EXPERIMENTAL RESEARCH ON THE EFFECT ON THE GASTRO-INTESTINAL TRACT OF THE EXCRE- TION OF POISONS, CONSIDERING THE AGE OF THE ANIMALS *

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It is well recognized that a part of the poisons absorbed by the blood is excreted in the gastro-intestinal tract and produces a certain effect on its mucous membrane. However, systematic histologic experiments concerning these effects are lacking, and especially as regards the differences of effect between grown and very young animals.

From my experiments I expected: (1) that the various kinds of poisons offered would produce different effects on the different regions of the intestinal tract; (2) that the pathologic-anatomic and pathologic-histologic study of these effects would show various results, depending on the kind of poison used; (3) that in such experiments the results obtained would differ to a certain degree in very young animals from those in grown animals.

It is certain that in diseases of the intestinal tract of infants the clinical signs and the pathologic-anatomic findings usually differ from those of the adult. For instance, we know that nutritional disturbances or the enterides of infancy are not localized in the intestine, as is the case with adults, but are accompanied by a general affection, causing severe disturbances in the general metabolism; however, contrary to expectation, the postmortem examination shows no such violent changes in the intestinal mucosa. Again, we know that dysentery, an infectious disease of the intestinal tract, often runs in infancy an atypical course, and pathologic-anatomic changes are not distinctly localized in the large intestine, as is usually the case in the adult, but often extend to the small intestine.

Experimental pathologic research concerning the above points seems to be lacking. In my experiment it was purposed to compare the function of the gastro-intestinal mucosa, in regard to the excretion of poisons, and the change produced thereby, in the intestinal mucosa of very young animals with that found in grown animals.

METHOD

The poisons used were, 1 per cent. colloidal bismuth in watery solution; mercury (chiefly from 0.5 to 1 per cent. sublimate sodium chlorid solution); 1 per cent. colloidal silver solution; from 0.1 to 1 per cent. arsenous acid solu-

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tion; from 0.3 to 5 per cent. potassium bichromate solution; ricin in physiologic salt solution (0.5 mg.: 10); from 0.2 to 0.5 per cent. cantharidin in olive oil; from 0.5 to 1 per cent. snake poison in glycerin-water solution; sterile emulsion of dysentery (Shiga) bacilli; paratyphoid B; typhoid, and cholera bacilli. These bacilli were cultured in agar mediums for twenty-four hours, and were emulsified in a physiologic salt solution in the proportion of 5 c.c. to one agar tube, and were sterilized for one hour at 60 C.

These poisonous solutions were injected intravenously or subcutaneously into rabbits (grown and very young), white rats (grown), dogs (grown, and very young), chickens (grown, and very young), and pigeons (grown).

The feeding of the animals was arranged according to their physiologic habits. The very young rabbits were nursed twice a day by the mother animals. The very young dogs were fed with cow's milk.

As regards the doses of poisons used, the animals were usually poisoned with a dose in proportion to their weight; however, because the disposition of each animal varied according to kind and age, a dose was often given from which the animal became distinctly prostrated, within a certain number of hours or days.

Method of Examination.—The animals were usually killed and dissected at various stages, such as in the acute stage of poisoning (from a few hours to a few days), or in the subacute or chronic stage (from a few days to usually one or two weeks).

Microscopic sections were made from several parts of the stomach, small intestine, cecum and large intestine, and were generally stained with hematoxylin and eosin. Sometimes a frozen section was examined by itself, or stained for fat by sudan III and sometimes by iron reaction. Moreover, I contrasted the intestinal tracts of normal animals of various ages.

EXPERIMENTS

1. *Bismuth Experiment.*—Findings in *grown animals* (6 rabbits, 4 white rats, 3 dogs, 5 chickens, and 3 pigeons): The important change in the intestinal tract was a brownish-black pigmentation in the mucous membrane of the cecum and large intestine, especially intense in the cecum of the rabbit, rat, and chicken, and in the large intestine and cecum of the dog. Moreover, in the cecum of the rat and in the large intestine and cecum of the dog, a necrotic inflammation was produced in part of the mucosa.

