Published February 1, 1905

THE TOXIC EFFECTS OF FORMALDEHYDE AND FORMALIN.

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Although the germicidal effects of formaldehyde and formalin have been in the last few years the subject of much discussion, yet the study of the action of these substances upon the animal economy has been practically neglected. Much of the literature on this subject is of little value because supported by insufficient experimental evidence, and because overhasty conclusions have been drawn. In the following pages I have collected the literature which bears most directly upon the subject of my paper. Wherever the term *formaldehyde* is used in this article, the gas formic aldehyde, CH_2O, is referred to. By the term *formalin* is meant a 40% solution of formaldehyde in water. The percentage of solutions relates to the amount of *formalin* in the solution. Thus a 10% formalin solution contains 4% of formaldehyde.

In the experiments, immediately after the death of an animal, brought about naturally, or induced by chloroform, ether or a blow on the head, the tissues were fixed in Zenker's fluid; in a few instances alcohol was used. In staining, eosin and haematoxylin were employed, supplemented when necessary by staining for fat with Sudan III, by Weigert's fibrin stain, and by polychrome methylene blue. When no special stain is designated, the description refers to the picture shown by eosin and haematoxylin.

The fixing action of formalin itself is to be remembered; and also that in consequence, a cell killed by contact with the chemical may histologically show no evidences of death.

I. CHANGES IN THE LUNGS AFTER INHALATION OF FORMALDEHYDE.

The following experiments were performed in a room of 5.5 cubic metres capacity. A large door opening into the room was closed but

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no attempt was made to prevent the egress of the formaldehyde or the ingress of air through the keyhole, cracks in the door, etc. Formaldehyde gas was generated by slowly volatilizing paraformaldehyde pastils in a Schering disinfecting lamp. The lamp was set in the middle of the room, the animals being in a cage near the door. In all, nine animals were used.

Exp. 1.—A guinea pig and a rat were exposed for 1½ hours; 3 grm. paraformaldehyde volatilized.

Exp. 2.—A guinea pig and a rat were exposed for 3½ hours to an atmosphere in which 5 grm. of paraformaldehyde had been volatilized.

Exp. 3.—A guinea pig and two rats were exposed for 6 hours to an atmosphere in which 11 grm. of paraformaldehyde were slowly volatilized.

When removed, the animals were slightly dazed but otherwise apparently well. At post-mortem, forty-two hours later, the lungs of the animals were somewhat reddened. In the third experiment crepitation was slightly diminished in the lungs of all three animals. The bronchi contained a small amount of mucus.

Cultures were made from the nose, mouth, throat and lungs of each of the animals. In three of the animals micrococcus tetragenus was isolated from the mouth. A single colony of the same bacterium was obtained from the lungs of one of the guinea pigs. All the other cultures were sterile.

Histological examination reveals distinct inflammatory changes in the lungs of the animals. The lungs of the rat and guinea pig exposed for one and a half hours show marked congestion. Many of the alveoli are filled with a homogeneous red-staining exudate. Slight desquamation of the alveolar lining cells has occurred. Many polymorphonuclear leucocytes are found in the capillaries, in the connective tissue of the lung and free in the alveoli. The eosinophiles are numerous (Fig. 1). Mononuclear leucocytes are present but are few in number. The bronchi are filled with serum containing a few leucocytes and desquamated and degenerated bronchial epithelium. The deeper layer of the cells of the bronchi are still

attached to the basement membrane. In the peribronchial connective tissue many leucocytes are found. Numerous red blood corpuscles are mixed with the leucocytes in the alveoli and bronchi. The trachea shows no change.

In the two animals exposed for three and a half hours, the changes are more severe. The most striking difference is noted in the character of the leucocytic infiltration. Localized areas of pneumonia are found involving either a single alveolus or several alveoli; often these are peribronchial or perivascular (Fig. 2). The major part of the leucocytes which have accumulated are of the mononuclear variety. The polymorphous variety has also increased but not in proportion to the mononuclear variety. The number of leucocytes and alveolar epithelial cells in the bronchi is larger than in the foregoing experiment.

In the three animals exposed for six hours, the pneumonia is similar to that just described, but the process is more diffuse and involves large areas of the lung substance. A beginning tracheitis is found in the animals exposed for three and a half hours (Fig. 3), but in the last series of experiments this is more marked. The blood-vessels of the submucosa are congested and leucocytic infiltration has occurred. The latter is mainly eosinophilic. Many leucocytes are found between the epithelial cells lining the trachea. The epithelial cells themselves show slight degenerative changes, and are often desquamated.

Exp. 4.—A spaniel, wt. 25 kilo., was left for 5 hours in the before described room. The formaldehyde lamp was set on a high shelf and 5 grm. of paraformaldehyde volatilized in the course of the first half hour. The door of the room was opened several times. The slight dry cough present when the dog was removed from the room became moist in character several hours later. On the following day the animal coughed incessantly; and this coughing continued until the third day when the dog was bled to death.

Exp. 5.—A large cat was allowed to run about in the room while 250 cc. of methyl alcohol were oxidized to formaldehyde in a Moffat lamp. Time, 2¾ hours.

At autopsy the lungs are less crepitant than normally, œdematous, and float low in water. Small areas of consolidation are scattered through the lung substance. The bronchi are filled with a greyish, creamy mucus. The trachea is covered with mucus.

By histological examination a diffuse pneumonia, with here and there areas of more intense infiltration, is found to be present in the lungs of both animals. There is general vascular congestion. In the dog the blood-vessels contain an enormous number of eosinophiles and other polynuclear leucocytes. Only rarely can a mononuclear leucocyte be found. In the cat the polymorphonuclear leucocytes are much less in evidence, and the mononuclear forms are predominant. Many of the alveoli are filled with a homogeneous red-stained exudate. This is most marked in the cat in which over half of the alveoli are filled. The leucocytes are mainly of the polymorphous variety, and are most numerous in the walls of the alveoli. The alveoli themselves contain leucocytes and large epithelioid cells which probably represent desquamated alveolar epithelium. The bronchi are filled with large numbers of leucocytes, broken down bronchial epithelium, and granular detritus. The superficial lining cells of the bronchi are swollen and stain poorly; the cellular reticulum is loosened and the cells have lost their sharp contour. The nuclei are swollen and stain palely. Between the cells are found many leucocytes. Desquamation is common, and, when severe, the submucosa is entirely uncovered. In the submucosa and in the peribronchial connective tissue large numbers of leucocytes are found. A more severe bronchitis is found in the dog than in the cat.

It can at once be seen that my observations are directly opposed to those of Aronson, Phuhl, Rosenberg, Fairbanks, Grawitz, Babes, de Schweinitz, Kobert and Moeller, all of whom conclude that formaldehyde produces no effects upon the animal economy.

Aronson (1) subjected several white mice and a rabbit to the vapors of formaldehyde and found, after twenty-four hours, that the animals were alive and well. A histological examination showed no tissue changes. Fairbanks (2) found the same true of rabbits and mice

which he had subjected to formaldehyde inhalation for twenty-five hours. De Schweinitz (3) kept a calf in a 2% atmosphere of formaldehyde for five hours, and beyond a slight watering of the eyes and an occasional cough, could find no deleterious effects. Kobert (4) found that guinea pigs permitted to run loose in a room during formaldehyde disinfection did not become sick. Moeller (5) allowed six guinea pigs to run about in rooms which were disinfected upon four consecutive days. After that time he found the animals lively and well and they remained perfectly well thereafter. Doty (6) could find no tissue changes in insects, fowls, guinea pigs, mice, etc., subjected to formaldehyde gas for periods of from three to fifteen hours; occasionally a guinea pig would show a slight inflammation of the respiratory tract.

