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THE PRODUCTION OF ULCER OF THE STOMACH BY INJECTION OF STREPTOCOCCI *

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Hemorrhages, superficial erosions and definite ulceration of the mucous membrane of the stomach and duodenum occur not infrequently during severe infections in man and in experimentally infected or otherwise severely intoxicated animals. In some of these instances there can be no question but that infection in some instances plays a rôle in the etiology of ulcer.[1] Ulcer also has been produced experimentally by injecting bacteria into the gastric artery. The association of mouth and tonsillar infections with ulcer of the stomach has been emphasized. It is said that ulcer of the stomach is more common in regions in which throat infections are particularly prevalent. Clinicians have observed aggravation of symptoms in ulcer of the stomach or duodenum following sore throat. Experimental proof, however, showing that certain bacteria may have a special affinity for the stomach mucous membrane, producing a localized infection, and hence may play a rôle in the causation of the common acute and chronic peptic ulcer in man where the usual symptoms of infection are slight or wholly absent has not been brought forward. In a short note on the etiology of rheumatism[2] I pointed out that ulcer of the stomach followed not infrequently intravenous injections of organisms isolated from rheumatism, especially after animal passage; of laboratory strains of streptococci after they had attained a certain grade of virulence from animal passage, and of emulsions of tonsils which were removed chiefly during convalescence in cases of rheumatic arthritis. I wish here to report experiments along this line.

Ulcer of the stomach or duodenum, or both, have been produced by intravenous injection of certain streptococci in eighteen rabbits, six dogs and in one monkey. The ulcers are usually single, although at times two or more may be present. The primary hemorrhages and later the ulcers are small and deep. The base of the ulcer is usually clean or filled with a brownish blood-clot. There may or may not be a localized peritonitis. Perforation into surrounding adhesions occurred in two dogs and in the monkey. The tendency to bleeding in these ulcers is great. Two dogs died of an acute hemorrhage, while another was bleeding when chloroformed. The rabbits often showed considerable blood in the intestines, although death could not be attributed definitely to hemorrhage in any. Both punctate hemorrhages and ulcers have been found most frequently in the pyloric end of the stomach, then in the fundus, and least often in the duodenum. It should be pointed out that the hemorrhages and ulcers in these experiments are small and sharply circumscribed, and there is not the tendency to digestion and sloughing of mucous membrane—in contradistinction to hemorrhages and erosions—observed after anaphylactic shock, after overwhelming bacteriemic infections and other severe intoxications. In most of the rabbits and in some of the dogs which showed ulcers there was also arthritis, in some myositis and the picture of an "ascending" nephritis. Cholecystitis, with beginning formation of gall-stones, and appendicitis have also been found.

It must not be supposed that the ulcers are accidental, because they occur, commonly, only when streptococci of a certain grade of virulence are injected. To illustrate: Strain 319, originally a pneumococcus which was isolated from the blood in lobar pneumonia six years ago, and which had lost its virulence, resembling now a streptococcus, was passed through nineteen rabbits. The first thirteen passages (intravenous injections) failed to show ulcer in any, while the next six passages showed ulcer of stomach three times. Strain R51A, originally a pneumococcus isolated from the blood in pneumonia nearly eleven years ago but recently transformed into a hemolytic streptococcus, was passed successively through twenty rabbits. In the first fifteen animals ulcer was not found, while the next five passages showed ulcer of stomach twice. The strains from rheumatism before animal passage produced ulcer in two out of sixteen animals; after from two to five passages ulcer was produced in seven out of eighteen rabbits, while after from five to ten passages again only once in eight animals injected. When the virulence is very low ulcer occurs very rarely; when virulence is of a certain grade, slightly higher than that of the streptococcus from rheumatism, it occurs commonly; but when the virulence becomes still higher ulceration of the mucous membrane is again rare. It is practically impossible to produce this type of ulcer of the stomach with *Streptococcus viridans* as isolated from the blood in endocarditis or with highly virulent hemolytic streptococci or pneumococci.