Microscopic examination of frozen sections of these pigmented areas showed a pigmentation in the tissue of the mucosa. The epithelial cells on the ends of the villi contained fine, more or less irregular, brownish-black granules in the protoplasm on the superficial side of the nucleus. The capillary walls near the apex of the villus were brownish-black in color; large migratory cells filled with coarse brownish-black pigments were found here and there in the membrana propria and between the epithelial cells. In some cases, in which the animals were poisoned by large doses, similar pigmentation, but very slight, was also seen in the mucosa of the stomach, especially in the fundus, and just a trace was, rarely, found in the small intestine.

Sawai¹ has proved chemically that this pigment is a sulphur compound of bismuth, and he has shown experimentally that it is the result of excretion, not of resorption.

From the sections stained with hematoxylin-eosin a degeneration and necrosis of the epithelial cells occurred showing granulated or vacuolated protoplasm and figures of karyorrhexis or karyolysis, together with a slight infiltration of round cells in the distinctly pigmented regions. In cases of dogs and rats, a necrosis of the tissue of the mucosa was seen, with some hemorrhage and moderately intensive infiltration in the submucosa, in the lower portions of

1. Sawai: Kyoto Igakuzassi (Japanese), 1916, No. 5.

the intestinal tract. Some catarrhal changes were occasionally found in the mucosa of the stomach and small intestine.

Findings in *very young animals* (18 rabbits ranging from 3 to 18 days of age, a dog 3 days old, 7 chickens ranging from 3 to 10 days old): In most cases a slight brownish-black coloring was produced in the mucous membrane of the stomach and small intestine, especially distinct in the fundus and jejunum, sometimes extending as far as the large intestine, but here much slighter.

Microscopic examination showed that the pigmentation of the mucosa was more intensive in the stomach and small intestine than in the lower portions.

The mode of excretion of the bismuth was so characteristic that the excreting granules were found moderately diffuse, not only in the surface epithelium, but often in the glandular epithelium of the mucosa; while in cases of grown animals the metal was excreted principally and in more concentrated form by the epithelium on the ends of the villi in the lower portions of the intestine. The pigmentation of the mucous membrane in the cecum and large intestine of very young animals, however, was more intensive in comparison with the findings in the stomach and small intestine of grown animals.

The capillary walls were colored, the pigmentation of the migratory cells was rarer and slighter than in grown animals.

In animals about 3 weeks of age the pigmentation in the lower portions appeared more intensive and was slighter in the stomach and small intestine. In animals 2 months old the findings were similar to those of grown animals.

These different findings, comparing very young animals with grown animals, may be due to the scarcity of sulphur in the intestinal contents of the former. To prove this the following experiment was performed:

An ammonium sulphid solution, or flowers of sulphur, was given to several groups of very young and grown rabbits by esophageal catheter twice a day, and in some cases, also, at the same time *per ani*, soon after the injection of bismuth. On the third or fourth day after this treatment the animals were killed and examined. The pigmentation of the mucosa was found in the very young animals to be most intensive in the stomach and small intestine; while in grown animals the lower region was more distinctly pigmented.

Hence, these differences must have been chiefly due to the different modes of intestinal excretion, according to the age of the animals.

2. *Mercury Experiment.*—Findings in *grown animals* (9 rabbits, 3 white rats, 3 dogs, 6 chickens, and 3 pigeons): The important changes were catarrhal inflammation in the first stage, hemorrhagic inflammation in the second stage, and necrotic inflammation in the third stage, produced in the lower portions of the intestine. All of these changes were especially distinct in the cecum of rabbits, rats and chickens, and in the large intestine of dogs. From histologic examination of the first stage, a degeneration and necrosis of the epithelial cells were revealed, containing very scanty and irregular black pigment (iron reaction negative), especially in the ends of the villi. In later stages a moderate hemorrhage was found, with necrosis of the mucous membrane and with intensive infiltration of round cells in the submucosa or in the muscle strata.

