulmonary arteries, a piece of ordinary thin wall glass tubing was used and as an obturator a wooden applicator, such as is used by rhinologists, with a pledget of cotton on the end. The right jugular vein was opened aseptically under deep ether anesthesia, four turnip radish seeds placed in the end of the cannula, the cannula inserted from four to six inches toward the heart, and the seeds slowly discharged by means of the obturator. The vein was ligated and the skin wound closed with Michel clamps.

For ligation of the upper intercostal arteries, the anesthetic was administered by the Meltzer and Auer intratracheal insufflation method. The thorax was opened by resecting the left fifth and sixth ribs near the spinal column and the small branches of the aorta below the left subclavian (these frequently supplying bronchials), and including the first and second pair of intercostal were ligated en masse with a heavy silk suture thrown around by means of a large pedicle needle. The muscles were approximated with silk and the skin closed with clamps.

For the ligation of branches of the pulmonary veins draining lobes in which seeds were found, two methods were used. That of splitting the sternum under insufflation anesthesia was discarded because of the attendant shock. The second method was extremely satisfactory, the incision being placed in the seventh or eighth interspace and after

cutting the intercostal muscles between the posterior axillary and parasternal lines on the left side a spreading retractor was inserted and the root of the lung exposed. In all our cases so operated seeds were found in the left lung so that the operation did not need to be repeated on the opposite side. A silk ligature was thrown around the vein by means of a pedicle needle and tightly tied. In closing the wound one silk tension suture was thrown around the upper and lower ribs, by a full curved round pointed needle and the cut muscle brought to the lower rib by interrupted sutures carried through the muscle near the cut edge and around the lower rib. The external thoracic muscles were approximated with a single button-hole suture and the skin closed with skin clamps. The danger of pneumothorax was obviated by compressing the trachea about the insufflation tube and then compressing the chest before the last suture was tied. The method is that described by Quinby and Morse [32] and is much the same as that used by Carrel.[33]

The olive oil was sterilized by heating twenty minutes in the autoclave at twenty pounds pressure. The apparatus for injection consisted of a bottle with a two-hole rubber stopper into which were inserted two glass tubes, one of which was connected with a two-way trocar-cannula and the other connected with compressed air inlets supplying cotton filtered air under about ten pounds pressure. The oil was thus forced into the thorax at the rate of five hundred cubic centimeters in about twenty minutes. The amount of oil injected (under ether anesthesia) was determined by the appearance of gasping respirations and distinct smallness of femoral pulse.

All animals were killed with chloroform, the tissues fixed in Zenker's fluid, embedded in celloidin and stained with Delafield hematoxylin and eosin.

Bland embolism and its results. — Orientation experiments with various seeds showed that seeds smaller than the turnip radish seeds did not produce any grossly observable change in the lungs at the end of forty-eight hours. Therefore, not wishing to disturb pulmonary function, but to insure a sufficient number of emboli, four turnip radish seeds were injected into the superior vena cava and dogs killed one-half, three, six, twelve, twenty-four, and forty-eight hours, two, four, and seven days, three, four, and five weeks afterward.

At the end of one-half hour a sharply defined area of pallor was found, but no other gross changes. This area was generally triangular, the apex toward the point of lodgment of the seed and was clearly visible in both the distended and collapsed lung. Such areas, as frequently was

found in subsequent intrathoracic experiments, usually are about a third again as large as are the later areas of more marked vascular disturbance. Histologically, no changes were found other than very slight conglutination of the corpuscles in a few of the larger vessels.

At the end of three hours, however, changes very suggestive of infarction were visible. In the animal killed at this period two such areas were found, one in the sharp edge of the third right and lower left lobes. These areas extended two centimeters along the edge of the lung and the same distance into the lung, the apex of the doubly truncated cone appearing at the position of the lodged seed. On the outer surface they were well defined, slightly elevated, seemingly somewhat firmer than the normal lung and of dark red or crimson color with a very slight tinge of blue. On cut surface, the diamond-shaped area did not bulge but was sharply defined, crimson in color, moist and bleeding. No areas of distinct consolidation were discerned. Histologically, a vaguely defined area was found in which there was well marked capillary dilatation and very distinct conglutination of erythrocytes in capillaries and larger vessels. The alveoli were of about normal size and almost universally filled with a clear, slightly acidophilic, homogeneous mass (edema), but there was no evidence of hemorrhage or desquamation. The interstitial tissue about the larger blood vessels was slightly edematous. The bronchi showed many goblet cells, but little other change. This area extended to within one or two millimeters of the pleura, the intervening lung tissue being normal, free from capillary distention, conglutination or any other changes described in the central area. The pleura was normal throughout.

