TABLE I.

Summary Table Showing Type of Corneal Injury and the Average Healing Time in Control and Amino Acid-treated Animals.

Expt. No.	Experimental injury	Treatment: Control	Treatment: Amino acid treated	No. of Animals	Healing time*: Control eye	Healing time*: Treated eye
	Guinea pigs					
1,a	Vertical 2 mm. erosion	Physiol. saline hourly	Amino acid soln. hourly	18	64(55-108)	22(15-32)
1,b		5% boric acid ointment twice daily	5% boric acid ointment containing amino acids twice daily	18	78(66-120)	26(12-42)
2	Round erosion. 3.5 mm	physiol. saline hourly	Amino acid soln. hourly	6	62(50-112)	21(14-38)
	Rabbits					
3,a	Deep non-perforating trephine wound	,, ,,	,, ,, ,,	2	95(86-104)	35(28-42)
3,b		5% boric acid ointment twice daily	5% boric acid ointment containing amino acids twice daily	10	108(96-120)	40(32-56)

* The first figure gives the average and the values in parentheses the minimum and maximum values of the individual experiments.

forating trephine wounds of the cornea was examined. In 12 rabbits a central defect 2.5 mm in diameter and 0.4 mm deep was made into the substance of the cornea of both eyes. The right eye was treated in 2 animals (3,a) with hourly administration of drops containing amino acids while the left eye received saline solution. The other animals received ointment applications as in the first experiment (3,b).

In the eyes treated with amino acids, the corneal defect was covered with epithelium within 32 to 56 hours and in the control eyes between the 4th and 5th day. The biomicroscopic parallel with the histological examination showed that in the amino acid-treated eyes the same phase of the healing process is reached after 2 days which the control eyes reached only after the 6th day of experiment.

The results of treatment of over 100 clinical cases in man with the same ointment will be published elsewhere. Although it is difficult to evaluate these data quantitatively since the ointment was never applied alone, it would appear that the application of amino acids accelerates the healing of corneal wounds particularly when ulcerative processes are involved.

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Accidental Air Embolism and Fibrin Formation in the Heart of Rabbit.

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During operations on the spinal column, cord and skull, a number of rabbits died more or less acutely and their death was at first attributed to that diffuse symptom-complex "vascular shock." Autopsies, however, soon revealed cleaner factors that played an undoubted rôle in the fatal outcome; gas bubbles were seen in the pulmonary artery associated at times with fibrin formation in the heart, especially in the right ventricle.

The danger of air embolism during operations on the neck and chest, because of negative intra-thoracic pressure, is well known[1] though possibly not fully appreciated and we shall show that this danger also exists for operations on the skull. The experimental and clinical literature contains numerous reports of air embolism following the injection of air or oxygen into various cavities and spaces of the body.[2] It will be further shown that fibrinous masses may develop acutely in the heart during air embolism; this observation has only been reported once before as far as we know: Richardson, Coles and Hall[3] observed occasional flecks of fibrinous material around the chordae tendineae of the right ventricle, and in 3 cases saw a friable clot of blood and air that possibly acted as a ball valve against the pulmonary artery; these investigators used nembutalized dogs and injected air into a femoral vein.

Although Kleinschmidt[4] has published an excellent experimental study of air embolism in rabbits, we shall report our own findings because Kleinschmidt and other experimenters injected air intravenously, while our work deals with air embolism following operations on the skull and spinal region.

Technic. The rabbits were generally narcotized by the subcutaneous injection of 150 mg of sodium barbital per kilo and operated 30 to 45 minutes later; in a few instances morphine or ether was used. The chief operations were tracheotomy; exposure of the thoracic spinal column and cord; transection of the cord combined at times with pithing below the site of transection; exposure of the diploic veins in the parietal bones or removal of the outer lamella of the squamous portion of the occipital bone. In some series, the vagi were sectioned in the neck; in others they were left intact. Inspiratory dyspnoea was often produced for short periods by an ordinary flap-valve slipped over the tracheal cannula. In the curare experiments, artificial respiration was given at the rate of 30 per minute. The blood pressure was recorded by a mercury manometer in a number of experiments.

If the animal succumbed acutely, an autopsy was carried out at once; otherwise a biopsy was performed 30 to 55 minutes after the operative interference.

