A GASTRO-ENTERITIS OUTBREAK PROBABLY DUE TO A BOVINE STRAIN OF VIBRIO*

A. J. LEVY

Acute disorders of the gastro-intestinal tract are generally precipitated by certain groups of pathogenic bacteria, such as the salmonella, shigella, and proteus groups,^{1, 20, 21, 30, 39, 41, 42, 45, 52, 53} or by a metabolic product, as enterotoxin, which is formed by some strains of hemolytic staphylococci and streptococci and liberated into the food.^{4, 7, 17, 34, 48, 54, 66} Hemolytic staphylococci have been identified most frequently as the offending agents in gastro-enteritis,^{9, 13, 15, 16, 18, 49, 50, 51, 55, 56} yet the medical literature reveals that an almost equal number of outbreaks have been due to shigella and salmonella. Recent articles have described outbreaks of epidemic form, showing diarrhea, nausea, and vomiting, attributed to an unknown cause, possibly a virus.^{2, 6, 36, 47}

Many epidemics can be traced to a definite source and the causative organisms can be successfully isolated and identified. Occasionally, even though the facts are at hand, their correlation may not be easily accomplished^{5, 11, 14, 24, 43, 46} and reliance must be placed on circumstantial evidence. Such was the situation in the following outbreak.

Epidemiology

On May 8, 1938, the Communicable Disease Division of the Illinois State Department of Public Health was notified of an acute outbreak of gastro-enteritis among the inmates of two adjacent institutions, N and O. The former is located about six miles north, the latter, two miles east, of a city of 40,000 population. The epidemic which began on May 4, 1938, was investigated three days later, when the attack rate had gained considerable momentum. At the beginning, a diagnosis of "intestinal flu" was made by the institution physician, because, in addition to the salient symptoms nausea, vomiting, abdominal cramps, diarrhea, and fever—patients complained of general malaise, headache, backache, profuse per-

^{*} From the Illinois State Department of Public Health, Chicago, Division of Communicable Diseases, District No. 1.

spiration, conjunctivitis, and general prostration. No cases of similar infection were reported in the adjacent city. However, at Institution O, which was in close contact with N, cases appeared almost simultaneously. This contact consisted not only of an occasional transfer of inmates, but also of the conveyance of food, three times daily, from N, where the food was prepared for both institutions.

The epidemiologic data obtained were limited to 151 hospitalized patients, 123 at N and 28 at O infirmaries. The study was confined to these groups because these cases were better controlled and the information gathered was more accurate, as careful records were kept on patients admitted to the infirmaries where clinical observations were made and laboratory studies followed up. As for the rest of the patients who were not hospitalized, it was felt that clinical and epidemiologic information collected from them was too inaccurate and unreliable to be incorporated in this study. However, in order to estimate the magnitude of the rate of the attack these cases are included in the registry of daily cases.

Table 1 lists the combined number of cases as they were reported daily to the administration of both institutions. Inmates were asked to report when they developed any of the salient symptoms, as vomiting, abdominal cramps, diarrhea, elevation of temperature, headache, and backache. The table also shows the number of patients admitted daily to the infirmary of each institution. Because of the limited bed space, only those acutely ill were admitted. There were 11 cases on May 4, the first day of the outbreak, but no record had been kept of them. On May 6, 29 patients had general prostration accompanied by headache and fever, but they showed no gastro-intestinal symptoms. The cases that appeared after May 11, exhibited very mild symptoms of headache, a low-grade temperature, and nausea, but no diarrhea or abdominal cramps, and they were not hospitalized. The epidemic lasted for 13 days. The rate of attack among the 6019 inmates at both institutions at the time of this investigation was 5.9 per cent. The average days of illness was from three to five days. The shortest duration was two days, and the longest was two weeks.

TABLE 1

| Date | Combined number of cases at both institutions | Number of cases admitted to infirmary N | Number of case admitted to infirmary O | |
|-----------|---|---|--|--|
| 5- 4-38 | 11* | | | |
| 5- 5-38 | 29 | 20 | 5 | |
| 5- 6-38 | 74† | 15 | 4 | |
| 5- 7-38 | 52 | 40 ' | 6 | |
| 5- 8-38 | 51 | 13 | 9 | |
| 5- 9-38 | 57 | 20 | 2 | |
| 5-10-38‡ | 48 | 15 | 2 | |
| 5-11-38\$ | 7 | | | |
| 5-12-38 | 7 | | | |
| 5-13-38 | 7 | | | |
| 5-14-38 | 5 | | | |
| 5-15-38 | 4 | | | |
| 5-16-38 | 5 | <u> </u> | — | |
| Total | 357 | 123 | 28 | |

DAILY REGISTRATION OF GASTRO-ENTERITIS CASES

* No record kept.