Klipstein (7) allowed two rabbits to inhale formaldehyde gas from a heated formalin solution. The first of these inhaled the gas for one-half hour; the other for one-half hour on three consecutive days. The post-mortem examination showed rhinitis, laryngitis, tracheitis and catarrhal bronchitis. These changes were more severe in the second animal. A muco-purulent material was found in the bronchi. The lungs were normal. Except for the last statement these findings agree with those in my experiments.

Harrington (8) has found that cats and dogs accidently confined in rooms undergoing disinfection rarely survive the process. As proof he cites two experiments of his own, and refers to the experience of several persons daily engaged in house disinfection. Likewise, Francis, of the health department of St. Louis, Mo., several times put rats into rooms undergoing disinfection. Except in one instance they were all killed in one and a half hours. Two guinea pigs, likewise experimented upon, remained well. The death of the investigator Staub has been attributed to the inhalation of formaldehyde.

Schlossman has worked with a combination of glycerine and formalin (glyco-formol) and urges the necessity of wearing a gas mask when entering a room in which disinfection has been performed.

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II. INJECTION OF FORMALIN INTO THE STOMACH.

Formalin was injected directly into the stomach by means of a soft rubber catheter introduced through the oesophagus. The symptoms following the injection of formalin differed in the different animals. In all, eleven animals were used.

Exp. 1.—Rabbit, wt. 500 grm. Injected 8 cc. of concentrated formalin. The animal falls upon its side and expires in five minutes.

Exp. 2.—Rabbit, wt. 500 grm. Injected 4 cc. of 10% formalin. The animal died immediately.

Exp. 3.—Rabbit, wt. 510 grm. 6 cc. of 10% formalin were injected. The animal died in one minute.

Exp. 4.—Rabbit, same wt., size and age as preceding. Injected 6 cc. of 10% formalin. The rabbit loses weight rapidly and dies in three and a half days.

Exp. 5.—Kitten, wt. 902 grm. Injected 5 cc. of 10% formalin. Catheter was bitten in half on withdrawal, and a few drops of the formalin got into the mouth. Death ensued in one hour.

Exp. 6.—Kitten, same wt., size and age as preceding. Injected 1 cc. of 10% formalin. On the following day the kitten has developed an intensely foul breath which continues to the day of death, three and a half days later.

Exp. 7.—Kitten, wt. 1021 grm. Injected 3.5 cc. of 10% formalin. Death occurs on the ninth day after the injection of the formalin.

Exp. 8.—Rabbit, wt. 1380 grm. Injected 8 cc. of 5% formalin. Death occurs in six days.

Exp. 9.—Terrier, wt. 53 kilo. Injected 17 cc. of 5% formalin. After a minute the dog vomited a frothy mucus which had a strong odor of formalin. After half an hour the animal becomes quiet. Death occurs in forty hours.

Exp. 10.—Kitten, wt. 980 grm. Injected 3 cc. of 10% formalin. The kitten is killed three weeks after the operation, in which time it has grown and gained in weight.

Exp. 11.—Rabbit, wt. 1401 grm. Injected 6 cc. of 5% formalin. The animal ate and increased in weight. After a month it was killed.

On post-mortem examination no macroscopic changes except a reddening of the mucous membrane of the stomach and duodenum are

found in the animals that died immediately after the injection of the formalin. Histologically, only an intense vascular congestion exists.

The stomach of the rabbit in the fourth experiment contains only a few drops of a turbid liquid. The mucous membrane is grayish, soft, and can be easily scraped off; the pyloric end of the stomach is ulcerated. The intestinal tract is empty, except the caecum, which is filled with a soft, brownish, gruel-like material.

Histologically, the serosa and the muscularis show no change. The submucosa has undergone loosening so that the connective tissue fibrillæ are widely separated from each other. The blood-vessels are markedly congested, but no haemorrhages have occurred. There is only a slight leucocytic infiltration. An increase in the staining reaction of the gland cells is the most striking change noted in the mucosa; all the cells are more deeply colored with haematoxylin than normally, and in the late stages of degeneration they stain a uniform, deep purple. The changes are more severe upon the rugæ than in the tissue between them. In the latter locality the cells are swollen and granular. The outlines of the cells are lost and the nuclei are irregular in shape. The peptic cells are swollen, granular, and stain red with eosin. Upon the rugæ the glandular cells are contracted. Many of the nuclei are lost, while those remaining are misshapen beyond recognition. Desquamation of the gland cells is everywhere present. At the top of the rugæ desquamation of all these cells has occurred, so that the gland cells are represented by a deep purplish-staining detritus within the connective tissue casing of the tubules. Many of the tubules are widely distended with necrotic matter. In some places only the intertubular connective tissue is found remaining. Areas are found in which a total loss of the mucosa has taken place, exposing the bare submucosa beneath. The large ulcer seen with the naked eye is found to be due to such a loss of the mucosa.

The stomach of the dog in Exp. 9 contained a few cubic centimeters of a turbid fluid similar to that found in the stomach of the rabbit just described. The mucous membrane was similarly gray and soft.

The histological findings are similar to those previously described, but the more deeply stained glandular cells extend only half way down the tubules. The cells are separated from each other, and a well-marked desquamation is present. A marked infiltration with polymorphonuclear and large and small mononuclear leucocytes has occurred. This is confined to the mucosa and submucosa. The changes, gradually diminishing in severity, extend through the duodenum into the small intestine for the distance of about a foot.

The kitten in Exp. 5, which died an hour after the injection of the formalin, showed the following changes on post-mortem examination. The mouth, pharynx and posterior nares are red and covered with mucus. The mucous membrane of the oesophagus is reddish in color and soft; and can be scraped off leaving a raw surface studded with red points. The stomach is filled with food from which emanates a strong odor of formalin. The mucous membrane is soft and reddish. All the vessels are markedly congested. Similar changes are found in the duodenum.

Histological examination shows a marked vascular congestion of the tissues of the mouth, pharynx and oesophagus. The connective tissue elements of the oesophagus are loosened so that the fibrillæ are widely separated from each other. No changes can be found in the epithelial cells. The congestion of the stomach and duodenum is very marked; in the latter location the separate capillaries can be traced to the tip of the villi. The glandular elements show no change. An acute oedema, manifesting itself by exudation into the submucosa, has occurred and in consequence the stomach wall is the seat of an immense bleb. The exudate makes up about half the thickness of the wall, and is stained homogeneously red. There is no leucocytosis.

In the stomach of the kitten in Exp. 6 are found 4 cc. of a dirty, turbid fluid. The mucous membrane is grayish, soft and can be scraped off easily. The stomach of the kitten in Exp. 7 is filled with a soft, pus-like material. The mucous membrane is grayish and soft; in some parts it has ulcerated. The mucous membrane of the

duodenum has a similar character. The gall-bladder is enormously distended with bile, and a bristle can with difficulty be pushed through the bile duct.

The microscopic findings in these two experiments are quite similar. In both cases we have to do with an intense gastritis. In the first of them the leucocytosis is most severe in the mucosa; the submucosa is also infiltrated with leucocytes, but in the muscularis only a few are seen. In Exp. 7 the inflammatory process involves the muscular tissue especially in those parts where the mucous membrane has ulcerated. The leucocytes present are mainly of the mononuclear variety; only a few polynuclear leucocytes are seen. The gland cells of the superficial parts of the mucosa are in various stages of disintegration. The infiltrating leucocytes show karyolysis and karyorrhexis. A granular, violet stained, necrotic material, mixed with mucus and broken down nuclei is found lying upon the mucosa. The mucosa and submucosa of the duodenum in Exp. 7 is the seat of marked inflammatory changes. This probably brought about an atresia of the gall duct, and a consequent distension of the gall-bladder with bile.

