

Section of Therapeutics and Pharmacology.

President—Dr. H. H. DALE, C.B.E., M.D., F.R.S.

Kaolin in the Treatment of Asiatic Cholera: Its Action and Uses.¹

By R. R. WALKER, B.Ch.

THE cholera bacillus is a small, highly motile organism, 1·5 to 2 μ in length, curved on one axis and provided with a single flagellum. It grows freely in alkaline broth or on alkaline agar. It stains readily with weak carbol fuchsin and solutions of the culture give a rose-pink colour reaction on the addition of pure sulphuric acid; also, according to Greig, true *Vibrio cholerae* is non-hæmolytic. Agglutination tests against a high titre anti-cholera serum will differentiate between the true cholera and paracholera or El Tor vibrios.

The disease in man is characterized by general systemic disturbance—vomiting, profuse watery diarrhœa, muscular cramps, cold, clammy condition of the surface, suppression of urine, are the general characteristics. The onset is sudden as a rule, and in the most virulent infections a condition of cholera sicca occurs, in which the patient dies before the diarrhœa has set in.

Treatment has been directed to meet all conditions which occur. Potassium permanganate, opium, saline injections, subcutaneously and intravenously, with hypertonic solutions of saline (Rogers) have been used with considerable effect.

During the epidemic at the close of the Balkan War, 1900, Stumpf's bolus treatment (bolus albus) was tried at Nish by Dr. Victor Kuhne² with remarkable results. Bolus albus or kaolin (China clay) is aluminium silicate $H_4Al_2SiO_6$, a salt insoluble in water, with crystals of 1 μ in length in a fine state of division. This salt was in use in early Roman times, and was also used by the natives of the Orinoco. It has been employed in diphtheria in Germany, as a powder, insufflated on the fauces and tonsils, and also as a mixture internally. It has been used in ptomaine poisoning with success (Mutch), also in dysenteries, and in the treatment of sprue, and toxic conditions. The general effect of the salt seems to point to the adsorption of toxins. Kuhne claims that the mortality in the cases treated with kaolin was reduced from 60 to 3 per cent. The method of preparation was as follows: A suspension was made of equal amounts of water and kaolin, the kaolin being stirred into the cold water (i.e., 100 gm. kaolin to 250 c.c. aq.). Half-pint doses of this suspension were taken half-hourly for the first twelve hours. During the second twelve hours several glasses were taken according to the patient's condition. Vomiting soon ceased, the pulse improved, and the patient slept.

¹ At a meeting of the Section, held April 19, 1921.

² *Rev. Med. de la Suisse Rom.*, September, 1918, p. 555.

24 Walker: *Kaolin in the Treatment of Asiatic Cholera*

In the summer of 1919 China was visited by a severe epidemic of cholera. Dr. Louis Braafladt, of Tsinanfu, gives, in the *China Medical Journal* of May, 1920, the result of the use of kaolin. The method of administration was somewhat different from Kulme's, and his results are as follows: Patients having—

(1) Hypertonic saline treatment (after Sir Leonard Rogers), mortality 22 per cent. Convalescents discharged on the eighth day.

(2) Kaolin and hypertonic treatment, mortality 29 per cent. Convalescent patients discharged on the sixth day.

(3) Kaolin treatment only, mortality in thirty-five cases one patient (this patient died of gangrene of uterus after miscarriage). Convalescent patients discharged after four days.

All these patients had true cholera vibrios isolated during their stay in hospital.

In the cases of Asiatic cholera treated in Foochow at the American Red Cross Hospital when first opened, no definite hard and fast line of treatment was maintained. Cases were treated by continuous subcutaneous injection of normal saline, with administration of potassium permanganate by the mouth until the motions became green. Hypertonic intravenous saline injections (Rogers) were given in amounts up to 3 litres or until the blood-pressure became normal. Dextrose was added in some cases to the intravenous solutions.