+ 29 cases had only headache and fever; no gastro-enteric symptoms.

[‡] Milk was ordered boiled.

§ From this date patients were not hospitalized; none acutely ill.

An epidemiological investigation was conducted among the 151 patients admitted to the infirmaries because of acute gastro-enteritis and general prostration. This number (151) constituted 42.3 per cent of the 357 cases reported during the epidemic.

The predominant symptoms among the hospitalized group were fever and diarrhea. A rise in temperature to between 99° and 102° axillary was seen in 79.6 per cent of the cases, lasting for from two to five days. There were 71.5 per cent who had diarrhea. Three successive watery bowel movements mixed with mucoid matter were considered as diarrhea. There were four patients who had ten bowel movements for a day or two. Chills, followed by profuse perspiration, were experienced by 24.2 per cent; headache and backache by 22 per cent; vomiting, abdominal cramps, and nausea by 15.4 per cent; aching limbs by 14.5 per cent. General prostration was common to 92 per cent of the patients admitted to the infirmaries. Since more than 70 per cent developed gastro-enteritis, it was believed that some common food or drink, served on several successive days, was the incriminating factor. All food and drinks served during the week prior to the outbreak, as well as during the epidemic, were investigated. Breakfast was served from 7: 30 to 8, lunch from 11: 30 to 12, and dinner from 5 to 5: 30. The usual breakfast consisted of cooked or dry cereal with milk, bread and butter or a bun, with coffee; the lunch was hamburgers, salmon patties, or stew and potatoes, bread, coffee, and a dessert consisting of either applesauce or stewed prunes; for supper, salmon, macaroni, fish or cold cuts. Thoroughly washed vegetables grown on the farm owned by Institution N were served three to four times a week. Bread, water, and milk were the only food articles served regularly every day.

The State Sanitary Engineer inspected the wells supplying both Institutions and found them safe. Samples of water sent to the State Laboratory were free of contamination. After investigating all food and beverages served to the inmates prior to and during the epidemic, milk appeared to be the most likely source of infection.

With a very few exceptions, all patients had milk for every breakfast. Since milk was the only food used daily, it was assumed that milk served as a possible vehicle for the offending factor.

The epidemiologic investigation showed that 108, or 71.5 per cent, of the observed cases developed gastro-enteric manifestations between 10 A. M. and noon (see table 2), which meant that the incubation period varied between three and four hours, following breakfast. This study will consider the three- to four-hour incubation period, but it should be borne in mind that a possibility exists that the incubation period may have started a day or two previous to the appearance of the epidemic, as the exact day on which the contaminated milk was consumed is not known. This would probably account for the small number of cases that developed at the end of the epidemic, after the milk was rendered safe. There were 14 cases, or 9.1 per cent, who became ill in the afternoon, five to six hours following breakfast, and a still smaller group of patients, 5, or 3.5 per cent, that developed symptoms between the evening and the following morning. In the latter groups there were two cases who experienced nausea, abdominal cramps, chills, fever, and headache, while the third patient, who was in isolation and consumed only bread and water, developed diarrhea with no other symptoms. Among the first group (132) there were two who claimed that they partook of no milk. There was no way of checking their statements.

| Date of onset | Length of incubation period | | | | |
|------------------|-----------------------------|--------------|--------------------|--|--|
| | <i>Hours</i> 3-4* | Hours 5-8 | Hours 12 and up | | |
| 5- 4-38† | | | | | |
| 5- 5-38 | 23‡ | 2 | | | |
| 5- 6-38 | 16 | 3§ | | | |
| 5- 7-38 | 39 | 4 | 3¶ | | |
| 5- 8-38 | 20 | 2 | | | |
| 5- 9-38 | 19 | 2 | 1** | | |
| 5-10-38 | 15 | 1 | 1** | | |
| Total | 132 | 14 | 5 | | |

| TABLE 2 | | | | | | |
|---------|----|------------|--------|--|--|--|
| STUDY | OF | INCUBATION | PERIOD | | | |

* The beginning of the incubation period was unknown. It may possibly have been from 24 to 48 hours prior to the estimated period.

[†] No reliable record kept.

[‡] 2 cases claimed not to have used milk.