Findings in *very young animals* (13 rabbits ranging from 3 to 20 days old, 2 dogs a few days old, 10 chickens ranging from 3 to 11 days old): A diffuse catarrh in all regions, especially distinct in the stomach and small intestine; sometimes erosions here and there; necrotic inflammation was found nowhere. Histologic examination showed a moderately diffuse degeneration of the epi-

thelial cells; here and there necrosis of the epithelium on the ends of the villi, with more or less hemorrhage and a very slight infiltration of round cells.

In the case of rabbits 3 weeks of age there was a moderate hemorrhagic inflammation in the cecum. The findings in animals 2 or 3 months old were similar to those in grown animals.

Experimenting with *artificial sulphuration*, as with the bismuth cases, a necrotic inflammation in a part of the fundus ventriculi and in the cecum of grown rabbits was found, while a catarrh and erosion in all regions of the intestine were observed in very young rabbits.

It is well recognized that intoxication by mercury produces a diphtheritic inflammation in the lower regions of the intestinal tract. The production of this inflammation, however, is variously explained; for instance, it was thought to be produced by the excretion of the metal (Heilborn²); or it might be produced secondarily to a disturbed circulation (Kaufmann³); or possibly it was caused by secondary bacterial infection (Virchow⁴). Sawai¹ first proved this inflammation to be caused by the sulphuration of the excreting metals. From my findings, let me say, the excretion of mercury in the intestinal tract of grown animals is most distinct in the lower portions, while in very young animals it is moderately diffuse.

3. *Silver Experiment*.—In grown animals (3 rabbits, 4 white rats, 1 chicken, and 2 pigeons) the capillary walls in the mucosa of the intestinal tract were, here and there, black in color, especially distinct in the lower regions. The migratory cells were moderately filled with black pigments. In the epithelial cells, however, pigment was seldom found in any region. A catarrh or very slight hemorrhage was seen in the mucosa of all regions.

In three *very young rabbits* the findings were of a little different character. The coloring of the capillary walls and the phagocytosis of the migratory cells were only slight in degree, and the excreting pigment in the epithelium was found especially in the stomach and small intestine, even though slight.

4. *Arsenic Experiment*.—In grown animals (7 rabbits, 7 white rats, 1 dog, 3 chickens, and 3 pigeons), a hemorrhagic inflammation was noticed in the small intestine, especially distinct in the middle portions, and more or less catarrhal changes in the other regions of the intestine. Histologic examination showed degeneration, necrosis, and desquamation of the epithelial cells, with moderate hemorrhage and infiltration of round cells.

In four *very young rabbits* ranging from 4 to 9 days old, a diffuse catarrh in the intestinal tract, especially distinct in the stomach and small intestine, was in most cases produced. In the histologic examination, swelling and degeneration of the epithelium, hyperemia and very slight infiltration of round cells were found.

5. *Chromium Experiment*.—In grown animals (5 rabbits, 3 white rats, 2 dogs, 5 chickens, and 2 pigeons) a catarrhal inflammation was produced which extended from the lower regions to the small intestine. In the case of dogs, erosions and partly necrotic inflammations were found in the large intestine, but these were slighter than in the case of mercury poisoning. Histologic examination showed degeneration, necrosis, and some desquamation of the epithelial cells, with infiltration of round cells, and slight hemorrhage, except in cases of necrotic inflammation.

2. Heilborn: Arch. f. exper. Path. u. Pharmakol., 1878, 8.

3. Kaufmann: Virchow's Arch. f. path. Anat., 1889, 117, 227.

4. Virchow: Deutsch. med. Wchnschr., 1887, p. 1047.

In *very young animals* (five rabbits ranging from 4 to 18 days old, and a dog a few days old) a diffuse catarrh was found, especially distinct in the stomach and small intestine, and sometimes accompanied with miliary hemorrhages and erosions. Histologic examination showed a diffuse swelling and degeneration of the epithelium, edema, slight hemorrhage, and very slight infiltration of round cells.

6. *Cantharides Experiment*.—In *grown animals* (5 rabbits, 4 white rats, 1 dog, 3 chickens, and 2 pigeons), a catarrhal enteritis was produced which was most intensive in the small intestine, and was distinguished by its desquamative nature. Histologic examination showed a diffuse swelling, degeneration, necrosis and intensive desquamation of the epithelial cells, together with intensive exudation and infiltration of round cells; but hemorrhages were rare and slight.