The grade of virulence of the organisms when ulcer is obtained, commonly, is such that they disappear from the general circulation and the uninjured tissues. This fact afforded opportunity to study the exact relation of the organisms injected to the small areas of hemorrhage in the mucous membrane and to the ulcers. The areas of hemorrhage and ulcers were cut out, in four animals, together with corresponding pieces of the healthy stomach wall, washed thoroughly in repeated changes of sodium chlorid solution, crushed in a mortar, suspended

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1. For a comprehensive discussion and bibliography on the pathogenesis of ulcer of the stomach see Möller: Ergebn. d. inn. Med., 1911, vii, 520.

2. Rosenow, E. C.: The Etiology of Articular and Muscular Rheumatism, THE JOURNAL A. M. A., April 19, 1913, p. 1223.

in sodium chlorid solution and a series of blood-agar plates made. Cultures from the blood were also made. In one animal which died twenty-four hours after a third injection the blood still contained a moderate number of streptococci. Streptococci were recovered from the healthy, the hemorrhagic and the ulcerated area. The healthy area showed five, the hemorrhagic area eighty-two, the ulcerated area sixty colonies. Saprophytic bacilli and colon bacillus were present in small numbers in each. In the other three in which the blood was sterile the cultures from the healthy portion showed no streptococci in any, while the ulcerated or hemorrhagic areas yielded streptococci in varying numbers in each instance. Smears and blood-agar plate cultures from the base in other acute and in more chronic ulcers showed streptococci resembling those injected.

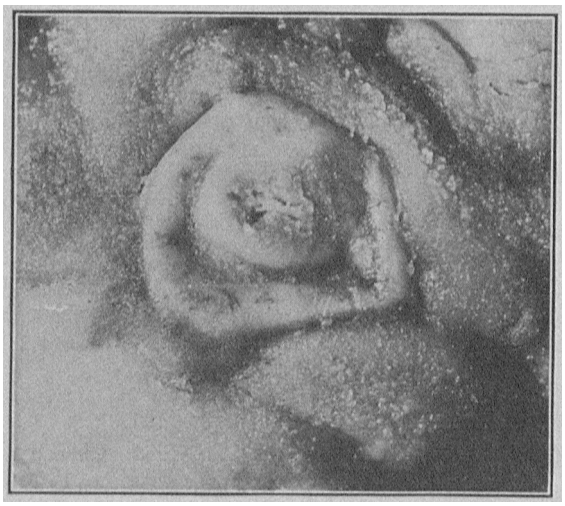

Fig. 1.—Necrosis with beginning ulceration of mucous membrane of stomach in a dog injected intravenously thirteen days previously with a streptococcus of low virulence; from photograph × 5.

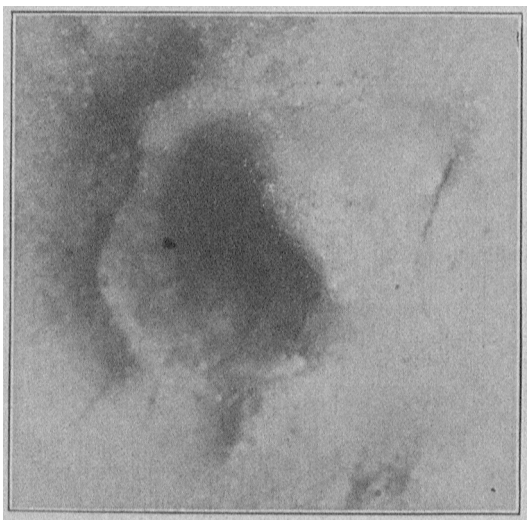

Fig. 2.—Deep, round ulcer at pyloric end of stomach of dog injected intravenously one month previously with a strain from rheumatism after ten animal passages; from photograph × 5.