§ 1 case attributed his illness to fish.

 ¶ 1 case was in isolation and had only bread, butter, and water.

** Only chills, fever, and headache; no gastro-enteric symptoms.

The possibility of admitting to the institution a convalescent carrier suffering from gastro-enteritis prior to his admission was seriously considered. However, none of the histories prior to this epidemic confirmed this assumption. Suspecting that a carrier or convalescent carrier of enteric disease might be handling food in an unsanitary manner, all food handlers were required to submit specimens of feces and urine to the laboratories for study.

Assurance was given by the administration of the Institution that every drop of milk was adequately pasteurized. Samples of milk were studied bacteriologically by the laboratory of the Institution and checked by the state laboratory.

On May 10, when the epidemic still continued, a thorough check-up was made on food supplies and on the method of food handling in kitchens and dining rooms. A study of the milk supply revealed two different sources; source A, a minor supply, consisted of whole milk, and source B, a major supply, of skimmed milk. Milk from source A was produced on the Institution Farm and was pasteurized on the premises, while milk from source B was obtained from Dairy E, a private concern, located about twenty miles away. This milk was pasteurized and delivered to the Institution in tengallon cans. Inspection revealed that the can covers were loosely fitted. When foreign substances were seen floating on the top of one can, suspicion was aroused as to the sanitary handling of the milk at source B. Therefore, all milk was ordered to be boiled before serving.

An inspection of Dairy E revealed that the process of pasteurization was carried out properly, but the company handled raw as well as pasteurized milk. Both types of milk were poured into identical ten-gallon cans, without any distinguishing labels, and placed in a cooler side by side. The foreman of the company when questioned, admitted that a driver could easily have picked up a can of raw milk and shipped it by error as pasteurized milk. This was probably the source of the trouble.

The milk distribution at the institutions apparently bore a direct relationship to the disease. Milk from source A went to the kitchens of the infirmaries, to the inmates working on the farms, and to the employees. Not a single one of the 500 employees and inmates who consumed source A milk developed gastro-enteritis. Milk from source B was the sole supply to all other inmates, and all cases occurred among inmates consuming this milk.

Clinical and bacteriological laboratory study

There were two laboratories at hand for service during this epidemic. The one at the Institution was equipped to do both clinical and bacteriological work; the other, a trailer laboratory, supplied by the State Department of Public Health, was equipped only for bacteriologic investigation. The work described was done by both laboratories.

Vomitus of 6 patients were examined macroscopically and revealed remnants of some undigested food, mixed with a dirty brownish liquid. Cultures were made of vomitus on plain agar, blood plates, and Endo medium. No typhoid, salmonella, or shigella, and no hemolytic streptococcus or staphylococcus was found.

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There were 73 specimens of feces submitted for study on acutely sick patients. Excreta examined macroscopically revealed watery stools mixed with some mucoid substance. No blood was seen, with the exception of one case which apparently was caused by internal bleeding hemorrhoids.

Fresh microscopic specimens and smears were prepared for parasitologic and bacteriologic study. Examination for parasites revealed *Amoeba coli* in two cases, and ova of intestinal parasites (*Ascaris lumbricoides*) in three.

Smears were prepared from the mucoid substances and stained with methylene blue, Gram stain, and carbol fuchsin. Some specimens prepared from the mucoid material disclosed vibrio-like microorganisms, almost in pure culture (Fig. 1). At first the smears were disregarded because the laboratories were unable to grow the organism in media on which vibrios ordinarily thrive. However, since the vibrio was observed in 31 cases more weight was given to this finding.

Endo, brilliant green, and desoxycholate media were inoculated with excreta, in the hope that the causative agent might be found. Bile medium was used because of the vibrio-like findings. All cultures gave the common result, predominantly *B. coli*.

At the end of the third week of the outbreak 306 patients, who had loose stools during the epidemic, submitted feces for examination before being released. Out of the 306 patients, 16 specimens were still positive for the vibrio.

The food handlers (57) submitted feces and urine for examination. None were found to be carriers of enteric disease.

Urine and blood studies

Urinalysis: When urine was collected immediately after the chills, the specimens of 16 patients revealed on three occasions a trace of albumin. No sugar was found. Microscopic examination revealed nothing unusual.