Whatever method was used, some features of the disease remained constant:—

First, although the patient on arrival might appear moribund, being cold, rigid and with imperceptible pulse, the introduction of saline could usually be relied on to produce return of consciousness and a greatly improved pulse. With the hypertonic intravenous solutions a rigor of great intensity could be looked for before the end of the introduction of the second litre. This, however, was disregarded, and the saline was continued until the blood-pressure had attained the normal.

Secondly, relapses were the rule—in fact sometimes even before the completion of the injection of a second patient was completed, the first patient, through excessive diarrhoea and vomiting, might be urgently requiring more fluid.

Thirdly, cases which could be supported until the acute diarrhoea and vomiting had passed, were still in grave danger from suppression of urine. This persisted in some of the cases six days. The only remedy seemed to be the use of almost continuous "cupping," usually by means a de Bier's suction glass over both kidneys.

During the epidemic in Foochow, in the summer of 1919, kaolin was used by myself with considerable success, but there was difficulty in obtaining a good supply. On my return to Hing Hwa, where cholera was raging, I had no difficulty in obtaining kaolin, as the famous Blanc de Chine clay beds are situated near this district.

The method of administration was somewhat different from Stumpf's methods. A large supply of half-and-half suspension was placed near the patient, and the patient was encouraged to take as much as possible. At first large quantities could be tolerated, but as the vomiting and diarrhoea ceased the liquid was refused. In all cases food was withheld for eighteen to twenty-four hours, then rice water was allowed, and later milk and rice water. In all cases rectal lavage was done with kaolin solution thickened until it would

comfortably pass through the rectal tube. At first some was returned, later much was retained. If the condition was precarious on arrival at hospital, subcutaneous bilateral infusion usually restored the patient sufficiently to take the kaolin by the mouth. In desperate cases hypertonic salt solution was given intravenously (Rogers) but not in such large quantities as we used before the introduction of the kaolin treatment (2 litres). This is shown to be of value by the results obtained by Braafladt with hypertonic saline and kaolin, which were not, however, so good as those obtained with kaolin alone.

After the introduction of the kaolin method the following differences were noted :—

If the patient's condition was "fair," that is, if the pulse was perceptible and the patient conscious, the introduction of large quantities of kaolin suspension by the mouth and *per rectum* would ensure continued recovery. After two hours all vomiting ceased, a sense of safety had been reached, and the patient usually slept.

In the lighter cases the diarrhoea ceased within twelve hours and urine was passed within from twenty-four to thirty-six hours.

In the most critical cases, which required the introduction of saline to bring about an improvement of the pulse, rectal introduction of heavy suspensions of kaolin was commenced at once and had a perceptible effect in preventing the further loss of fluid. On return of consciousness and during the introduction of the saline, kaolin was given by the mouth, and was usually retained, while in those cases in which there was vomiting, it was thought that some kaolin which had been deposited on the walls of the stomach had begun to adsorb the toxic products of the cholera vibrio, and the second administration of the kaolin suspension by the mouth was frequently retained, or only partially returned.

The distinctive advantages of the kaolin treatment were :—

- (1) Simplicity of method.
- (2) Absence of relapse.
- (3) Cessation of loss of fluid.
- (4) Great improvement owing to adsorption of toxins, the patient becoming rapidly free from a general "toxic condition."
- (5) Early return of the passage of urine.
- (6) Early and rapid convalescence.

In St. Luke's Hospital, Hing Hwa, we had a series of seventy-five cases from one village, situated two hours' journey from hospital, with no fatal results, and this in spite of the fact that many of the patients arrived in a condition of extreme collapse. The mortality of untreated cases at this village was stated by the village headman to be exceedingly high, though I was unable to obtain exact figures, as in China there is no registration of deaths.

LABORATORY EXPERIMENTAL WORK ON THE ACTION AND EFFECT OF KAOLIN.