By far the most interesting series of pathological changes are found in the rabbit of Exp. 8. The stomach contains about 8 cc. of a foul-smelling, brownish, gruel-like liquid. The mucous membrane is deeply red, mottled with smaller areas of white, and traversed by thick, firm ridges. The whole is covered by mucus mixed with a whitish necrotic material; when the hand is brushed over the lining of the stomach the mucous membrane is scraped off, and a raw surface studded with red points is left.

On histological examination the changes in the stomach wall are found to be irregularly distributed and of varying intensity. Desquamation of the serosa has occurred in some places. The connective tissue of the subserosa retains a distinct bluish tinge after staining with haematoxylin. The muscularis shows changes ranging from a slight inflammatory condition to total necrosis. In those regions in which the muscular coat is least affected the muscle cells are slightly

swollen and stain palely. Many of the muscle cells are entirely separated from their bundles, and are in various stages of degeneration. With these changes is found an infiltration of polynuclear and mononuclear leucocytes. The muscular layer is affected first on the side nearest the mucous membrane, whence the changes progress downward until the serous side of the muscularis is reached.

The submucosa is the seat of an enormous fibrinous exudate which varies in thickness in different parts of the sections; at one time the layer of fibrin is scarcely recognizable, at another it is three times as thick as the normal wall. The ridges mentioned in the anatomical description are entirely due to submucous fibrinous exudation. The exudate, especially in its deeper portions, contains many polymorphonuclear leucocytes; some mononuclear leucocytes are also found. The muscularis mucosæ shows changes similar to those of the muscularis. The mucosa shows a series of changes; in the least affected parts only a few swollen cells are found, but in the more altered parts there is slight desquamation and necrosis accompanied by leucocytic infiltration. The entire thickness of the mucosa is at times wholly destroyed; it is then found lying upon its basement membrane as a necrotic mass, stained in various ways from a light red to a deep purple. Large areas of haemorrhage into the mucosa and underlying fibrinous exudate are found; the blood-vessels are enormously distended and in places the walls of ruptured vessels are seen.

The stomachs of the animals in Exp. 10 and Exp. 11 were filled with food; and no macroscopic or microscopic changes were demonstrable.

The wide range in the character of the pathological changes has forced me to describe these experiments in detail. Briefly summarized, the histological findings in the eleven stomachs examined are as follows:

Intense vascular congestion in Exp. 1, 2 and 3.

Infiltration of the mucosa with leucocytes together with necrosis of gland cells in Exp. 4 and 9. The necrotic material is hyaline and stains deep purple with haematoxylin.

Intense vascular congestion with acute oedema of the submucosa in Exp. 5.

Gastritis involving the entire wall of the stomach, and characterized by marked leucocytosis, karyorhexis, and necrosis in Exp. 6 and 7. The necrotic material is granular and stained violet with haematoxylin.

Marked leucocytosis and necrosis in all the tunics of the stomach, together with an intense fibrinous and haemorrhagic exudation into the submucosa in Exp. 8.

No recognizable changes in Exp. 10 and 11.

It is evident that I failed in my attempt to get a series of experiments which would show a progressive increase in the severity of the pathological changes corresponding with a progressive increase in the strength and amount of formalin injected. Likewise the severity of the symptoms following the injection of formalin into the stomach is by no means proportionate to the strength or amount of the injected chemical; nor is there a definite series of symptoms following the injection of a definite amount of formalin of a definite strength. The results obtained in the first three experiments in this series lead me to class formalin with that rare group of poisons which are capable of producing sudden death when swallowed.

Other things being equal, it might be expected that the rapidity with which death occurs after the injection of formalin into the stomach would be influenced by the following conditions: The amount or strength of the chemical; the time of retention after ingestion (absence of vomiting); the condition of the stomach; whether empty or not and the size of the animal experimented upon.

How small a rôle these factors play may be judged from the following: Although the rabbit of Exp. 2 was heavier and received only two-thirds the amount of formalin that was given to the rabbit of Exp. 4, the first died immediately after the ingestion of the chemical, while the second lived several days. Similarly, although the rabbits in Exp. 3 and 4 were identical in size, weight and age, and were injected under the same conditions, with the same amount of formalin, one died immediately while the other survived several days. In Exp. 6 the injection of 1 cc. of 10% formalin proved fatal in three and a half days. In Exp. 7 the injection of 3.5 cc. of formalin of the same

strength was followed by an attack of vomiting, and the animal lived nine days. It might be concluded that the animal's life was preserved because the toxic agent was vomited. Contrary to this conclusion are Exp. 8 and 9, for while the rabbit in Exp. 8 lived six days after the ingestion of 8 cc. of 5% formalin, the dog in Exp. 9 survived the administration of 17 cc. of the same strength by only forty hours, even though the animal began to vomit almost immediately after the ingestion of the chemical.

That the weight of the animal is not an important factor is evidenced by the fact that the dog, weighing nearly fifty times as much as the rabbit, was unable to withstand a proportionately smaller dose. The presence of food in the stomach does not seem to influence the toxic action of the chemical. In Exp. 1 and 2 post-mortem examination showed the stomachs filled with food yet both died immediately after the injection of the formalin. The rabbit of Exp. 4 was kept for several hours without food. It survived the injection of formalin for several days, yet its fellow, kept under exactly the same conditions, died immediately after the operation. In Exp. 9, on the other hand, the rapid death of the dog might be in part at least attributed to the ready absorption of the chemical by an empty stomach, for the animal had been kept without food for twelve hours.

That small amounts of formalin when taken into the stomach are capable of producing deleterious effects upon the animal economy is evidenced by the experiments of Annett and Grady.

Annett (9) noticed in kittens fed with milk containing formalin, loss of appetite and diarrhoea with noisy, gaseous motions, gaseous distension of the abdomen and roughening of the fur; in some instances there were emaciation and death. The younger animals were most susceptible, and showed, in contradistinction to the control kittens, little increase in weight with increase in age. F. F. Grady, of the health department of Chicago, has obtained similar results.

III. INTRAPERITONEAL INJECTION OF FORMALIN.

In this series of experiments twelve guinea pigs, two rabbits and five dogs were used. The injections were made through the abdominal wall, under antiseptic precautions, by means of a hypodermic syringe.

The symptoms following the injection of formalin into the peritoneum are fairly constant, and vary in intensity according to the strength and the amount of the injected chemical.

The anatomical findings after intraperitoneal formalin injections are quite similar. After the injection of 1-1000 formalin, macroscopic changes cannot be discovered. Sometimes there is slight vascular congestion. Marked vascular congestion with slight exudation follows the injection of 1% formalin. The intestines are usually contracted, especially at the points where they rub against the abdominal wall or against each other. When undiluted formalin is injected an abundant inflammatory exudate accumulates. Two days after the injection of 3.5 cc., I withdrew 160 cc. of a turbid, bloody fluid from the abdominal cavity of a dog. After coagulation the coagulum constituted 70% of its bulk. In the second dog 140 cc. of ascitic fluid were found post-mortem three days after the injection of 2.5 cc.; 90% of the total volume was formed by the clot after coagulation of the fluid. In the abdominal cavity of a third dog 50 cc. of an intensely bloody fluid were found eight days after the injection of 4 cc. of undiluted formalin. Histological examination of the ascitic fluid reveals desquamated epithelium, red blood corpuscles, large numbers of leucocytes and granular detritus.