At the end of six hours the same appearance was found grossly, but histologically there was beginning hemolysis, somewhat more noticeable interstitial edema and in the area immediately under the pleura, where no circulatory changes could be found, well marked distention of the alveoli, with apparent rupture of the alveolar walls but no hemorrhage.

At twelve hours the gross appearance was the same and

histologically small areas of intra-alveolar hemorrhage were found, principally as a few corpuscles in the alveoli, but occasionally completely filling several alveoli.

At twenty-four hours the areas grossly showed a distinctly blue tinge in the red and histologically there were found in the larger vessels and in the edematous fluid of the alveoli numerous granules of golden yellow pigment resembling in every way hemosiderin granules.

At two days the same appearances were found grossly and histologically, and at four days no further changes were found.

At the end of one week the congestion was not so marked grossly and the area was correspondingly less well defined, but no notable changes were found histologically.

At the end of two weeks, instead of swelling, the area showed slight retraction on the inner surface, but not on the cut surface. Histologically, the air spaces had begun to open and there was considerable vesicular emphysema throughout the area. The peribronchial and perivascular interstitial edema was by this time hardly discernible.

At three weeks no other notable changes were found grossly. Histologically, however, there was distinct thickening of the alveolar walls especially near the large connective tissue septa. No nuclear figures were seen, but the morphology of the cells in the latter position was that of fibroblasts.

At the end of five weeks the area was still somewhat, but very slightly, congested, swollen as if by emphysema, and poorly defined. On section, the outline was very sharp, the area somewhat more congested than on the outer surface and still moist. Histologically, there was little change except that the alveolar edema had almost disappeared and the thickening of the non-emphysematous alveolar walls was very well marked. Pigmentation had disappeared. A few capillaries showed conglutination, but in the vast majority the corpuscles were discrete. Most of the larger vessels were normal, but a few showed organization of thrombotic masses.

Throughout this series it was noted that the lodgment of seeds in those vessels whose terminals were directed toward a lung surface rather than an edge produced no noticeable change in the lung. The occlusion of vessels whose terminals were directed toward an edge or an angle of the lung almost invariably produced the changes indicated.

Conglutination was found histologically in most of the cases, but no subsequent changes were noted except slight hemolysis.

To summarize, it may be said that while an embolus of sufficient size produces definite and progressive circulatory and tissue changes in the lung, embolism is not in itself a cause of true infarction where one considers hemorrhage and necrosis as the criteria. Pallor of the embolic area was rapidly followed by congestion, swelling, and edema. These changes were followed histologically by granular pigmentation, emphysema, and fibrosis of alveolar walls.

Bland embolism and subsequent ligation of bronchial arteries. — In this series the dogs were killed one, five, seven, and fourteen days and four weeks after operation.

Grossly and histologically the changes were much the same as those formed in Series I. except that congestion and edema were not so well marked either grossly or histologically. Emphysema was more prominent in the microscopic sections and the changes observed in the areas extended as far as the pleura instead of leaving a marginal area of normal lung tissue.

Bland embolism and subsequent ligation of pulmonary vein. — In this series the dogs were killed three, six, twelve, and twenty-four hours, two, four, and seven days, two, three, and four weeks after operation.

In the earlier cases, including the twenty-four-hour animal, the gross appearance of the area of embolic circulatory disturbance was the same as that seen in Series I. at the same periods except in size. As a result of the ligation of the vein, the congested lobe was considerably larger than

normal and the embolic area measured three to four centimeters along the edge and extended approximately the same distance into the lung. Definition, swelling, color, and character of cut surface were the same as in the earlier series. By contrast with the deeply congested lobe the areas appeared lighter in color, but on comparison with areas in non-ligated lobes of the same lungs the color was found to be the same under both conditions.