MICROSCOPIC ANATOMY

The areas of hemorrhage which occur within twenty-four hours after injection usually extend through the whole thickness of the mucous membrane. The blood escapes from the capillaries in the acini and not from a larger vessel in the submucosa. It is most marked and extends over a wider area as the inner surface is reached. Leukocytic infiltration is already present in twenty-four hours, while at the end of forty-eight hours when ulceration has begun it is often quite marked and later is found to extend into the submucosa and muscular coat. The reaction indicating an infection in some ulcers largely disappears after the ulcer has existed for a long time. This is especially so in those ulcers in which invasion of the underlying structures is absent or slight.

The ulceration begins on the surface and rapidly extends to the submucosa. The tendency to invade the submucous and muscular coat is marked and was present in every instance when marked hemorrhage was observed (Fig. 5). The margins are usually abrupt, often undermined and infiltrated. The early picture is well illustrated in Figure 6 and the later appearance in Figure 5. In the former ulceration has not yet extended through the entire thickness of the mucous membrane, whereas in the latter the round-cell infiltration and ulceration have extended well into the muscular coat. In the latter there is a layer of leukocytic infiltration invading the normal tissue. Inside of this the cells show granular degeneration, the nuclei become fragmented as they lose their affinity for stains until finally a more or less homogeneous necrotic layer lines the ulcer. In horizontal sections the ducts along the margin of the ulcer frequently are found to contain leukocytes and red blood-corpuscles. Under high power the early infiltration in the wall of the ulcer is found to be made up chiefly of leukocytes and red blood-corpuscles; later lymphocytes and large mononuclear cells predominate. Here, also, what appear to be plasma cells are found in small numbers. Giant cells have not been observed. The chief cells disintegrate earlier than the parietal cells, giving the erroneous impression that the latter have actively multiplied. The connective tissue stroma of the acini is most resistant and can be made out for considerable distance beyond the place where the other cells, including leukocytes, have disappeared.

Fig. 3.—Ulcer of stomach in monkey injected intravenously with a strain of streptococcus from rheumatism after it had been converted into the hemolyzing variety and passed through one animal; from photograph × 5.

Thrombosis of adjacent blood-vessels has not been found in the acute ulcers but has been found in veins in two of the more chronic, deep ulcers in dogs. One of these died of acute hemorrhage. The other was chloroformed while bleeding was going on. Sections stained

for bacteria by the Gram-Weigert method showed diplococci and short chains in the ulcers, as early as forty-eight hours and as long as twenty-eight days after single injections of streptococci. These were found here repeatedly when the cultures proved their absence in the blood, pelvis of kidney, joints and gall-bladder. Figure 7 shows a moderate number of organisms. They are approximately half way between the free surface of the ulcer and where the cells still stain in a normal way. In this instance the injection of an emulsion from the tonsils was made thirteen days previously (see protocol, Dog 22). The organisms were easy to find. Some areas showed many hundred streptococci in linear arrangement in the connective tissue stroma of the disintegrating acini. Single diplococci were found in the deeper and less disintegrated areas (Fig. 7). The ulcer in one dog which was chloroformed twenty-eight days after a single injection showed fewer diplococci, well down from the free surface of the ulcer. Leukocytic infiltration in this instance had almost entirely disappeared.

It is interesting to note that in all the examinations which were made for bacteria only two Gram-staining bacilli were found and these were on the surface of the ulcerated area. Gram-staining diplococci were found in the thrombus of an adjacent vein in one instance. A painstaking search for similar organisms was made in the normal structures away from the ulcer, but none were found.

Fig. 4.—Ulcer of duodenum just beyond pyloric ring in rabbit injected intravenously with a streptococcus of low virulence.

ILLUSTRATIVE PROTOCOLS

The rabbits were fed carrots, hay and oats, the dogs a mixed diet with liberal quantities of meat.