The intestines after the injection of undiluted solutions are usually contracted. At the points of irritation are found ecchymoses varying in size. When these are of a mild grade they appear as delicate, subserous, reddish-brown or purple lines running parallel with the long axis of the gut. In the severer cases the entire thickness of the intestinal wall is soft and blood-soaked. Those parts of the intestinal tract which are protected by the omentum or by mutual contact may suffer but slightly in the destructive process, but the omentum may suffer severely. Slight ecchymoses are present in several of the ani-

mals even after the use of 1% solutions. When undiluted solutions are employed the fat columns of the omentum are seen as dark red, boggy masses of clotted blood. The parietal peritoneum shows changes similar to those described above. In one of my dogs extravasation of blood was present through the entire thickness of the abdominal wall. Fibrin is commonly found upon the omentum and mesentery, even when only dilute solutions (1-250) have been employed. In one of the dogs the pancreas was embedded in a fibrinous capsule. In another, fibrinous adhesions existed between all the pelvic viscera. The fibrin was always soft and oedematous.

The endothelial cells of the peritoneum after the injection of 1-1000 formalin, swell, show nuclear degeneration, and are loosened from the basement membrane. Sometimes single cells are found lying upon the connective tissue; at other times small plates of endothelial cells are found in process of desquamation. The muscularis is contracted and its nuclei compressed. In the outer muscular sheath the number of nuclei are diminished. Leucocytic infiltration, mainly polynuclear, has taken place into the serosa and between the layers of the muscularis; it is also found well-marked in the connective tissue of the submucosa. The mesentery is similarly infiltrated. Marked vascular congestion prevails.

Solutions of 1-250 formalin produce similar lesions.

All of the above changes, occurring with greater severity, are found after the injection of 1% formalin. The pathological findings range from an intense inflammation to total necrosis. The connective tissue elements stain intensely red with eosin and show a loss of nuclei. The mucosa is often represented by a mass of blue stained, necrotic material. The submucosa is crowded with polynuclear, and large and small mononuclear leucocytes; the mesentery shows similar changes. Marked vascular congestion and extravasation of blood are general. Abundant fibrinous exudation into the mesentery was found in some of the sections.

The following histological changes in the intestine were found after the injection of undiluted formalin into the peritoneal cavities of dogs:

The peritoneal lining cells are entirely lost in some places; in others, a few poorly stained cells still adhere to the subserosa. The subserosa is hyaline and stained red; its nuclei are decreased in number, misshapen and fragmented. The nuclei of the outer muscular tunic are lost and the muscular tissue is bright red, brownish or purple in color. The same is true but to a less marked extent of the inner muscular layer. The cells lying nearest the supporting connective tissue always suffer the most. The submucosa shows a fairly well-marked leucocytic infiltration. The mucosa suffers only slightly. Only in the dog which lived ten days after the injection could leucocytes in any considerable number be found in the subserosa and muscularis. The parietal peritoneum suffers changes similar to those affecting the visceral.

The most striking feature in these cases is the intense haemorrhage; in some of the sections examined this occupies the entire thickness of the intestinal wall except the mucosa. Blood cells or blood pigment are so abundant that the tissues into which the haemorrhage has occurred are unrecognizable. Well-preserved red blood corpuscles and granular pigment are often associated in the same section; and while one part of the intestinal wall shows naught but red cells other parts may show nothing but blood pigment. The mesentery is in all cases the seat of fibrinous inflammation, often accompanied by profuse haemorrhage.

The peri-pancreatic and interlobular connective tissue of the pancreas of the dog before alluded to is the seat of an intense fibrinous inflammation; the fibrin is delicately fibrillar, and mixed with leucocytes and granular necrotic material formed from the neighboring pancreatic parenchyma. The changes in this organ diminish in severity as its more central portions are reached; here the cells are ill contoured, granular, and show evidences of nuclear degeneration.

The peritoneal fat suffers markedly under the action of formalin. Frequently the fat cells are found filled with purplish, hyaline material. At other times, instead of the changes described above,

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necrosis of fat cells has occurred and is accompanied by intense leucocytic infiltration. In the mesenteric fat, the deleterious action of the formalin most often manifests itself by the production of a fibrinous inflammation. Leucocytosis, karyolysis and karyorrhexis are often extreme.

The results of an experiment performed by Adler (10) agree well with my own. This investigator introduced several pith balls saturated with 4% formalin into the peritoneum of a rabbit. After twenty-four hours small ecchymoses were found on the surface of the colon where the pith cubes, surrounded by a soft, translucent, mucoid exudate had lodged. Microscopical examination of the cubes revealed polynuclear and large and small mononuclear leucocytes, plasma cells, " mastzellen," red blood corpuscles, tissue cells and epithelioid cells.

Borst (11) introduced fish bladders filled with blood into the peritoneal cavities of rabbits. When the bladders were sterilized in formalin and then washed in water, the usual cellular infiltration did not occur. This he believed to be due to a swelling of the cells in the fish bladder, or to a negative chemiotaxis exerted by the retained formalin.

The pancreatitis in one of my experiments is similar to the pancreatitis associated with fat necrosis which Flexner (12) produced in two dogs by injecting 2% formalin into the pancreatic ducts.

Experiments to determine the lethal dose of formalin introduced intraperitoneally were performed upon guinea pigs with the following result:

(a) Two guinea pigs died within two days after the injection of 1 cc. of a 1-1000 formalin solution for each 100 grm. of body weight.

(b) Five guinea pigs died within twenty-four hours after the injection of 2 cc. of 1-1000 formalin for each 100 grm. of body weight.

(c) One guinea pig, weighing 345 grm., died three days after the injection of 6 cc. of 1-1000 formalin.

(d) One guinea pig, weighing 306 grm., withstood the injection of 3 cc. of 1-1000 formalin; at the end of four weeks the animal weighed

400 grm., and withstood the injection of 8 cc. of formalin of the same strength.

(e) Four guinea pigs were killed by 2 cc. of 1% formalin in periods ranging from six to twelve hours.

IV. INJECTION OF FORMALIN INTO THE LUNG.

In these experiments slow injection through the chest wall was resorted to.

Exp. 1.—Guinea pig, wt. 405 grm. Injected 1 cc. of 1-1000 formalin into right lung.

Exp. 2.—Guinea pig, wt. 372 grm. Injected 2 cc. of 1-1000 formalin.

Both animals remained apparently well. The first was killed on the sixth and the other on the second day after the injection.

On post-mortem examination the lung on the injected side is not as perfectly collapsed as that of the other side, and on cross-section the lung tissue feels slightly granular.

Exp. 3.—Terrier. Injected 5 cc. of 10% formalin into right lung. After two days, during which the animal coughed from time to time, the dog was killed.

Post-mortem shows only the right middle lobe to be affected. This does not collapse, is firm, and does not crepitate; pieces of it sink in water. The cut section is brownish-red and from it drips a light, straw-colored fluid. In the center of the lobe is found a sharply defined red area the size of a dime. The bronchi contain thin mucus.

Exp. 4.—Terrier. Injected 3 cc. undiluted formalin into right lung. Death occurred in 18 hours.

On post-mortem examination the left lung is pink in color and crepitates throughout. The right lung is dark red, firm, non-crepitant, and sinks in water; from the cut section drips a bloody fluid. In the center of the lower lobe is found a cavity 2 cm. in diameter filled with a bloody, necrotic material.