At the end of two days, however, true infarction had developed. The area was sharply defined, elevated, solid, and of a very deep red, almost black color. On cut surface, it bulged slightly, was of the same color, sharply defined and of the texture and degree of dryness of a freshly cut relatively old blood clot. The non-infarcted portion of the lobe showed edema in addition to the congestion.

At the end of four days no gross change had occurred, but after one week the cut surface showed numerous dry, gray areas of necrosis, generally circular, situated near the middle and measuring one to two millimeters in diameter. At two weeks the necrosis was more extensive and still centrally distributed.

In three weeks the lobe had regained its normal size and grossly showed nothing but rich pigmentation. Correspondingly the infarct was smaller, measuring two centimeters along the edge of the lobe and extending fifteen millimeters into the lung substance. The infarct was firm, of the usual shape, distinctly and abruptly depressed, smooth and of a deep slate color. On cut section it was well defined, slightly depressed, moist and of the same slate color, except that near the center was a small relatively dry, slightly protruding area, yellowish white in color and of pulpy consistence. The plate colored peripheral portion had a gelatinous sheen. At the end of four weeks no further gross changes had appeared.

Microscopically, the sections from animals killed before and including twenty-four hours showed almost the same appearance as in the non-ligated lobes and in Series I., the chief differences being the fact that the circulatory disturbance

extended as far as the pleura, there was relatively little edema, but considerably more alveolar and interstitial hemorrhage when the venous outflow was obstructed. The non-infarcted lung showed much congestion and moderate edema. By the end of forty-eight hours, the hemorrhage had become very extensive, involving the entire lobe. In the infarcted area, however, it was extreme, the blood being packed tightly into the alveoli and markedly conglutinated, but this great degree of hemorrhage did not appear about the peripheral part immediately underlying the pleura, in which position, as with the earlier series, there was considerable emphysema. Desquamation of alveolar epithelium was moderate in the non-infarcted as well as the infarcted area, but in this period neither pigmentation nor phagocytosis was observed.

Numerous areas were found in the infarct where the alveolar walls and their nuclei had disappeared, but no such necrosis was observable grossly. The larger septa showed no degenerative changes and the large vessels although containing thrombi, both fibrinous and conglutinative, showed well preserved walls. The bronchi were filled with blood and fibrinous clot, but the epithelium remained normal. By the end of four days the densely packed hemorrhage had extended as far as the pleura, there were numerous fine golden yellow granules of pigment in the blood masses and edematous fluid and the large mononuclear phagocytes were filled with this pigment, but they appeared to show no migration to the lymph spaces. Conglutination was advanced and necrosis of the alveolar walls was emphasized by well marked karyorrhexis. Leucocytic infiltration was found in moderate degree about the margin between infarcted and non-infarcted lung, beneath the pleura and about the large vessels within the infarcted area. Most noticeable at this stage was the active connective tissue proliferation in the same regions as indicated for leucocytosis. Nuclear figures were found in all three regions, but were most frequent beneath the pleura, in which position also endothelial proliferation and new capillary formation were most marked.

The non-infarcted lung also showed connective tissue proliferation of less activity about the large vessels and under the pleura.

By the end of a week little change was to be seen except that leucocytes, fibrosis, and necrosis were more marked and decolorization of the blood masses appeared in circumscribed areas near the middle of the infarct.

At two weeks central decolorization was well marked, granular pigmentation was evident at the margin of the decolorized areas, and the fibrosis was considerably more marked than in the earlier infarcts. Nuclear figures in the connective tissue were less noticeable than in the four-day infarcts. Necrosis was complete in the central areas at this time. Edema had entirely disappeared.

At the end of three weeks the fibrosis had invaded the entire infarct except for a small area near the center, where open air spaces with heavy fibrous walls appeared. It evidently was this area which gave the gross appearance of necrosis in contrast to the more gelatinous connective tissue about it. Nuclear figures were still to be found, but were infrequent. A moderate amount of anthracotic pigment was present, but most striking was the rich hematogenous pigment present in macrophages scattered throughout the area but most marked near the periphery. The connective tissue of the pleura had become hyalin. The bronchi showed organization of the blood masses within them, numerous large macrophages containing blood pigment, but almost complete preservation of the epithelium.