Blood counts and cultures: Blood counts, both red and white, were made on 17 patients during chills. The red blood cell count varied between 4,650,000 and 5,300,000. The white count also showed considerable variation from 9,600 to 15,000 with the majority above 10,000. The differential count varied in different patients. However, the lowest neutrophile count was 63 per cent and the highest 75 per cent. The lymphocyte count varied from 20 to 32 per cent. Other cells, as basophils and eosinphils varied from 0 to 5 per cent.

During the chills, three specimens of 20 cc. of blood were taken from each patient and cultured in beef heart broth. Smears prepared from these cultures revealed the spirilla observed in the feces of the same patients. Of the 39 patients whose blood was thus cultured, 13 showed the above findings (see Fig. 2).

Transfers were made from the blood cultures to Loeffler's medium and blood agar. Some signs of scanty growth were noted on Loeffler's medium after 5 days of incubation, but no growth appeared on the blood agar. A week later only four cultures remained alive, 544 R, 20 S, 3490 G, and 3531. Specimens 3490 G and 3531 showed no sign of growth on the second transfer to Loeffler. Culture 544 R was taken to the State Laboratory for further study, but it died after a few transfers. Hence, all experimental studies were carried out on specimen 20 S.

Experimental study*

This micro-organism was a spirillum greatly resembling the cholera vibrio in morphology, comma-shaped or having a double undulation. It varied in length from 1.5μ in young cultures to 3.5μ in older cultures. The organisms were actively motile, each possessing one polar flagellum. They were killed at 55° C., in 10 minutes. They took the Gram stain negatively and poorly, but stained well with carbol fuchsin. In its biologic behavior the vibrio differed from the cholera vibrio and other pathogenic strains, but it resembled those of the "Vibrio fetus" described by Theobald Smith⁵⁷ and by Welch and March.⁶⁵ In fact, it bore an even closer resemblance to the "Vibrio jejuni" noted by Jones, Orcutt, and Little.³³

An attempt was made to replate on Endo medium, blood agar, plain agar, Herrold's, Loeffler's, liver agar, and milk agar, but no sign of growth was noted even after two weeks of incubation at

^{*} The bacteriologic study on the specimen of Vibrio 20 S was carried on for a year and a half, at the Laboratory of the Illinois Medical School, Dept. of Bacteriology and Hygiene.

either 37°C. or at room temperature. Transfers were made to Loeffler, blood agar, North's gelatin and plain gelatin, Herrold's egg medium, and tryptose phosphate agar. Good growth occurred in tryptose phosphate beef broth or brain broth in 48 hours, or longer, at room temperature. Incubation of the culture at 37°C. did not greatly accelerate the growth.

In a liquid medium the growth appeared at the surface. No pellicle was formed. No liquefaction was noted in plain gelatin, but some occurred in North's gelatin. The following sugars were used: lactose, dextrose, mannite, saccharose, maltose, glycerol, galactose, and levulose, but no positive reactions were noted, even after a week of incubation. There was no indol or cholera red, and no growth in plain or litmus milk, but later, after about 20 transfers, some growth was noted in plain milk.

After approximately 30 transfers on tryptose phosphate broth, subcultures on plain or tryptose phosphate agar showed fine grayishwhite growths at the bottom of the slant where condensation water had collected. This growth showed a tendency to spread very slowly on the side of the slant between the agar and the wall of the tube.

Two rabbits and three pigeons were injected intravenously and intramuscularly, respectively, with 2 cc. of a 36-hour culture of the vibrio in tryptose phosphate brain broth. The animals exhibited no signs of discomfort or illness, either immediately or during the two-week period of observation. However, when a 3 cc. dose of the same culture of vibrio in tryptose phosphate was injected into the femoral vein of a 40-pound dog, the animal developed a severe diarrhea within 24 hours, which terminated fatally. Autopsy revealed a distended stomach containing a slightly blood-tinged fluid. Macroscopically, the lungs, liver, spleen, and kidneys showed no gross pathologic changes. No microscopic sections were made. The peritoneal cavity contained a slightly sanguineous fluid. Examination of the internal surfaces of the gastric and intestinal mucosa showed no significant pathology. A small quantity of mucoid liquid fecal material adhered to the mucosa in some areas of the small intestine. No evidence of gross ulceration was noted.

Direct smears from the cut surfaces of the liver and spleen revealed the vibrio in these organs. An attempt to culture material taken from these organs failed to show any growth. Direct smears from the intestinal material adhering to the wall of the mucosa showed numerous vibrios.

A 4 cc. dose of a 48-hour culture of the vibrio in tryptose phosphate brain broth was injected intraperitoneally into two guinea-pigs and one rabbit. The vibrio was detected in the blood of these animals within from 3 to 4 hours following the injection.