In three *very young rabbits* ranging from 3 to 9 days old, and a dog a few days old, a diffuse catarrh was found in all regions, especially intense in the stomach and small intestine. Histologic examination showed a diffuse retrogressive alteration of the epithelium, edema, and a very slight infiltration in the membrana propria and submucosa.

7. *Ricin Experiment*.—In *grown animals* (9 rabbits, 1 dog, 7 white rats, 6 chickens, and 3 pigeons) were found catarrhal inflammation in the first stage, hemorrhagic inflammation of Peyer's patches in the second stage, diffuse hemorrhagic inflammation in the small intestine in the third stage, especially distinct in rabbits and rats. In other regions of the intestine more or less catarrh was observed, and some hemorrhage. Histologic examination showed intensive hyperemia and hemorrhage, with infiltration of round cells in the mucosa of the small intestine. In the lymph nodes, especially in Peyer's patches, diffuse hemorrhage was found, associated with swelling, phagocytosis, and degeneration of the reticuloendothelial cells of the follicles. The epithelium of the mucosa was degenerated, necrosed, and desquamated.

In the case of *very young animals* (11 rabbits ranging from 3 to 30 days old, 3 dogs ranging from 2 to 30 days old, and 2 chickens 3 days old) a diffuse catarrh was produced, extending throughout all regions of the intestinal tract; sometimes more or less hemorrhage was found in various regions, but never distinctly located in the small intestine. Histologic examination showed slight infiltration and hemorrhage, with swelling or some degeneration of the epithelium.

In cases of rabbits 3 months old the findings were similar to those of grown animals.

Kusama⁵ also wrote as the result of experiment that ricin produced a hemorrhagic inflammation in the intestinal mucosa.

8. *Snake Poison Experiment*.—Findings in *grown animals* (9 rabbits, 4 white rats, 2 dogs, 2 chickens, and 3 pigeons) showed catarrhal inflammation in the first stage, hemorrhagic inflammation in the second stage, and necrotic inflammation in the third stage in the stomach mucosa. Necrotic inflammation was especially located in the middle third of the larger curvature, *at the same place where metals such as bismuth and mercury were sometimes noticeably excreted*. In the convalescent stage the mucous membrane of this part became cicatrized. Catarrhal changes were also observed to some extent in other regions, gradually diminishing as one approached the lower portions of the intestinal tract.

Histologic examination in the first stage showed an intensive swelling and some degeneration of the epithelial cells in the mucosa of the stomach, together with a moderate hyperemia. In the second stage, a moderate hemorrhage was found, principally in the propria. In the third stage, a diffuse necrosis of the mucous membrane was observed, together with intensive hemorrhage and infiltration in the submucosa. And in the convalescent stage, an intensive proliferation of the connective tissue was produced, with retrogressive altera-

5. Kusama: Zieglers Beitr. z. path. Anat. u. z. Allg. Path., 1913, **55**, 459.

tion of the epithelial cells. In other regions of the intestine a trace of the foregoing changes only was seen, but nowhere was necrotic inflammation found.

Findings in eight *very young rabbits* ranging from 4 to 9 days old showed a diffuse, intensive, catarrhal inflammation, especially in the stomach and small intestine, together with a slight hemorrhage and some erosions; necrotic inflammation was nowhere found. Histologic examination showed swelling, degeneration, some desquamation of the epithelium, hyperemia, and, rarely, a slight hemorrhage.

Two animals were fed starch paste, *that the content of the stomach might be analogous with that of grown animals*, but no new results were found.

9. *Dysentery Toxin Experiment.*—Findings in *grown animals* (10 rabbits, 4 white rats, 2 dogs, 3 chickens, and 3 pigeons): First stage, catarrhal inflammation; second stage, hemorrhagic inflammation; third stage, necrotic inflammation, and in later stages, a cicatrization in the cecum (especially of rabbits) and large intestine (especially of dogs). These results are similar to those of Flexner⁶ and Doerr.⁷ In rats and pigeons a hemorrhagic inflammation was observed also in part of the small intestine.