RABBIT 475.—Injected intravenously on May 9, 12, 15 and 19, with the growth from 16 c.c. of ascites-dextrose-broth of Strain 744 from a case of articular and muscular rheumatism. May 19: Lameness in and swelling of right knee-joint; very ill. May 22: Chloroformed and examined at once. A few lesions in the flat muscle of the groins and shoulder. Myocardium, gray and flabby, shows a few whitish areas in papillary muscles. Clear fluid in pericardial sac. Fluid from three joints turbid, containing leukocytes, while that from another joint is clear. The stomach is normal except for the presence of two circumscribed, punched-out ulcers in the pyloric end. The larger is 4 by 2 mm. The base of each is occupied by brownish clotted blood. The margins are elevated, undermined and infiltrated (Figs. 4 and 6). Duodenum is normal. The contents of the large bowel are dark brown in color and give a strong Weber test for blood. The kidneys show no changes except a few whitish elongated areas in the medullary portion. The gall-bladder is filled and the ducts are distended with a slightly greenish viscid mucus containing large masses of pus. Pressure on the gall-bladder, after the plug of pus and concretions in the ampulla of Vater is removed, easily expels the contents into the lumen of the intestines. The masses of pus, on washing and disintegration, are found to contain concretions the size of millet-seed which have the consistency of putty. Smears of the pus show many leukocytes and streptococci. The addition of hydrochloric acid to the concretions liberates carbon dioxid. In the wall of the gall-bladder are found three small round whitish areas which seem to involve chiefly the mucous membrane. Over the largest of these at the fundus there is an adhesion to the omentum.

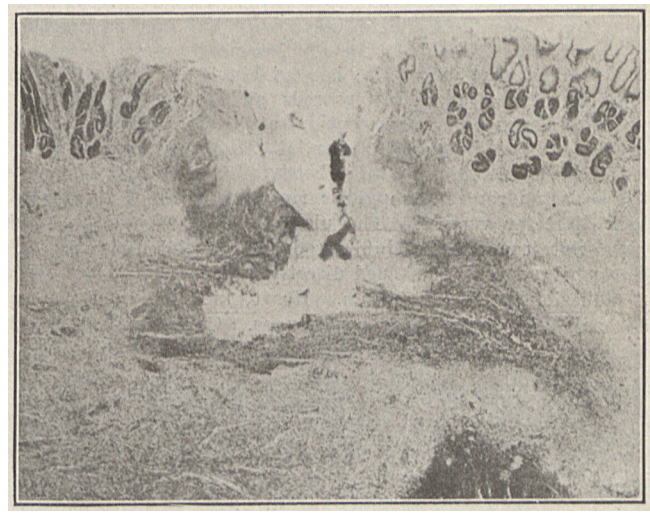

Fig. 5.—Section of ulcer of stomach in Dog 22; died from hemorrhage (see protocol). Note the leukocytic infiltration in the submucosa at base of ulcer, the great depth and extension of the ulcer beyond the mucous membrane. Hematoxylin and eosin; from photograph × 35.

The lungs, liver, brain, intestines, appendix and adrenals show no changes. The spleen is not enlarged. Cultures from the blood, peritoneum, pericardium, pelvis of kidney and two joints prove sterile. The most turbid joint fluid gives a few and the bile a large number of slightly hemolytic streptococci in pure culture, while the base of one of the ulcers in the stomach gives a few of these and saprophytes. One of the concretions, thoroughly washed in sodium chlorid solution, then crushed and used for plate cultures gives a pure culture of streptococci.