Rabbit fed with 20 c.c. of a 50 per cent. kaolin suspension : on chloroforming eighteen hours later, it was found that there were well-marked traces of kaolin over the walls of the stomach, duodenum and upper small intestine, increasing in amount down the lower small intestine to the cæcum, which was full of liquid contents mixed with kaolin. The colon was full of dry masses of dark brown faeces which, on opening, showed white kaolin inside.

Rabbit fed with 20 c.c. of a 50 per cent. kaolin suspension and also 20 c.c. of a 50 per cent. kaolin suspension rectally, chloroformed forty-two hours later :

the stomach and duodenum distended by a new vegetable meal showed no signs of kaolin, but there were traces on the walls of the upper small intestine which increased in amount to the cæcum, while the transverse and descending colon were full of dry masses of kaolin and fæces mixed.

A further experiment showed the microscopical appearance and the position of the kaolin in the intestinal tract. A rabbit was fed at 9 a.m. with 20 c.c. of a 30 per cent. kaolin and water mixture. At 12 mid-day this was repeated, and the rabbit killed at 2 p.m. Sections of the stomach, upper and lower small intestine and large intestine were taken, the gut being stretched on cork rings to prevent retraction on hardening. These were fixed, hardened and cut, and stained with eosin and methylene blue. Under a low power the kaolin could be seen, lying in a thin line in close apposition to the mouths of the glands. Much of the kaolin had fallen away in the course of preparation. Under a high power it was possible to make out the kaolin, sticking closely to the cells, and in some cases the cells adherent to the kaolin layer had been torn away in process of preparation.

Cultures of *Vibrio cholerae* from Guy's Hospital Bacteriological Laboratory and the Lister Institute were used throughout the following experiments in duplicate.

Intraperitoneal inoculations were made through three series of guinea-pigs to raise the virulence. The resulting cultures gave typical pure cholera reactions and were those used in the following experiments.

To broth cultures of *Vibrio cholerae* varying strengths of kaolin were added. Later, agar plates were planted from this mixture. In every strength growth was obtained, thus showing that kaolin has no bactericidal effect.

Suspensions of *Vibrio cholerae* were filtered through varying thicknesses of kaolin deposited on silk, and the filtrate planted on agar. In all cases growth occurred, thus showing that cholera bacilli can pass through kaolin.

Agar tubes were prepared with kaolin mixed in the agar in varying amounts. It was found that the presence of kaolin had no effect on the growth of the cholera bacillus.

From the above experiments it is clear that the presence of kaolin in the bowel has only a mechanical effect on the *Vibrio cholerae* itself. This mechanical effect, however, may be instrumental in sweeping out a large quantity of the vibrios, and it should be remembered in using this treatment that the disinfection of the stools is essential, also that it is quite possible that many of the patients return home as cholera carriers.

PREPARATION OF TOXINS.

Half-litre flasks of alkaline peptone water were used, incubated at 37° C. for periods of four, six or fourteen days and filtered by means of an exhaust pump through a porcelain candle. The filtrate was sterile, shown by planting on culture media. The hollow tube of the candle was scraped to remove the deposited bacilli, which, mixed with normal saline, were heated at 60° C. for an hour. Both the filtrate and the saline emulsion containing the dead bacilli were filtered through kaolin by means of a vacuum pump. No indol reaction was obtainable with the filtrates. Commercial indol, on the other hand, filtered through a kaolin bed. These results were confirmed by repeated experiment.

The fact that the substance producing the "indol reaction" is held back by the filter bed while indol solution comes through, points to the possibility that the "toxin" giving indol reactions is not a true indol, but a larger

(2) The deposit was scraped from the hollow tube of the candle, mixed with a small quantity of 0·8 per cent. salt solution, and then "killed" by one of three methods: (a) Heating at 60° C. (one hour), (b) exposure to Finsen light (one hour); (c) adding chloroform to the solution in sufficient amount to leave a clear layer of chloroform showing, then shaking the mixture (five minutes). The method of killing the vibrio appeared to have no distinctive effect on the results: the "toxins" could be heated at 60° C. to dryness and yet retain their virulence. This "killed" deposit was then injected intravenously into rabbits: 2 c.c. was fatal, the time varying with the strength of the toxin.