Histologic examination: In the earlier stages, the epithelial cells were swollen in the lower portions; their nuclei seemed vesicular, or they were degenerated, showing the figures of karyolysis, or they were necrotic and desquamated. The membrana propria and submucosa were intensely edematous, with an infiltration of round cells and some bleeding. The hemorrhage and infiltration were most intensive in the area of necrotic inflammation, often extending into the muscle strata. In the protracted course of the intoxication some proliferation of the connective tissue in the mucous membrane was seen. In the lymph follicles of the vermiform process was found a swelling, a degeneration, and at times a necrosis of the reticulo-endothelial cells.

Findings in *very young animals* (11 rabbits ranging from 3 to 30 days old, 3 dogs, ranging from a few days of age to 2 weeks, and 7 chickens ranging from 5 to 11 days old): In cases examined in less than three weeks after birth the most distinctive changes were catarrhal or hemorrhagic inflammation in the stomach and small intestine, with more or less bleeding in the lumen. Of course, in the cecum and large intestine certain slighter catarrhal changes and some erosions were found; nowhere was a typical necrotic dysenteric inflammation found.

Histologic examination: The epithelial cells were diffuse and moderately swollen; their cytoplasm became distinctly granular and often showed vacuolation; their nuclei were vesicular or showed some figures of karyolysis, and occasionally the epithelium was necrotic and desquamated, especially on the ends of the villi. In the section stained for fat, a moderately diffuse fatty degeneration of the epithelium was seen, not only near the ends of the villi, but often on the glandular parts. The membrana propria and submucosa were more or less edematous, with more or less hemorrhage and slight infiltration of round cells. These findings were especially distinct in the small intestine and stomach. Peyer's patches were often swollen, lymph follicles were often proliferated in some degree, and sometimes there was bleeding.

In animals over 2 months of age the findings were similar to those in grown animals.

10. *Paratyphoid B Toxin Experiment.*—In *grown animals* (6 rabbits, 5 rats, a dog, 2 chickens, and a pigeon) catarrhal or hemorrhagic inflammation was produced, which was usually distinct in the cecum and large intestine and slight in the small intestine. In the last stage of the poisoning a necrotic inflammation was found in the cecum of rabbits and rats. In comparison with cases of dysentery toxemia, this necrotic inflammation was of a more localized character and of smaller area. Histologic examination showed that the necrosis

6. Flexner: Jour. exper. Med., 1906, 8, 514.

7. Doerr: Ergebn. d. allg. Path. u. path. Anat., 1912, 16, 122.

of the mucous membrane was of a superficial character, but hemorrhage was moderately distinct. In the earlier stages the swelling and degeneration of the epithelial cells were found, with more or less infiltration of round cells.

The lymph follicles in the intestinal tract were more or less swollen. Histologic examination showed a moderate proliferation of the reticulo-endothelial cells in the follicles, especially distinct in the vermiform process and the ileocecal patch; necrosis of the proliferated cells was nowhere observed, as is found in the case of typhoid-toxin poisoning. The lymph cells, also sometimes were more or less proliferated.

In *very young animals* (3 rabbits ranging from 3 to 10 days old, a dog 5 days old, and 6 chickens ranging from 3 to 13 days old) catarrhal inflammation was chiefly found, together with slight hemorrhage, at times, in all regions, and especially distinct in the stomach and small intestine. Moderately diffuse swelling and degeneration of the epithelial cells, slight hemorrhage, and a slight emigration of round cells were seen histologically.

In the lymph follicles a proliferation of the lymph cells was seen in the foreground, while the reticulo-endothelial cells were not so distinctly proliferated.

An Experiment with Typhoid-Toxin.—In the case of a *grown rabbit*, which was poisoned with typhoid toxin, was observed an intensive proliferation and a diffuse necrosis of the reticulo-endothelial cells in the vermiform process and ileocecal patch—typical typhoid changes—while in two cases of *very young rabbits*, under the same conditions, no such typical typhoid changes were produced. In other regions of the intestine nothing more was seen than a catarrh of the mucosa.