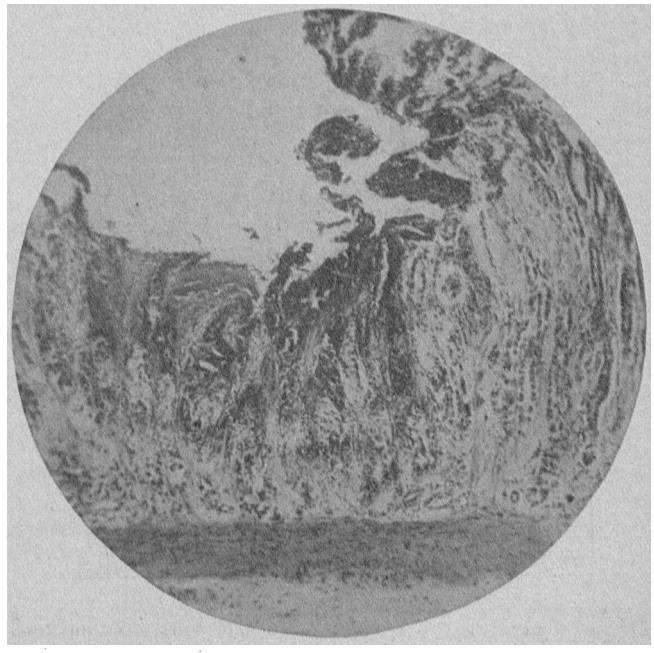

Fig. 6.—Section of ulcer of stomach in Rabbit 475. Note the hemorrhagic base (dark material), the tendency to undermining of margin, and the cellular infiltration at base. Hematoxylin and eosin; from photograph × 90.

Dog 22.—Small young dog. Injected March 18, 1913, with 5 c.c. of an emulsion of a tonsil, removed from a patient following an attack of tonsillitis and articular rheumatism. March 19: Lame in left front leg. Smears from left front wrist-joint show leukocytes and Gram-positive diplococci. Cultures yield green colonies only. March 21: Cultures from blood show a few hemolytic colonies only. Lameness still present, wrist-joint swollen. March 24: Lameness absent, wrist-joint no longer swollen, has lost in weight, lies quietly in corner, drinks water but eats little. Cultures from blood negative. March 29: Still quite well but has grown thin, does not eat. March 30: Dead. Muscles, mucous membrane and other tissues very pale; hemoglobin 12 per cent. Smears from the blood show a few reds and leukocytes. Recent, probably agonal, intussusception at ileocecal valve, easily reduced. Large quantity of partially digested blood in bowel above intussusception, nothing below. Stomach normal except for a deep ulcer in the pyloric ring, measuring 7 by 4 mm., long diameter vertical. The ulcer is filled with a brownish blood-clot, the margins infiltrated and grayish red (Fig. 5). The peritoneum is thickened directly over the ulcer and there is adhesion to the omentum. Heart, kidneys, liver, spleen, adrenals and brain show no changes. Cultures from blood, pericardium, joints, pelvis of kidney and bile sterile, but a blood-plate from material at the base of the ulcer after removing the blood-clot gives an almost pure culture of streptococci (Fig. 7).

Dog 21.—Small, brown and white. Injected intravenously March 13, with the growth from 300 c.c. of ascites-dextrose-broth of Strain 734, ten anima. passages after isolation from a case of rheumatism. Dyspnea, vomiting and great weakness following injection. March 14: Seems fairly well but has developed severe double conjunctivitis; smears from pus contain Gram-staining diplococci. March 15: Blood-agar plates from pus from eyes show almost pure cultures of green colonies resembling those injected. March 18: Seems ill; has lost in weight. Marked tenderness and swelling of right wrist and elbow-joints. Muscles of back and about shoulders seem tender. March 21: Cultures from joints show few green colonies. Seems better but eats very little and continues to lose in weight. Heart action slow and very irregular. Discharging sinus above right wrist. March 23: Cultures from discharging sinus contain chiefly green colonies. April 10: Chloroformed. Mucous membrane and tissues quite pale. Sinus above wrist leads along muscle sheaths. Fluid from elbow-joint turbid; no connection between elbow-joint and the suppuration adjacent to it. Pericardium empty; whitish linear areas in myocardium; endocardium normal except for a nodular thickening in posterior leaflet of tricuspid valve. Localized adhesive pleuritis. Stomach normal. Duodenum shows a rather large, round ulcer, 2.5 cm. from the pyloric ring and measuring 8 mm. in diameter. The margin is thickened and undermined, the base covered with a brownish blood-clot. The omentum is adherent. The contents of the large intestine blackish and gives a strong Weber test for blood. Liver shows moderate fatty degeneration. The kidneys present a number of small whitish areas in cortex. There are a number of whitish streaks in skeletal muscles, most numerous in the muscles about shoulder and in intercostal muscles; none in diaphragm. Several teeth are loose and there is osteomyelitis of lower jaw. Smears from pus around elbow-joint and lower jaw contain large numbers of Gram-staining diplococci. Cultures from blood, pelvis of kidney and pericardial sac sterile, from elbow-joint give a moderate number, from pus of discharging sinus and pus in lower jaw a large number of slightly hemolyzing colonies.