Each of three kittens was fed 30 cc. of milk with 10 cc. of vibrio culture. Though each kitten consumed its ration, none showed any reaction to the vibrio inoculum.

| | Dilutions of serum from patient S 20 | | | | | |
|-----------------------------------|--------------------------------------|----------|------|------|-------|-------|
| Organisms | 1:10 | 1:20 | 1:40 | 1:80 | 1:160 | 1:320 |
| Hemolytic staphylococcus | + | + | - | | | |
| E. typhosus | + | + | - | - | - | - |
| S. typhi murium | + | <u> </u> | - | — | - | |
| Staphylococcus, stock strain | + | + | - | - | - | - |
| Streptococcus, stock strain | + | - | - | - | - | - |
| Flexner V | + | + | - | | - | - |
| Brucella | + | + | + | - | - | |
| Vibrio cholerae, stock culture | + | + | - | - | - | - |
| Vibrio S 20 | + | + | - | - | - | - |

TABLE 3 AGGLUTINATION TESTS

Serologic study

Ten cubic centimeters of blood were drawn from each of six patients recovered from the diarrhea. As can be seen from table 3, there was no indication that the serum (S 20) would agglutinate any organism to a higher titer than it would another. Titers of 1:40 or even 1:80 are not acceptable for identification purposes.

Table 4 includes data for two different periods: (a) the first, a month following the epidemic, and (b) eight months later. Vibrio S 20 was used with different sera taken from the same inmate. Serum from S 20 did not at first agglutinate higher than 1:40, and eight months later no higher than 1:80. This agglutination is not conclusive since serum 349 V gave a similar titer.

TABLE 4

| | Dilutions | | | | | |
|--------|------------------------|----------------------------------|------|------|-------|-------|
| Sera | 1:10 | 1:20 | 1:40 | 1:80 | 1:160 | 1:320 |
| |] | (A) One month following outbreak | | | | |
| 544 R | + | + | - | · | - | - |
| 20 S | 1 + | + | + | | - | - |
| 3490 G | + | + | + | - | - | - |
| 3531 | + | + | - | - | - | - |
| 349 V | + | + | - | - | | - |
| 789 M | + | + | + | - | - | - |
| | (B) Eight months later | | | | | |
| 544 R | + | + ` | ÍŤ | - 1 | - | _ |
| 20 S | + | + | + | + | - | - |
| 3490 G | + | + | - | _ | - | - |
| 3531 | + | + | - | - I | - | - |
| 349 V | + | + | + | + | _ | - |
| 789 M | + | + | + | - | - | - |

SERA FROM INMATES: AGGLUTINATION WITH VIBRIO S 20.*

* 0.1 cc. of Vibrio S 20 culture in tryptose phosphate brain broth added to each of the dilutions.

Discussion

Since the cholera vibrio was discovered by Koch³⁵ in 1884 many vibrios of different strains have been described by various investigators.^{8, 22, 23, 25, 26, 27, 31, 38, 44, 63, 64} Only very few of these vibrios were pathogenic to man. Theobald Smith found that abortion in some animals was not due to Brucella but to spirilla.⁵⁷ The amniotic fluid of the fetuses contained pure cultures of a vibrio. Smith succeeded in finding these organisms in the gastro-intestinal tract, as well as in the spleen, liver, lungs, and kidneys of the fetus. Subsequent animal experiments with *Vibrio fetus* proved conclusively that this organism like the Brucella was responsible for abortion in animals. Cases of abortion in sheep due to the vibrio have been reported by many investigators.^{8, 22, 25, 27, 38, 64}

Smith,^{59, 61} Welch,⁶⁴ and Gilman²⁵ encountered great difficulties in culturing the bovine vibrio, since it would not grow on ordinary media. Smith gives a detailed description of the methods used for culturing the vibrio. The organism grows in condensation water on the slant only when fresh blood or bits of tissue are placed on the slant and the tubes are sealed with wax.

Jones and Little,⁸² and Smith and Orcutt⁶⁰ have demonstrated

pathogenicity in some strains of the vibrio causing gastro-enteritis in cattle. Jones and his associates isolated a vibrio from cows suffering from diarrhea and from calves affected with enteritis. Healthy calves and cows fed and injected with cultures of these vibrios developed both diarrhea and enteritis.