From the foregoing findings we may conclude that the paratyphoid B toxin produces changes closely related to but slighter than those of experimental dysentery in the lower portions of the intestine, combined with changes nearly related to those of experimental typhoid in the lymph follicles of the intestine.

Pathologic-anatomic observations on paratyphoid B disease, as far as I know, has not been reported on extensively until recently. Huebschmann⁸ wrote that this disease produced, in most cases, slight dysenteric changes in the large intestine, without typical typhoid changes anywhere. Ring⁹ and Buday¹⁰ have seen miliary ulcers in Peyer's patches and in the mucosa of the small intestine; Saltykow¹¹ has found typhoid changes in several cases and dysenteric changes in others.

From the findings of these men it is evident that the paratyphoid B disease should produce changes closely related to those of dysentery, combined with changes nearly related to those of typhoid, justifying the conclusion that the changes which result from experimental poisoning with paratyphoid B-toxin are caused by the excretion of this toxin into the intestinal tract.

11. *Cholera Toxin Experiment.*—In cases of *grown animals* (8 rabbits, 2 rats, a dog, 3 chickens, and 2 pigeons) catarrhal inflammation was chiefly found in the small intestine (together with some hemorrhage) distinguished especially

8. Huebschmann: Ziegler's Beitr. z. path. Anat. u. z. allg. Path., 1913, **56**, 514.

9. Rings: Med. Klin., 1907, p. 1007.

10. Buday: Centralbl. f. Bact., Part 1, Orgl., 1911, **60**, 449.

11. Saltykow: Virchows Arch. f. path. Anat., 1913, **211**, 467.

by its desquamative nature. Histologic examination distinctly showed desquamation of the superficial epithelium and a moderate swelling of the deep epithelium, and also a moderate infiltration of round cells.

In cases of *very young animals* (3 rabbits ranging from 3 to 5 days old and 5 chickens from 3 to 30 days old) the changes in the stomach mucous membrane were also distinct, so that the stomach contents were often mixed with blood, and in the stomach and small intestine the alteration of the epithelial cells was diffuse, while the infiltration of round cells was always very slight.

CONCLUSION AND DISCUSSION

1. *Excretion of Poisons in the Gastro-Intestinal Tract.*—The mucous membrane of the gastro-intestinal tract of the animals poisoned by the injection of the poisons mentioned usually showed certain changes. These changes were not of the same degree in all regions, but acted most violently on a certain region; for example, on the stomach, small intestine, cecum or large intestine, depending on the kind of poison used; even though some differences were found, these were caused by the varied forms of intestinal tracts, or by the peculiar predisposition of different animals.

A problem arises, How far does the chemical action of the intestinal content (combined with excreted poisons) influence these principal changes of the intestine? No definite answer can be determined by experimental findings, but I shall state several important facts concerning this problem.

The principal change in grown animals caused by bismuth and mercury was most distinct in the cecum of rabbits; in the case of rats it was moderately localized to about the middle portion on the side toward the mesenteric fixation of the cecum; while in dogs it was most distinct in the large intestine.

The dysenteric changes in the case of rats usually extend to the middle portions of the small intestine, while it was chiefly localized in the cecum of rabbits and in the large intestine of dogs.

In the mucosa of the vermiform process of rabbits, no such characteristic changes were produced as in the mucosa of the cecum, when poisoned with bismuth, mercury, dysentery, and paratyphoid B toxins.

The changes in the small intestine in most cases were most distinct in the middle portions.

The changes in the stomach were localized to a certain part of the fundus.

From these facts we may conclude that the poisons injected were excreted most distinctly in certain regions of the intestinal tract, and this was fundamentally responsible for the specific localization of the principal changes in the intestine, even though the chemical action of the intestinal content might take a part in causing the formation of these changes.

From the data obtained we can divide the poisons into five groups according to the principal region of their excretion in the intestinal tract.

Group 1. Poisons which are most distinctly excreted in the stomach mucosa; for example, snake poison.