Experimental Results. Cord operations were carried out on 28 rabbits. In 22 both vagi were cut and 11 died acutely; 8 of these 11 rabbits revealed air bubbles in the pulmonary artery; the remaining 11 rabbits were biopsied and one showed both air bubbles in the pulmonary artery and a good amount of fibrin in the right ventricle; a second rabbit revealed no air bubbles but both ventricles showed some fibrin shreds. In 6 rabbits, the vagi were left intact; none of these died acutely but a biopsy revealed air in the pulmonary artery of 2. Thus 11 out of 28 rabbits showed air bubbles in the pulmonary artery.

Skull operations were performed on 9 rabbits and the vagi were cut in all. Acute death occurred in 4 and 3 of these showed air bubbles in the pulmonary artery. Biopsy was necessary in 5 and 2 of these subacute cases showed air bubbles in the pulmonary artery. In one interesting experiment, both vagi cut, air bubbles were seen coursing through the exposed diploic veins of a parietal bone during deep inspiration. Biopsy was performed 27 minutes after the air was seen entering the diploic veins. At that time, the blood pressure was 80 mm Hg and the respiration 172 per minute. On opening the chest in the midline, the heart was beating powerfully and regularly, the pulmonary artery was distended by air bubbles and the right side of the heart was fuller than the left. Section of the heart revealed no air bubbles in the right atrium and ventricle, but the right atrium contained a small amount of fibrin while all other chambers were free of fibrin. It seems probable that this rabbit

[1] Coelen, W., in *Henke-Lubarsch Handbuch der speziellen pathologischen Anatomie und Histologie*, Berlin, Julius Springer, 1931, III, Part 3, 119.

[2] Reviews of experimental and particularly clinical cases: Breyfogle, H. S., *J. A. M. A.*, 1945, **129**, 342; Wolffe, J. B., and Robertson, H. F., *Ann. Int. Med.*, 1935, **9**, 162.

[3] Richardson, H. F., Coles, B. S., and Hall, G. E., *Canadian Med. Assn.*, 1937, **36**, 584.

[4] Kleinschmidt, O., *Arch. f. Klin. Chirurgie*, 1915, **106**, 782.

would have recovered.

In this series, 5 out of 9 rabbits showed air bubbles in the pulmonary artery.

Cord operations under curare and artificial respiration were studied in 16 barbitalized rabbits; the vagi were cut in 6. In this series, only one rabbit out of 16 showed air bubbles in the pulmonary artery and this exception was probably caused by imperfect curarization. No fibrin was found in any heart.

Fibrin Networks in the Heart. In a number of rabbits dying acutely or biopsied 30 minutes more or less after the operative procedure, a fibrin network was noted in the right ventricle, though it also occurred in the right atrium and sometimes in the left ventricle. The amount of fibrin varied considerably. In one extreme instance the elastic, reddish or reddish-black network interlaced the papillary muscles and chordae tendineae of the right ventricle practically filling this cavity and a portion extended up to the pulmonary artery; in most instances, however, the amount was much less. When fibrin occurred in the left ventricle, it was present only as a thin film.

In the series of 16 acutely fatal cases, 10 revealed fibrin in the heart; in 2 or 3 of these 10 fibrin-containing hearts, no air bubbles were detected, but air bubbles were seen in the other 7 hearts. The vagi had been cut in all 16.

In 21 subacute experiments, fibrin was found in the heart of 7 cases and in 4 of these no air was seen in the pulmonary artery; the remaining 3 showed air in the pulmonary artery. In 3 instances, fibrin was found in both ventricles without any sign of air. One rabbit (vagi intact) showed air bubbles but no fibrin; the remaining 13 rabbits (vagi cut in 9, intact in 4) showed neither air nor fibrin in the heart.

An instructive accident demonstrated that air embolism could produce the formation of fibrin in the left ventricle only. This happened when the lung alveoli were ruptured during artificial respiration. Immediate autopsy showed air bubbles in the aorta, carotid and mesenteric arteries, but no air was seen in the right side of the heart and pulmonary artery. In this heart, the left ventricle showed fibrin, while the right ventricle contained none.