Exp. 5.—Large cat. Injected 3 cc. of undiluted formalin into the right lower lobe. The animal died immediately.

On post-mortem examination a brownish-black solid area, the size of a small cherry, is found in the right lower lobe. The bronchi of the corresponding side contain bloody froth.

Histological examination of the lungs of the animals in the first two experiments reveals pneumonia on the right side. There is a

slight leucocytic infiltration of the alveolar walls, together with capillary congestion. Scattered throughout the lung substance, but especially common about the larger blood-vessels and the bronchi, are circumscribed areas of leucocytic infiltration. Here the alveoli are filled with eosinophiles, mononuclear and polynuclear leucocytes. Sometimes red blood corpuscles are found, but it is possible that their presence is due to the trauma consequent upon the hypodermic puncture. There is desquamation of the lining cells in some of the bronchi.

In Exp. 3 the pneumonia is much more severe. The dark area described in the anatomical findings is made up of red blood corpuscles, blood pigment and necrotic lung tissue. About this necrotic focus is a zone of intense leucocytic infiltration. Leucocytosis of a less severe type extends throughout the tissue of the affected lobe. About the blood-vessels and bronchi denser areas of infiltration are noted. The leucocytes are mainly of the polynuclear variety. Eosinophile and mononuclear leucocytes are comparatively rare. All the alveoli are filled with a homogeneous, red-stained exudate, mixed with leucocytes, strands of fibrin and desquamated alveolar epithelial cells. There is intense capillary congestion and the large vessels are also well filled. Extravasation of blood has occurred in many localities. The bronchi contain leucocytes, red blood corpuscles and necrotic material. Total loss of bronchial epithelium is a common feature of the bronchitis. The walls of the bronchi are oedematous and infiltrated with leucocytes.

The lungs in Exp. 4 show practically the same characteristics as those in the experiment just described. There is greater extravasation of blood and in places, actual breaks in the vessel walls can be made out.

In Exp. 5 the only discoverable change is a most intense capillary congestion. Except for an occasional red blood corpuscle the alveoli are empty.

V. SUBCUTANEOUS INJECTION OF FORMALIN.

Formalin, varying in strength from 0.1% to 10%, was injected under the skin of the hind leg, or under the skin over the ribs of guinea pigs and rabbits.

The histological findings were, in all cases, quite similar. They varied in severity and extent, with the strength and with the amount of injected formalin. The characteristic lesion is an intense exudation into the subcutaneous tissues. There is found underlying the skin a yellowish, jelly-like mass, from which when cut across drips a large amount of light straw-colored fluid. Such an exudate is most abundant eighteen hours after the injection of formalin, and may then be 3 or 4 cm. in thickness. Absorption of the exudate usually occurs in a few days, but may be markedly delayed when the formalin is not diluted. A marked proliferation of the connective tissue is concomitant with the absorption of the exudate.

The epithelial covering shows no changes. The exudate is stained red, and mixed with cellular debris, isolated connective tissue cells and leucocytes. All forms of the latter are present, but polynuclear cells, especially the eosinophiles, predominate in the specimens obtained soon after the injection. The number of connective tissue cells (formative cells) varies with the length of time that has elapsed since the injection, and with the strength of the formalin. Active proliferation of the existing connective tissue can be found on the second or third day after injection. When strong solutions of formalin have been used, proliferation is at first delayed, but once started, becomes excessive. A delicately fibrillar fibrin, differing in amount in the various experiments, is found scattered through the exudate. The blood-vessels are enormously congested.

VI. THE EFFECT OF FORMALIN UPON THE MUSCLES.

After the injection of formalin varying in strength from 0.1% to 100% into the leg muscles of dogs and rabbits, it is usually found at autopsy that the chemical has acted upon a circumscribed area of tissue. When strong solutions have been employed, the affected

muscle is brown in color, hard and dry, cutting much like a piece of dried bread. Exudation into the fascia usually takes place and soft boggy lines run through the dry areas. When dilute solutions are used the exudation is more severe, and the area of muscular tissue acted upon by the chemical is dark red and soft and from it drips a slightly bloody fluid. In one dog, I found within the muscular tissue fifteen days after the injection of 4 cc. of 10% formalin, a cyst containing straw-colored serum and a mass of clotted blood. The walls of the cyst had been formed by active proliferation of the connective tissue of the fascia.

Histologically, we have to deal with a myositis of varying severity. Between the muscular fibers dense aggregations of leucocytes are found. In specimens examined twenty-four hours after the injection of the formalin, infiltration is mainly of the polynuclear variety; in older specimens the mononuclears become very numerous. A homogeneous red-stained exudate often mixed with fibrin is found in the intermuscular septa. When a few days have elapsed since the injection of formalin, evidences of connective tissue proliferation manifest themselves. In the course of two or three weeks this becomes excessive. The muscular fibers are sometimes swollen, sometimes shrunken and wavy; they are hyaline and stain bright red. Total loss of nuclei and muscular striation is common. In many places segmentation of the fibers has occurred. Often, especially when strong solutions have been employed, the muscular fibers are shrunken and stain blue with haematoxylin; at other times the musculature stains a uniform deep purple. In these localities no leucocytes can be found. Any or all of the above conditions may be present in a single field of the microscope.

It is not necessary that the formalin be injected into the tissues in order that all the above changes may occur. Changes identical with those described occur in the musculature of the eyelids when formalin is dropped into the eyes, in the abdominal wall after intraperitoneal injections, or in the skeletal muscles after the chemical has been injected subcutaneously.

When formalin comes in contact with non-striated muscular tissue, changes similar to those observed in voluntary muscles result. In the intestinal wall, for example, after the injection of formalin into the peritoneum or into the stomach, the muscle cells are contracted, stain red with eosin or, if the destructive action has been more marked, purple with haematoxylin. A loss of nuclei is very common, and slight leucocytic infiltration is occasionally present.

VII. THE EFFECT OF FORMALIN AND FORMALDEHYDE UPON THE EYE.

Lacrymation and congestion of the conjunctival vessels are present in the eyes of all animals exposed to the vapors of formaldehyde. The intensity of these symptoms varies only slightly with the length of exposure, and seems to depend more upon the concentration of the gas to which the animals are exposed. The symptoms usually subside within twenty-four hours. Histological examination a few hours after exposure to the gas shows only vascular congestion.

The slight cloudiness and pupillary contraction which follow very soon after the injection of formalin, up to the strength of 1-500, into the anterior chamber of the eye, always pass off in a few hours. When a drop or two of a 5% solution are injected definite changes can be found after twenty-four hours. The anterior chamber becomes filled with delicately fibrillar, densely matted fibrin, with which polymorphonuclear leucocytes are mixed. These are most numerous in the angle between the iris and the cornea. The lining cells of the anterior chamber are swollen and often desquamated.

In three animals in which a few drops of 10% formalin were dropped into the eyes no changes except vascular congestion of the eyeball and eyelids resulted. For several hours after the introduction of the formalin there was intense lacrymation.

A single drop of undiluted formalin is sufficient to injure an eye permanently. The changes which result are generally as follows: Immediately after the introduction of the formalin there is lacrymation, blepharospasm and contraction of the pupil. After twenty-four hours the pupil is contracted to almost pin-hole size, and refuses

to dilate after the use of atropine. Intense oedema of the eyelids develops and prevents their closure; the cornea becomes dry and opaque. At the end of three days the lids become less oedematous and their margins may become agglutinated through fibrinous exudate.