At four weeks no other changes had appeared that were clearly distinguishable.

Bland embolism and artificial pleural effusion. — In this series the animals were killed at six, twelve, twenty-four hours, two and four days after operation. Other animals died eight, nine, ten, and eighteen days after operation. It seemed impossible to keep the animals of this series alive a longer time because of the serious disturbances of nutrition following the injection of the oil.

Six hours after the operation the areas of embolic disturbance of circulation, in keeping with the reduced size of the compressed lung, were smaller than in Series I., usually extending about fifteen millimeters along the edge and the same depth into the lung tissue. The lungs were moderately congested and the embolic areas were seen as well defined pallid areas without elevation; the cut surface showed the same appearance and was moist. In the course of twelve hours, however, the areas were somewhat more congested than the surrounding lung, slightly swollen, and slightly bloody on cut section. No gross change was observed until the end of four days when the area was found to be of slaty blue color, sharply outlined, firm and depressed; on cut surface of same color, well defined, moist, slightly depressed. At the end of eight days the area was relatively smaller and on cut surface distinctly drier than the surrounding lung. In ten days, however, there was a splotchy central decolorized area which was drier than the surrounding infarct. At the end of eighteen days the central necrosis was more marked, but the infarct showed no other observable gross change.

Histologically, the production of infarction was not seen until eight days had elapsed. Before that the areas showed partial or complete collapse of alveoli, well marked capillary congestion, slight edema and moderate interstitial and alveolar hemorrhage. Conglutination was prominent and after twenty-four hours blood appeared in masses in the bronchi. At the end of eight days, however, the area was packed with conglutinated blood, the alveolar walls were well preserved, there was considerable pigment within the alveoli and a small amount within the alveolar walls, sometimes free, but usually within macrophages. The connective tissue of the pleura showed moderate proliferation as did also that around the large bronchi and blood vessels. No nuclear figures were found, probably because the animal had been dead for several hours before autopsy. After ten days the most notable change was the refilling with air of some of the centrally disposed air sacs, which showed markedly thickened walls. The blood near the center showed moderate

decolorization. Most noticeable, however, was the moderate leucocytic infiltration and extensive connective tissue proliferation, similar to that seen at the end of one week in Series III.

At the end of eighteen days no additional changes were found.

Discussion. — In reviewing the entire investigation, it can be seen clearly that simple embolism does not produce pulmonary infarction and that the added disturbance of bronchial circulation caused by ligating the upper branches of the thoracic aorta makes no change in the result. The pleural vessels are unaffected by the embolism and just as with the capsule of the spleen and kidney the vascular supply of the organ near the surface continues. It is only by slowing the circulation considerably as by the ligation of the pulmonary vein or by compressing the lungs that the infarction puts in its appearance. Granting that the artificial " effusion " produces less circulatory stasis of a given lobe than the complete ligation of its draining vein; and noting further that with the former procedure the infarct is not evident for from four to eight days, whereas with the latter it appears in forty-eight hours, it would seem assured that the degree of stasis is an important factor in the production of the lesion. Hence it may safely be said that not only is stasis a necessary corollary of the infarct, but also the greater the degree of stasis the sooner is the true infarction likely to appear. The length of time that elapses before hemorrhage becomes prominent would indicate that the pressure in the congested area is not such an important factor as the increased permeability of the vessel walls; which, since it appears at least several hours after the obstruction to venous drainage is produced, is most probably of degenerative origin. As in the kidney and spleen the hyperemia and hemorrhage appear in the order named. In the spleen hemorrhage appeared at four hours, in the kidney from twenty-four to forty-eight hours, and in the lungs at about forty-eight hours. The degree of capillary congestion in the embolic areas is about the same in both

normal and congested lobes, but the capillary congestion is far more important in the lungs than in the kidney. Conglutination, prominent in the capillaries of the kidney and spleen, was by no means so prominent in the pulmonary capillaries.

Edema, both alveolar and interstitial, appeared in three hours and in the simple embolic process as well as in the lungs with additional ligation of the bronchial arteries, persisted to the end of the observation, becoming less marked as time passed. In the infarcts it disappeared in from one to two weeks, probably as a result of the extent and severity of the hemorrhage.