Since the right ventricle occasionally contained definite fibrin networks, it might be assumed that particles could be dislodged and finally plug some of the small subdivisions of the pulmonary artery. No definite signs of embolism, however, were detected in the lungs of rabbits that died acutely or that were biopsied although these animals showed fibrin in the right ventricle. Very frequently section of the various lobes of the lung showed reddish to red-black polygonal areas that were a few millimeters in diameter; these congested areas were surrounded by larger, grayish-white areas that were full of air and were largely bloodless. Microscopic sections also gave no evidence of embolism. The time, however, between the formation of fibrin and acute death or biopsy was probably too short to permit adequate stasis for infarction to occur.

Pulmonary edema in the great majority of our experiments was slight and limited at times to one lobe. This is contrary to Kleinschmidt's results ([4] p. 798) who always found strong pulmonary edema; Richardson, Cole and Hall also report marked pulmonary edema ([3] p. 587).

Discussion. The recorded experimental results show unmistakably that air embolism during operations on the spinal column, cord and skull in heavily barbitalized rabbits is an ever-present danger and that this air embolism may cause acute death or a subacute state from which recovery probably could ensue. Thus in 37 spinal and skull operations, 16 rabbits revealed air bubbles in the pulmonary artery. It is therefore clear that the diagnosis "shock" as the cause of death in rabbits after operations on the skull, neck and chest should not be made until a careful autopsy has determined whether or not air embolism was the primary factor. This diagnosis, however, is rendered more difficult by the fact that the air bubbles may have been absorbed before the autopsy was made. Here a practically unknown sign is at times available that indicates the previous existence of air emboli and that is the presence of

fibrin networks, particularly in the right ventricle. In our series, 7 rabbits showed fibrin networks in the heart without any detectable air bubbles.

It seems obvious that this fibrin must have been formed by churning of the air-blood mixture in the right ventricle during cardiac activity. Why every heart with air in the pulmonary artery did not show fibrin is probably due to a number of factors. If the air bubbles are promptly expelled into the pulmonary artery, no defibrination of the right ventricular blood can occur, and air in the pulmonary artery does not measurably obstruct the flow of blood according to Kleinschmidt ([4] p. 802). The longer the right ventricle is able to churn the blood-air mixture, the greater the chance of causing defibrination. If the amount of air is too large, right ventricular failure ensues, as is demonstrated by the bulging dark-colored right atrium and ventricle and the contracted, pink, and empty left atrium and ventricle. Posture of the body also is important; Kleinschmidt ([4] p. 791) states that air is expelled with greater difficulty when the apex of the heart is at a higher level than the base. Another factor is the coagulability of the blood; we attempted to correlate the coagulation times before and after the experiment with the appearance of fibrin in the heart, but our results in 10 experiments permitted no definite conclusion.

Our data do not permit a definite statement about the rôle played by section of the vagi in the production of air embolism because the number of controls with vagi intact is inadequate; it seems, however, that section of the vagi is not a vital factor. Acute death, however, was more frequent in the cord series of 28 rabbits when the vagi had been cut.

Summary. 1. In barbitalized rabbits subjected to operations on the spinal column, cord and skull, air embolism is not a negligible danger; 14 out of 37 rabbits showed air bubbles in the pulmonary artery. Acute death after such operations in the rabbit must not be diagnosed as "vascular shock," tacitly implying a nervous component, until a careful autopsy has excluded air embolism.

2. Air bubbles were observed entering and coursing through exposed sections of the diploic veins of the parietal bone during inspiration.

3. Absence of air bubbles in the right heart and pulmonary artery does not exclude air embolism for the air may have been absorbed. The diagnosis of air embolism may still be made if fibrin is found in the heart. Fibrin formation in the heart, especially the right ventricle, was seen 6, possibly 7, times when no air bubbles were detectable anywhere. Occasionally a slight amount of fibrin may also be detected in the left ventricle. Here apparently some air bubbles passed through the pulmonary circuit and entered the left ventricle. Fibrin may occur only in the left ventricle; this was seen once when artificial respiration ruptured lung aveoli and air entered the left heart and arterial system only.

4. No definite evidence of pulmonary infarction was seen in the lungs on macroscopic and microscopic examination. It seems probable that pulmonary infarction would have occurred had some of the animals been allowed to survive for longer periods of time.

5. Pulmonary edema was slight in the majority of our experiments.