Group 2. Poisons which are most distinctly excreted in the small intestine; for example, arsenic, ricin, cantharidin and cholera toxin.

Group 3. Poisons which are most distinctly excreted in the lower portions (the cecum and large intestine); for example, bismuth, mercury and dysentery toxin.

Group 4. Poisons which are most distinctly excreted in the lower regions, with a noticeable excretion in the small intestine; for example, chromium and paratyphoid B toxin.

Group 5. Poisons which are not distinctly excreted in any region of the intestine; for example, silver.

The excretion of poisons by the mucous membrane of the gastrointestinal tract seems to arise in three ways: (1) secretion by epithelial cells; (2) phagocytosis of the migratory cells; (3) phagocytosis of the reticulo-endothelial cells in the lymph follicles of the intestine.

These phenomena were recognized microscopically in cases of bismuth tested animals. In other cases, also, we noticed an alteration of the epithelium, an activity of migratory cells, and a swelling of reticulo-endothelial cells. In most cases, however, excretion by the epithelium appears to be the most important factor.

2. *Enteritis by Excretion*.—Enteritis by excretion, as I will call it, is an inflammation of the mucous membrane produced by the excretion of poisonous substances into the intestinal tract. The anatomic and histologic changes of this enteritis depend on the quality of the poisons. Enteritis by excretion of mercury, which has an intensively corrosive effect, is of a hemorrhagic and necrotic character; while the enteritis by excretion of bismuth, which has a milder effect, usually shows no such intensely destructive tendency. The dysentery toxin produces a necrotic affection in the lower regions of the intestine, while the excretion of the cholera toxin results in a desquamative catarrh of the small intestine.

Or, we may say that the changes of this enteritis depend on whether the excreting poison affects most intensively the epithelium, the vessels, or the connective tissue.

From data obtained we may divide poisons into three groups, according to the nature of enteritis produced by their excretion in the intestinal tract:

1. Catarrhal poisons: silver, bismuth, chromium, cantharidin and cholera toxin.

2. Hemorrhagic poisons: arsenic and ricin.

3. Necrotic poisons: mercury, snake poison, paratyphoid B, and dysentery toxin.

Of course, the catarrhal poisons may result in more or less hemorrhage, as in like manner, hemorrhagic poisons may produce, secondarily, partial necrosis, as in the first stage of poisoning by hemor-

rhagic or necrotic poisons we only observed a catarrh. Therefore, the changes of this enteritis also depend on the doses used and the stage of the poisoning. Moreover, the animals may show a peculiar predisposition, in some degree, toward each poison.

In all stages of poisoning, however, this enteritis showed a character which was specific to a certain degree for each kind of poison, but it was especially specific in the principal region of intestinal excretion.

In the histologic examination of this enteritis there were two factors noteworthy, namely, a destructive process and a reactive process, especially distinct in the principal regions of intestinal excretion. The reason why a poison elects a certain region of intestinal excretion, is not clearly explained. It is interesting that the principal changes found in experimental enteritis by excretion of dysentery, paratyphoid B, typhoid and cholera toxins are similar to those which we usually find in necropsies after dysentery, paratyphoid B, typhoid, and cholera. Therefore, each of these bacterial toxins will find a principal region for intestinal excretion, which region is the place of predilection of these bacterial infections. Hence, we may say that every poison will have the greatest affinity for its principal region of intestinal excretion.

3. *Compensational Excretion in the Intestinal Tract.*—In several groups of chickens and rats the cecum was extirpated; then the animals were poisoned with bismuth and mercury. The most distinctive changes were observed in the large intestine and in the middle portions of the small intestine. In the cases of pigeons, which anatomically have the most rudimentary cecum, the most intensive changes were usually produced in the large intestine and in part of the last loop of the small intestine, when they were poisoned with bismuth, mercury, and dysentery toxin. These changes in the small intestine must be due to the result of a compensational excretion of poisons.

Also, in cases of most acute poisoning of grown animals by all the poisons used in our experiments, the changes produced were found to be, to a certain degree, of a more diffuse character than in cases of subacute poisonings. This result must be also due to a compensational excretion in all regions of the intestinal tract, and it was more or less closely related to the general findings of very young animals.