Simple embolic disturbance of circulation resulted in swelling of the alveolar epithelium at the end of three hours, which at six hours was followed by desquamation. In the cases where the pulmonary veins were ligated and in the cases where artificial effusion was produced, desquamation appeared at three hours. Fibrin formation was not evident before twelve hours, at which time it was found to be independent of the hemorrhage. Necrosis was not observed in the simple embolic process or with the added ligation of the bronchial arteries. In the true infarcts necrosis appeared in the alveolar walls at the end of forty-eight hours and became more extensive as the condition progressed, but did not invade the larger connective tissue septa carrying the bronchi or large vessels. Throughout all the series the bronchial epithelium remained well preserved. The gross evidence of necrosis appeared much later than the microscopic. Necrosis in the lung appears later and progresses less rapidly than in the spleen and kidney.

The tissue reactions in the simple embolic areas were not marked. At the end of three weeks there was a noticeable thickening of the alveolar walls near the larger connective tissue septa. Marginal hyperemia and leucocytosis were not noted. In the case of the true infarcts, however, there was seen at four days a well marked leucocytosis and fibroblastic reaction in the connective tissue of the pleura, in the line of demarkation of the infarct and in the larger septa

within the infarct. Nuclear figures were clearly evident and the process continued most actively, so that at the end of four weeks organization was practically complete.

At two days, and more especially at four days, granular pigmentation appeared in all the series studied, much more markedly, however, in association with ligation of the pulmonary veins and with "effusion." Much of the pigment was in the bodies of mononuclear phagocytes apparently endothelial leucocytes. Pigmentation and phagocytosis of pigment are much more marked in the lungs than in kidney and spleen, probably because of the greater hemorrhage in the lung.

Decolorization of the infarct began to appear both histologically and grossly at the end of one week as small irregular areas situated near the center of the infarct and later fusing so as to produce a large pallid central zone. The central zone of decolorization was not seen to reach the margin of the infarct at any time, almost certainly because the rapid ingrowth of connective tissue, with its richly pigmented macrophages prevents marginal decolorization. The depraved condition of human patients with pulmonary infarction probably prevents such rapid organization, hence the complete pallor of old human pulmonary infarcts. The decolorization of the pulmonary infarcts appears later than that of the kidney and spleen infarcts, progresses more slowly and is never so complete. Essentially, however, it seems to be the same process in all three organs.

Although organization is rapid, there is no evidence of any attempt whatever at regeneration of either the alveoli or bronchi, the latter at no time showing any evidence of marked destruction. There was central emphysema in the infarcts of four and five weeks, apparently an opening up of old alveoli that had not completely undergone necrosis. This, however, cannot be regarded as a true regenerative process.

CONCLUSIONS.

1. Simple bland embolism of the pulmonary artery produces definite circulatory changes in the lung area supplied,

provided this area extends along the sharp edge of the lobe and the embolus is of sufficient size, but no evidence of true infarction is to be found.

2. So far as technical limitations permit, occlusion of the bronchial arteries makes no change in the circulatory alterations following simple embolism.

3. In the presence of embolism in a lobe, ligation of the pulmonary vein of that lobe leads to the formation of a true infarct, regardless of the position of the embolus. Artificial pleural effusion influences the embolic process in much the same way as ligation of the vein.

4. Infarcts so produced show the same early congestion, conglutination of corpuscles and edema as are produced by simple embolism, these changes being followed by cloudy swelling and desquamation of alveolar epithelium, hemorrhage and necrosis, decolorization and organization, the last proceeding from pleura, large connective tissue septa in the infarct and marginal non-infarcted lung. Marginal hyperemia, if present, is concealed by the general congestion of the lobe.

5. The pallor of the older infarcts is due to necrosis and decolorization of the contained blood; decolorization begins, in a general way, in the middle of the infarct and proceeds peripherally; decolorization is due in part to breaking up of the blood pigment, phagocytosis, and peripheral transportation, and probably in part to plasmatic diffusion.

6. Organization progresses rapidly, but no evidence of true regeneration is to be found.

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