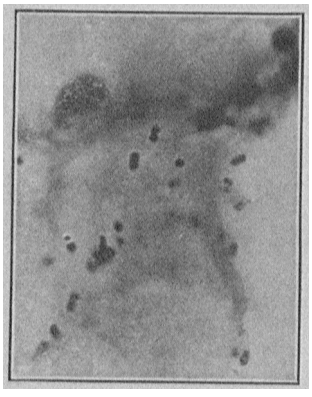

Fig. 7.—Streptococci in the disintegrating connective tissue in the margin of the ulcer shown in Figure 5; × 1200.

MONKEY.—Injected into vein of forearm on March 18 and 20 with the growth from 100 c.c. ascites-dextrose-broth of Strain 734H. Died on April 2 after severe diarrhea. Only the changes in the stomach are given here. The stomach is normal except for three deep ulcers, two near the pyloric end, the other and the largest in the pyloric ring. All have a clean base and are undermined with infiltrated margins. The largest has bridges of mucous membrane over undermined portions (Fig. 3). The omentum is adherent and, on dissection of the adhesions over the largest ulcer, a small perforation of the serous coat is found. Small intestines normal. The mucous membrane of the large intestines is red, the lymph follicles are much swollen and a number show superficial ulceration. The lymph-nodes in the mesentery and about the pyloric end of the stomach are enlarged and hyperemic. Purulent material in one ulcer in the stomach shows saprophytes and colon bacilli only, but from a small piece of the wall of one ulcer, thoroughly washed and crushed, there are obtained in addition to a few contaminating organisms fifteen colonies of streptococci, whereas a similar portion of adjacent healthy mucous membrane shows no streptococci.

SUMMARY

Intravenous injection of streptococci of the proper grade of virulence may be followed by ulcer of stomach and duodenum. The ulceration is due to a localized infection and secondary digestion. The ulcers are usually single and deep with marked tendency to hemorrhage and perforation, and resemble the human gastric ulcer in many respects. When we take into consideration this close resemblance, that injection of streptococci which have grown in tonsils produce the lesions, and that the virulence of the germs when the affinity for the stomach is greatest is of such character that a general infection does not occur, it appears altogether reasonable to suppose that in man gastric ulcer may be caused by streptococci also. The supposed relation between infected tonsils or gums and gastric ulcer may be due not to the swallowing of bacteria, as usually supposed, but to the entrance into the blood of streptococci of the proper kind of virulence to produce a local infection in the wall of the stomach. Many other observations might be cited such as associated infections of the gall-bladder and appendix, which suggest that gastric ulcer may be due to streptococci.

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Then as Now.—We are prone to surround the past with a kind of mystic glamor. We do not give honor where honor is new, but reserve our panegyrics for times and methods whose inaccessibility denies all chance of refutation. For example, we think the middle ages knew something about toxicology. So they did, but not a tithe of what we vaguely give them credit for. The old apothecary was not a pocket Borgia. Men were asked out to dinner and they sometimes died after it. But *post cibos* is not necessarily *propter cibos*, and one man's meat was not always poison for another. There was not always death in the pot. If we look at a sixteenth-century menu we have a general feeling, not of amazement that men should occasionally die after a banquet, but rather of surprise at the survivors. Then it is probable that modern surgery would have saved some of these moribund postprandialists—that perforation, not poison, ushered them into the *Ewigkeit*. In fact, these terrible toxicologic tales suffer from exaggeration. The morality of the times demanded sudden death in convenient form, and an alleged supply arose. It is much the same as if our day was judged by its patent-medicine advertisements. Reading them, a truthful age would sigh and offer illimitable gold for what we can buy for 1s. 1½d. As a matter of fact, we do not buy them. We know that some men are liars now, but we forget that there were liars in those days.—*Med. Press.*