The conjunctiva and cornea become infiltrated with leucocytes. In the angle between the visceral and parietal conjunctiva large collections of leucocytes are found; twelve or eighteen hours after formalin has been dropped into the eye the cornea is oedematous and its corpuscles show evidences of proliferation. About the canal of Schlemm there is intense infiltration with polynuclear leucocytes. The anterior chamber of the eye is filled with exudate stained homogeneously red with eosin and mixed with delicately fibrillar fibrin, and large numbers of leucocytes. The intensity of the process is subject to great variation.

As in the eye, the changes in the eyelids do not always give a definite reaction to a definite amount of injected formalin. When the reaction is but slight, there may be only well-marked leucocytic infiltration of the mucous lining of the eyelids; the muscular tissue may assume a brownish color after staining with haematoxylin and eosin; sometimes myositis is present. In very severe cases the mucous membrane is covered by a layer of fibrin, the blood-vessels are markedly congested, the tissues are oedematous, and between the necrotic cells are found masses of fibrin.

In addition to the local effects following the injection of formalin, pathological changes occur in the parenchymatous organs in consequence of the absorption of the chemical from the point of injection. These lesions will now be considered.

VIII. CHANGES IN THE LIVER.

Among the general changes produced by formalin in whatever way it is introduced into the body are those occurring in the liver. These consist essentially of cloudy swelling, varying in intensity associated with vacuolation of protoplasm and destruction of the nuclei; ultimately total destruction of cells may occur.

Changes in the liver may be noted after injections into the peritoneum of even dilute solutions. In guinea pigs after the injection of from 4 to 8 cc. of a 1-1000 solution, these changes are of a mild form; the liver cells are swollen, their outlines obscured and the protoplasm granular; the nuclei show no changes. After the injection of 1% solutions the changes are more severe. The columnar arrangement of the cells is partially lost and definite boundaries between the rows of liver cells cannot be distinguished. The cells are more swollen, the granulation is coarser than normal, and the cell outlines are entirely obscured; the nuclei in a few cases are somewhat crenated. The cells about the central veins stain more lightly than those at the periphery of the lobules. Accompanying these changes is a general vascular congestion; occasionally a leucocyte is found in the tissue.

Intraperitoneal injection of undiluted formalin into dogs results in the production of a diffuse cloudy swelling of the liver; the cells are swollen, the outlines lost and the protoplasm is granular. The nuclei are crenated and of bizarre shapes. Between the rows of liver cells are found a few polynuclear and mononuclear leucocytes. The interstitial tissue contains many nuclei and the blood-vessels are congested. These changes are noted from the second to the fourth day after the injection of formalin.

Subcutaneous injections of formalin are capable of producing only slight cloudy swelling of the hepatic cells. Severe changes cannot be found even after the use of strong solutions.

The most severe changes in the liver were noted in those experiments in which formalin was injected into the lungs or into the stomachs of animals, and after the inhalation of the vapors of formaldehyde. The changes under these conditions are very uniform; the columnar arrangement of the liver cells is almost entirely lost and the cells are enormously swollen, some of them having attained fully three or four times the size of the normal cell. The cellular outlines can rarely be distinguished and the protoplasm is greatly vacuolated and granular. The appearance of fatty degenera-

tion is produced, but the irregular contour of the vacuoles speaks against this view. The nuclei are somewhat swollen but have preserved their smooth contour in many cases; at other times the nuclei are crenated or bizarre in shape. Between the rows of liver cells are many polynuclear and occasionally mononuclear leucocytes. Figures simulating karyokinesis are found, but the exact nature of these I could not determine. It is possible that they represent broken down nuclei or polymorphonuclear leucocytes. An increase in the number of nuclei in the interstitial connective tissue is due either to cell proliferation or to infiltration with mononuclear leucocytes. The blood-vessels are filled with blood. The greatest leucocytic infiltration occurred in a dog into the lungs of which 10% formalin was injected.

A marked contraction of the hepatic cells associated with vacuolation, instead of the ordinarily observed swelling, is found in some of the specimens. In no case was I able to find an increased number of leucocytes in the liver sooner than forty hours after the injection of the formalin. In four of the animals which had inhaled formaldehyde I found areas of focal necrosis in the liver. Such foci are sometimes small and six or twelve liver cells have undergone destruction (Fig. 4); at other times areas as large as half a liver lobule are destroyed. Mixed with the granular debris and the shrunken and broken down remains of liver cells are polynuclear and mononuclear leucocytes. Eosinophiles are rarely found. That regeneration of the cells occurs is indicated by the fact that no histological changes can be discovered in the livers of animals which survive for two or three weeks the intraperitoneal injection of dilute formalin.

Hensen (13) has produced parenchymatous changes in the liver by injecting 1.5 cc. of from 0.5 to 4% formalin into the gall-bladders of cats. The changes varied from slight cloudy swelling to total necrosis of the liver cells. In all cases only a slight inflammatory reaction occurred, and evidences of regeneration were plentiful. My own observations agree well with those of Hensen, and it is of interest

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to note that formalin, no matter in what way introduced into the body can produce lesions in the liver similar to those resulting from the injection of the chemical directly into the organ.

IX. CHANGES IN THE KIDNEYS.

Changes in the kidneys are constantly present after the injection of formalin. Definite changes are noted in the kidneys within six or eight hours after the injection of from 3 to 6 cc. of 1-1000 formalin into the peritoneal cavities of guinea pigs. Macroscopically the kidneys are firm, swollen, dark red and bloody. Microscopically, the glomeruli show an indistinct structure. The sepearate cells cannot be distinguished from each other; the nuclei are polymorphous or crenated, and often show figures suggesting karyokinesis. The uriniferous tubules show a variety of changes; for the most part the cells lining the convoluted tubules are swollen, granular, and stained red with eosin, while often a faintly reticular structure can be made out. The cells are swollen to the extent of occluding completely the lumina of the tubules, and the cellular outlines are obscured. The nuclei of the cells are pale and swollen, and some have entirely disappeared. In some areas in the kidney the epithelial lining of the tubules has been lost so that nothing but empty holes remain; sometimes these holes contain a small amount of granular material, at other times, desquamated cells with fragmented nuclei. Often the entire epithelial lining is contracted and found lying free in its connective tissue casing. Some of the tubules are filled by a homogeneous, bluish staining mucus-like material. The changes in the straight tubules are similar to those in the convoluted tubules, the cells being swollen and granular. Often the arrangement of the cells upon the basement membrane is disturbed and sometimes total cellular necrosis has occurred, only the empty connective tissue tubules remaining.

In two guinea pigs, one dying eight, the other twelve hours after the intraperitoneal injection of 4 cc. of a 1% solution of formalin, all of the changes described above are found. No definite

structure can be made out in the glomeruli and intense vacuolation of the cells has occurred. In the glomeruli and in the tubules an occasional polymorphonuclear or mononuclear leucocyte can be seen and blue hyaline material is found in some of the tubules.

The administration of formalin by the stomach or its injection into the lungs produces the same changes in the tubules of the kidney as those just described. The same result follows intraperitoneal injections of undiluted formalin into dogs. The glomerular changes, however, are of a severe type. In one case after the injection of 3.5 cc. of undiluted formalin some of the glomeruli are entirely lost and in their places a small amount of poorly stained granular material is found. In another dog there are found only empty tubules containing red vacuolated bodies, probably the remains of necrosed cells.

In the animals exposed to the fumes of formaldehyde the cells of the uriniferous tubules are the seat of intense vacuolation. Further, the changes already described are found and some of the glomeruli are entirely destroyed. In three of the animals exposed to the fumes of formaldehyde areas of focal necrosis were found in the kidneys. Such foci are usually of small size, and cover an area corresponding to the cross-section of two or three tubules. Mixed with the granular debris and the broken down nuclei of the destroyed epithelium are found mononuclear and polynuclear leucocytes.