4. *Excretion of Poisons in the Intestinal Tract of Very Young Animals.*—The method of excretion of bismuth injected in very young animals was so characteristic that the excreted bismuth granules were found microscopically to be moderately diffused throughout all the intestinal tract; and not alone in the surface epithelium, but also in the deep epithelium; while in the case of grown animals the metal was

excreted, principally and in more concentrated form, from the epithelium on the ends of the villi in the cecum and large intestine.

In all stages of experimental poisoning with mercury, ricin, snake poison, dysentery and paratyphoid B toxins, the intestinal mucosa of the very young animals showed neither typical necrotic nor typical hemorrhagic inflammation in the described region, as is usually the case in grown animals, but an enteritis of a diffuse, and, in most cases, of a catarrhal nature.

By histologic examination a diffuse epithelial alteration (swelling and degeneration showing the figures of karyolysis, and often a diffuse fatty degeneration) was always found; a slight hemorrhage might also be found here and there, while the reactive infiltration of the round cells in the mucous membrane was usually very slight. In the lymph follicles of the intestinal tract, however, was often seen a swelling, especially in cases with bacterial toxins, and a proliferation of lymph cells.

From data obtained in regard to the excretion of poisons in the intestinal tract of very young animals, three characteristics are revealed:

1. The excretion takes place diffusely and is consequently thinned.
2. The enteritis by excretion is anatomically of a diffuse character and less specific to every poison offered.
3. The destructive process is relatively distinct in regard to the histologic findings, showing a diffuse epithelial alteration, while the reactive process is slighter in comparison with findings in grown animals.

The imperfect development of the tissue and the imperfect differentiation in the function of the mucosa ought to be responsible for these characteristics.

There are several reasons to support this opinion. From an anatomic standpoint, the intestinal tract of very young normal animals offers something of especial interest. The important points are that the formation of the glands in the intestinal mucosa is not yet perfected and the mucosa is poorer in connective tissue and wandering cells, while it is richer in vessels, in comparison with that of grown animals.

In cases of young animals ranging from 3 weeks (at which time the animals usually begin to take some food besides milk from the mother animals) to about 2 months of age, the physiologic structure of the intestinal mucosa gradually approaches that of grown animals; in like manner, I often saw, in experimenting with young animals of these ages, that the enteritis produced gradually approaches the findings in grown animals.

5. *Comparative Observations of the Pathologic-Anatomic Lesions of Enteritis in Infants with Enteritis by Excretion in Very Young Animals.*—In most cases of nutritional disturbance or infectious enteritis of infants the pathologic-anatomic lesions are of a diffuse nature

in all regions of the intestinal tract, often particularly distinguished by diffuse alterations of the epithelial cells.

Infectious diseases of the intestine of infants, such as dysentery and typhoid, often have atypical clinical signs, and pathologic-anatomic lesions often appear less severe in degree than in adults, but with atypical localization, inclined to be of a diffuse nature.

The foregoing characteristics in infants are closely related to the figures found in the enteritis by excretion of very young animals, and must be due to the imperfection of the development and function of the intestinal mucosa.

In regard to the imperfect development of the tissue of the intestinal tract in infants, there are statements by Baginsky¹² and Gundobin.¹³ I have examined the intestines of several infants and about forty infants dead of enteritis. The results will be made known in the future.

By the same method of reasoning it may also be explained that the so-called "enteritis by parenteral infection," which may be an enteritis by excretion, usually causes much severer disturbances in infants than in adults.

The swelling and proliferation of the lymph follicles which are often seen in nutritional disturbances or enteritis in infants, may be caused, to a certain degree, by poisonous substances produced in the intestine, according to the results of my experiments. This view is in accordance with that of Finkelstein.¹⁴

12. Baginsky: *Virchows Arch. f. path. Anat.*, 1882, **89**, 64.

13. Gundobin: *Die besonderheiten des Kindesalters*, 1912, pp. 263 and 303.

14. Finkelstein: *Lehrbuch der Sauglingskrankheiten*, 1912, **3**.