(3) The above deposit was then ground in a bacillary mill to break up the bacilli, mixed with 0·8 per cent. saline, and again filtered through the porcelain candle.

(4) The filtrate was found fatal to rabbits if 2 c.c. were injected intravenously.

(5) The deposit was also fatal to rabbits, being more rapid in its action than the filtrate.

(6) The addition of kaolin to any of the fatal toxic fluids destroyed their toxic properties.

GENERAL CONCLUSIONS.

The action of kaolin is twofold: (1) Mechanical; (2) adsorptive.

(1) *Mechanical*.—Such large quantities of kaolin as are used in the treatment of cholera, almost fill the bowel, and the passage of this mass through the bowel must enclose and carry with it a very large number of bacilli. Kaolin has no bactericidal effect, and this fact calls for energetic action in the destruction of fæces in all cholera cases treated by this method. The fact that the kaolin forms an adherent coating to the walls of the bowel point to its usefulness in ulcerative forms of colitis, though in these cases the rectal method of administration in the form of enemata and long tube lavage would be preferable owing to the possibilities of errors of digestion arising, after long administration, from the adsorptive properties of kaolin for ferments.

(2) *Adsorptive*.—This, the chief function of kaolin, is very characteristic—its extremely fine state of division promotes that end.

From the above experiments it is clear that, at least in the case of cholera and probably in diphtheria, ptomaine poisoning, bacillary diarrhoea, summer diarrhoea and general toxic conditions, kaolin has a wide range of use.

In the case of cholera, the first result of its administration is the cessation of vomiting. This seems to be due to the adsorption of toxic bodies in the upper alimentary tract. This is followed by the cessation of the diarrhoea and consequent loss of fluid caused by the presence in the bowel of irritant substances of a toxic nature. These, being adsorbed by the kaolin, cease to act as an irritant, and consequently the improvement of the patient is rapid and maintained.

The presence of a layer of kaolin on the walls of the intestinal tract appears to act in part as a filter bed preventing the transmission of toxins to the patient.

The adsorptive action of kaolin does not seem to be chemical. Professor Bayliss¹ has pointed out that kaolin is an electro-negative colloid, whose sign

¹ Bayliss, "Principles of General Physiology," p. 72.

may become changed by allowing it to absorb ions of opposite sign to itself. This apparently occurs in the small intestine.

I am indebted to Professor Russ and Mr. Clark for the following fact (experiments were made after Hardy's method, *Journal of Physiology*, xxxiii, p. 289): Cultures of *Vibrio cholerae* in an alkaline medium gave a definite electro-negative sign.

The adsorption of cholera toxins by the kaolin may be explained by the electrical reaction between the two, and the failure of the toxin to reach the circulation may be explained by the electrostatic attraction of the suspensoid kaolin for the cholera toxin, which thus forms one component of a Helmholtz double layer.

Professor Bayliss has pointed out that sodium chloride diminishes electro-negative charge, in accordance with Gibbs' principle; this may be the explanation of the difference observed between cases of cholera which have had saline injections preceding the kaolin treatment and those treated by kaolin only.

I am greatly indebted to Professor Eyre, of Guy's Hospital, for his kind help in the bacteriological experiments.

"THE SUCCESSFUL TREATMENT OF LEPROSY BY INJECTIONS OF SOLUBLE PREPARATIONS OF THE FATTY ACIDS OF CHAULMOOGRA AND OTHER OILS, AND ITS BEARING ON THE TUBERCULOSIS PROBLEM," by Sir LEONARD ROGERS, C.I.E., M.D., F.R.S.

This paper, read at a meeting of the Section, April 19, is printed *in extenso* in the *Practitioner*, August, 1921, pp. 77-101 (with references).