X. CHANGES IN THE LUNGS AFTER ABSORPTION OF FORMALIN.

Pneumonia and bronchitis, with or without haemorrhage, are found in the lungs of all animals after the injection of formalin. These changes are of about the same type in all the animals, and do not vary in severity with variations in the strength and the amount of the injected chemical.

The bronchi contain desquamated bronchial and alveolar epithelium, together with polynuclear leucocytes. The lining cells of the bronchi are swollen and granular, and in places partially desquamated. Many of the alveoli contain a finely granular or hyaline

material (oedema) with which are mixed desquamated alveolar epithelial cells and leucocytes. The epithelial cells of the alveoli are swollen and granular, and their nuclei are pale and misshapen. Many of these cells are in process of desquamation. The blood-vessels are congested and contain a large number of leucocytes.

XI. CHANGES IN OTHER ORGANS.

Except for an apparent increase in the number of polynuclear leucocytes, I was unable to find changes in the spleen of any of the animals experimented upon. There was always an abundance of blood pigment present and many of the leucocytes were filled with it. In the heart I found no definite changes. The suprarenals were unchanged.

A distinct eosinophilia was found in the bladders of two dogs. In addition the epithelial cells of the bladder had undergone well-marked necrosis (the cells were swollen and granular, with crenated and broken down nuclei) and desquamation. To what extent these changes were pathological, I am unable to say.

In the spinal cord and brain of four animals examined by Nissl's method, the ganglion cells showed chromatolysis, peripheral and central migration of the Nissl bodies, and eccentric location of the nuclei.

XII. CHRONIC FORMALIN POISONING.

Four animals were subjected to chronic formalin poisoning, receiving a series of intraperitoneal injections of dilute formalin. The results were as follows:

Exp. 1.—Rabbit, wt. 920 grm. Injected 6 cc. of 1-2000 formalin on four successive days. The animal seemed slightly uncomfortable but otherwise well. The rabbit was killed ten days later when no macroscopic changes could be found in the organs.

Exp. 2.—Guinea pig, wt. 765 grm. Injected 4 cc. of 1-2000 formalin on four successive days. The animal lost 27 grm. in weight. Twelve days later the pig had regained its former weight and formalin injec-

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tions were recommenced. Injections of 4 cc. of the chemical, beginning with 1-2000 and gradually increasing in concentration, were made every second day. No symptoms except a slight restlessness followed the injections. The animal succumbed after the ninth injection—4 cc. of a 1-625 formalin solution. At death the animal weighed 702 grm. Time of experiment 42 days.

Exp. 3.—Terrier, wt. 25 kilo. The experiment extended over a period of 38 days. The following injections were made, one day at least intervening between the consecutive injections:

Ten injections of 8 cc. of 1-1000 formalin; one injection of 16 cc. of 1-1000 formalin; three injections of 24 cc. of 1-1000 formalin; one injection of 32 cc. of 1-1000 formalin; one injection of 40 cc. and one of 50 cc. of 1-500 formalin. The dog was killed with chloroform.

Exp. 4.—Rabbit, wt. 1675 grm. The animal was observed for 106 days. The following injections were made, one day at least intervening between injections:

Twelve injections of 6 cc. of 1-1000 formalin; two injections of 8 cc. of 1-1000 formalin; one injection of 12 cc. and one injection of 20 cc. of 1-1000 formalin.

I now began to increase slowly the concentration of the chemical, as well as to increase the amount injected. After increasing the strength of the formalin I would at first decrease the amount injected so as to make the transition with as little shock as possible to the animal. In 61 days the amount of the chemical injected was raised from 16 cc. of 1-500 to 40 cc. of 1-150 formalin. After the ninth injection of 1-1000 formalin the animal had lost 75 grm.; thereafter the animal gained in weight and weighed, when killed, 1920 grm. For several days the animal weighed 2026 grm. After a series of injections the rabbit would lose weight; the weight would be regained when the injections were stopped. It was also noticed that an increase in the amount of formalin injected was followed by a corresponding increase in the loss of weight.

On post-mortem examination no macroscopic changes of a type much severer than those ordinarily observed could be found. The kidneys and liver of the dog in Exp. 3 were yellowish. In the rabbit of the last experiment the intestines had a distinctly granular feel, and the mesentery was firmer and thicker than normal. The capsules of the kidneys were also thickened.

Histological examination of the viscera gave the following result: In the first three experiments there is fibrino-haemorrhagic peritonitis such as I have already described. In the third experiment organization of the exudate is well advanced, while in the last experiment there is enormous proliferation of the connective tissue. The mesentery is made up almost entirely of embryonal connective tissue, and the serosa of the intestines and abdominal wall is very markedly thickened. Enormous proliferation of connective tissue has also occurred in the omentum. In places areas of fibrin mixed with red blood corpuscles are undergoing organization. A most striking infiltration with eosinophile leucocytes is present in the mesentery, omentum, serosa and submucosa of the intestines, and in the abdominal wall. Other polynuclear and mononuclear leucocytes are present but they are comparatively few in number. About the smaller blood-vessels and irregularly scattered through the young connective tissue are small, densely-crowded aggregations of lymphocytes.

The capsules of the kidneys, spleen and pancreas of the rabbit in the last experiment are thickened, show active proliferation of connective tissue, and are infiltrated with eosinophile and other forms of leucocytes. These changes, it seems to me, are due to the formalin which came in contact with these organs. It is probably the result of this proliferation of connective tissue and thickening of the serosa that the animals are able to bear without apparent suffering the injection of large quantities of the stronger solutions employed in the later experiments.

Severe cloudy swelling is present in the livers of the animals used in the last three experiments. In the dog there was marked fatty degeneration. Areas of focal necrosis are found in the liver of the guinea pig. In the guinea pig, and in the rabbit, more markedly in the latter, the interlobular connective tissue is infiltrated with small mononuclear leucocytes. Slight leucocytosis is present in the livers of all the animals except the first.

The kidneys are the seat of diffuse cloudy swelling. Fatty degeneration is marked in the kidneys of the dog (Exp. 3). The connec-

tive tissue in the kidneys of the last three animals is infiltrated with small mononuclear leucocytes, but other forms are rarely found. Areas of focal necrosis are found in the kidneys of the guinea pig. In the dog extensive areas in which kidney substance has disappeared are infiltrated with leucocytes of the mononuclear variety (Fig. 5). Many plasma cells are present.

The lungs of the four animals show the slight bronchitis and pneumonia usually present after the administration of formalin. Their spleens contain a large amount of blood and yellow pigment and in the last experiment a large number of eosinophiles.

I take pleasure in expressing my thanks to Dr. Hektoen for suggesting the subject of this paper to me; and for continued interest and guidance during its preparation.

SUMMARY.

The results of this investigation may be summarized as follows:

1. The inhalation of formaldehyde gas in even small quantities is followed by bronchitis and pneumonia. Pneumonia is due to the inhalation of the gas and not to secondary infection.

2. Formalin belongs to that rare group of poisons which are capable of producing death suddenly when swallowed.

3. The introduction of formalin into the stomach is followed by the production of a gastritis which varies greatly in character. The duodenum and upper jejunum may also be involved in the inflammatory process.