Jones and his associates isolated the vibrio from ulcers in the mucosa of the small intestine of animals suffering from enteritis. The growth appeared as a delicate line on the border of the agar, the wall of the tube, and beneath the surface. This strain, termed *Vibrio jejuni* because of isolation from ulcers in the jejunum, is distinguished from *Vibrio fetus*. According to these authors, "the induced disease resembles, to a certain extent, human cholera, and the vibrios from bovine diseases resemble the human organisms in young cultures. However, the bovine vibrios differ markedly from the comma vibrio in cultural characters. The bovine groups are more difficult to grow; they fail to liquefy gelatin or blood serum and will not survive on strong alkaline media. They have not been shown by means of acid or gas production to utilize carbohydrates."

The above description of the biologic behavior of V. jejuni, corresponds very closely to that of the vibrio found in the blood and feces of patients during the outbreak of acute gastro-enteritis described in this paper. All attempts to trace the vibrio to some diseased herd supplying milk to Dairy E were unsuccessful, since the farmers involved were reluctant to disclose any illness among their herds. The samples of milk collected came from animals which had not previously been stricken with diarrhea. There was no special media or technic known for growing and isolating the vibrio from milk.

Although it was not possible to demonstrate definitely that the milk served as a vehicle for the infecting agent, the circumstantial evidence was very strong. First, all inmates who were taken ill had consumed milk from Dairy E, and that inmates and employees who consumed milk from the Institution Farm were entirely free from gastro-enteritis. Second, the micro-organisms were isolated from the blood of patients who suffered with chills and diarrhea. Third, the same organisms were found in the feces of the same individuals. Fourth, evidently one or two cans of non-pasteurized milk were included by mistake with the daily shipment of pasteurized milk. Fifth, when the milk was boiled the number of cases dropped to almost none. Sixth, diarrhea among cows of different herds and enteritis among calves due to a bovine vibrio have been described. It remains to be established whether the vibrio is excreted in milk of a cow suffering from diarrhea and enteritis and whether the milk of cows affected with diarrhea produces gastro-enteritis in man as is the case in Brucellosis.

Summary

1. An outbreak of gastro-enteritis which occurred simultaneously in two adjacent institutions is described.

2. Epidemiologic study pointed toward milk as the vehicle for the infective agent, for when the milk was boiled the number of cases was reduced to almost none.

3. Blood cultures from patients suffering with chills showed a spirillum. Of 39 blood cultures, 13 yielded the spirillum. The vibrio-like organism was found in the feces of 31 of 73 patients.

4. Study of a culture of the vibrio, S 20, both in vitro and in vivo, disclosed its characteristics.

5. The literature dealing with vibrio-like organisms has been reviewed and the vibrio causing diarrhea in cows and enteritis in calves is discussed. The likelihood that this vibrio, S 20, might be identified with *Vibrio jejuni* is suggested.

6. That the vibrio pathogenic to cattle may also be pathogenic to man seems a possibility from this investigation. However, because of the lack of conclusive evidence, we shall have to await further epidemiologic, clinical, and laboratory investigations to confirm the suggestion that a bovine vibrio transmitted through the milk supply may have been the cause of the epidemic.

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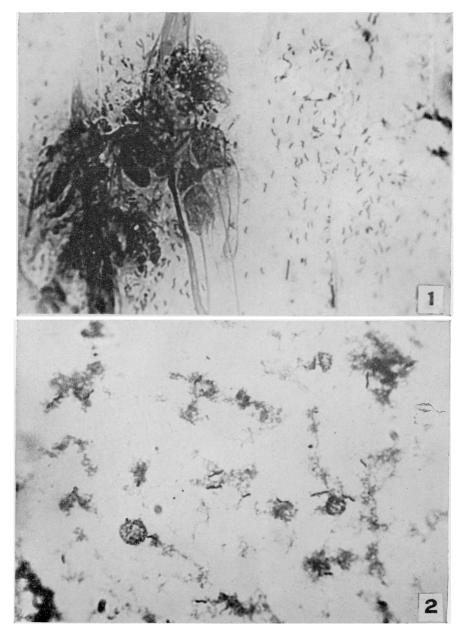


FIG. 1. A direct smear from a whitish flake found in feces taken from a patient with diarrhea on May 9, 1938. Stained with carbolfuchsin for vibrio-like bacteria. Magnified 400 times. FIG. 2. A smear from a blood culture in beef heart broth after incubation for 48 hrs. Carbol fuchsin stain showing vibrio-like micro-organisms, taken from a patient with chills and diarrhea on May 9, 1938. Magnified 400 times.