4. Intraperitoneal injections of formalin cause peritonitis of a fibrino-haemorrhagic character. A definite reaction is obtained when very dilute formalin (1-1000) is employed. In the peritoneal cavity formalin exercises a destructive action upon all organs (pancreas, liver, peritoneal fat, Fallopian tubes, etc.) with which it comes in contact and causes inflammation in these organs.

5. The lethal dose of formalin when injected intraperitoneally into guinea pigs is approximately 2 cc. of 1-1000 formalin for each 100 grm. of body weight.

6. The injection of formalin into the lungs is followed by pneumonia and bronchitis.

7. The inflammation which follows subcutaneous injections of formalin is characterized by intense exudation.

8. The injection of formalin into the muscles produces myositis.

9. The injection of formalin into the anterior chamber of the eye causes the accumulation of an exudate containing leucocytes and fibrin. When formalin is dropped into the conjunctival sac iritis follows and may be severe enough to destroy the eye.

10. Formalin in whatever way introduced into the body is absorbed, and is then capable of producing lesions in the parenchymatous organs.

11. Changes in the liver after absorption of formalin consist of mild or severe grade of cloudy swelling accompanied by vacuolation of the pretoplasm, changes in the nuclei and leucocytic infiltration. Focal necrosis may result. Similar changes follow the inhalation of formaldehyde.

12. The injection of formalin or the inhalation of the vapors of formaldehyde produces cloudy swelling of the parenchyma of the kidney. Focal necrosis may result.

13. Pneumonia and bronchitis are found in all animals after the injection of formalin.

14. The leucocytic infiltration which follows the introduction of formalin into an organ has these general characteristics: The eosinophiles are the first leucocytes to appear; these are followed by the other polynuclear leucocytes; last appear the large and small mononuclear leucocytes. Similar phenomena occur in the trachea, bronchi and lungs of animals subjected to formaldehyde inhalations.

15. Formalin is, directly or indirectly, chemiotactic for leucocytes. The tissues which are not infiltrated with leucocytes after the injection of formalin are those which have been so injured by the chemical that an inflammatory reaction is impossible.

16. Animals subjected to chronic poisoning with formalin administered by intraperitoneal injection develop fibrinous peritonitis,

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associated with marked eosinophilia. The changes in the kidneys and liver consist of cloudy swelling, fatty degeneration, focal necrosis and leucocytic infiltration.

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EXPLANATION OF PLATES.

Fig. 1. Eosinophilic pneumonia in a guinea pig exposed for one and a half hours to formaldehyde. (Sec. I, Exp. 1.)

Fig. 2. Pneumonia at a later stage, in a rat exposed for three and a half hours to formaldehyde. (Sec. I, Exp. 2.)

Fig. 3. Eosinophilic tracheitis in a guinea pig exposed to formaldehyde inhalation for three and a half hours. (Sec. I, Exp. 2.)

Fig. 4. Focal necrosis in the liver in a guinea pig killed forty-two hours after exposure for five hours to the vapors of formaldehyde. (Sec. I, Exp. 4.)

Fig. 5. Extensive leucocytic infiltration found in the kidney of a dog subjected to chronic poisoning with formalin. (Sec. XII, Exp. 3.)

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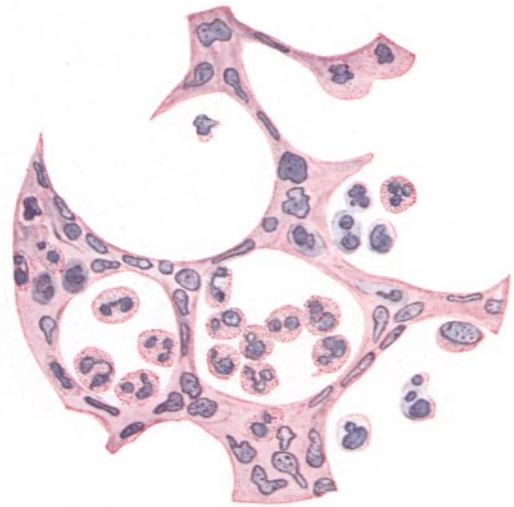

FIG. 1.

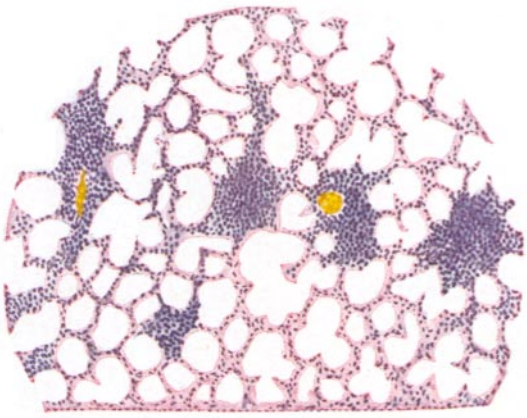

FIG. 2.

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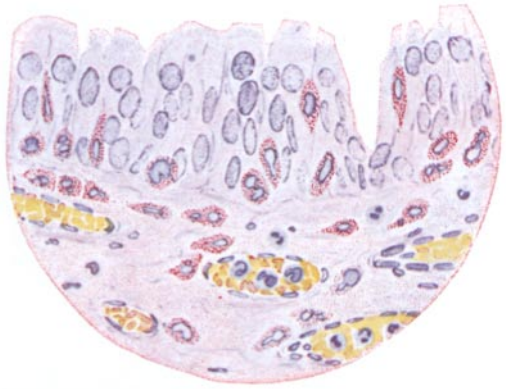

FIG. 3.

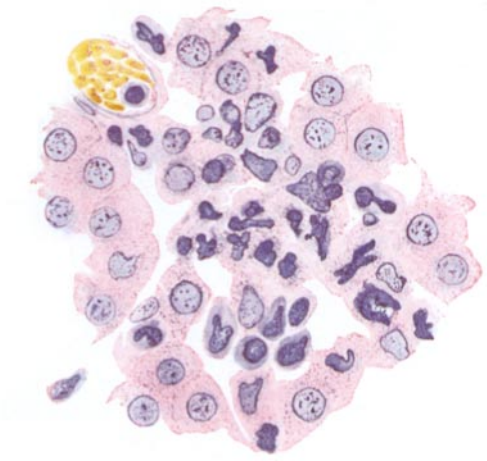

FIG. 4.

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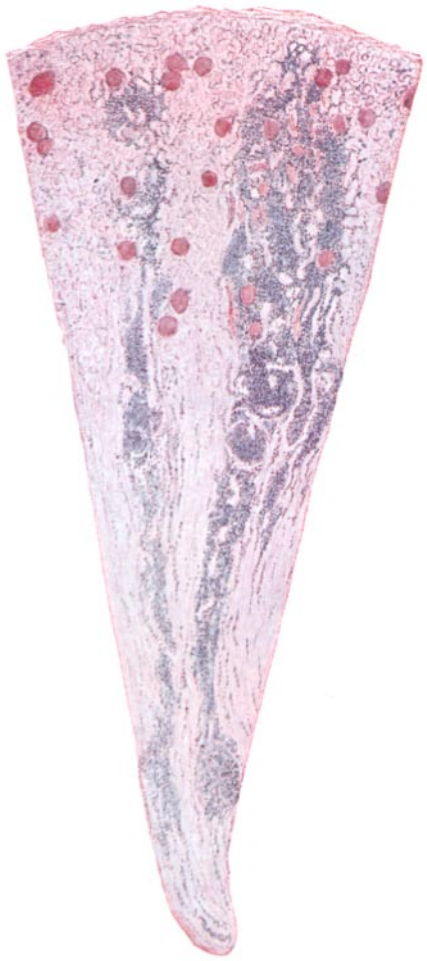

FIG. 5.