

danger of overdose. Overdose is also indicated by the "alkaline tide urine" approaching the "rest urine" in character.

Since hearing Sir Almroth Wright's lecture on Acidosis delivered at St. Mary's Hospital subsequent to these notes being compiled, we have come to the opinion that the reason why, during treatment with acid, a rise in the blood pressure is reversible—i.e., followed by a more or less similar fall, while this subsequent fall in blood pressure is not easily reversible—is because an acidosis may be transferred to the tissues, the acidæmia thus being changed into a histo-acidosis, and this causes a fall in the blood pressure. If a histo-acidosis be established it is not easy to raise the blood pressure again, because of the difficulty either of raising the acid content of the blood above that of the tissues or of reducing the acidity of the tissues below that of the blood, the fluid pressure thus persisting towards the tissues, while the balance is against the blood. Such a hypothesis would explain what occurred in the two cases referred to above, in which acidæmia took place.

In these cases cedema and a very considerable fall of blood pressure occurred after the discontinuance of the acid and the condition was not readily reversible. The administration of the alkalies did not remove the cedema, although following on very small infrequent doses of acid the cedema disappeared, and there was a slight rise in blood pressure. This sequence of events would seem to support the idea that an acidæmia had developed into a histo-acidosis.

THE ACTION AND USES OF KAOLIN IN THE TREATMENT OF ASIATIC CHOLERA.¹

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POSSIBLY the earliest mention of cholera is in the time of the Yellow Emperor of China, circa 1500 B.C., when five general "body conditions" were described. The Ganges bed in India is, however, generally regarded as the home of the disease, and in late historical times, epidemics in 1500 and 1700 A.D. are on record. In 1817 and 1837 there were world-wide epidemics. In every case the infection followed lines of travel—e.g., caravan routes, pilgrimages, lines of ships, &c. Between 1817 and 1823 this plague spread from India through China and as far west as Egypt. During 1826–27 Europe became infected, and thence, via England, Canada and the U.S.A. From 1837–93 Europe has had successive visitations resulting in a death-rate in Russia in one year of 800,000, and in Hamburg of 8600.

In the year 1883 Koch discovered the cholera organism, which he called the comma bacillus or cholera spirillum. This spirillum is a small organism 1.5–2 μ in length, curved on one axis and provided with a single flagellum which causes it to be highly mobile. The bacillus 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; according to Grieg, true cholera vibrios are 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 characterised by general systemic disturbance. Vomiting, profuse watery diarrhoea, 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, where the patient dies before the diarrhoea has set in.

Bolus or Kaolin Treatment.

Treatment has been directed to meet all conditions which occur. Potassium permanganate, opium, saline injections, subcutaneously and intravenously, hypertonic solutions of saline (Rogers) have been used with considerable effect. It was, however, during the Balkan epidemic at the close of the Balkan War, 1913, that Stump's bolus treatment (bolus alba) was tried at Nish by Dr. Victor Kulme² with remarkable results. Bolus alba, or kaolin (China clay), is aluminium silicate, $H_4Al_2Si_2O_9$, 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 also been employed in diphtheria in Germany, as a powder insufflated on the fauces and tonsils, and also a mixture internally. It has also been used in ptomaine poisoning with success (Mutch), also in dysenteries, summer diarrhoea of children, and its use is indicated in the treatment of sprue and toxic conditions. The general effect of the salt seems to point to the absorption of toxins. By the use of this salt Kulme claims that the mortality in the cases treated was reduced from 60 per cent. 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 g. kaolin to 250 c.cm. aq. Half-pint doses of this suspension were taken half-hourly for the first 12 hours, the second 12 hours several glasses were taken, according to the patient's condition. Vomiting soon ceased, the pulse improved, and the patient slept.

During the summer of 1919 China was visited by a severe epidemic of cholera, and Dr. Louis Braafladt,³ of Tsinanfu, has given the result of the use of kaolin. The method of administration was somewhat different from Kulme's; and his treatments and results are as follows:—

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

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

3. Kaolin treatment only—mortality in 35 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 cases of the 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 three 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, that 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. (A point of interest was noted in the treatment of these cases—namely, that when no superficial vein of the body could be demonstrated suitable for the introduction of the saline, through the extreme loss of fluid, or through the

¹ A paper read at the Section of Therapeutics and Pharmacology of the Royal Society of Medicine, April 19th, 1921.

² Revue Médicale de la Suisse Romande, September, 1918.

³ China Medical Journal, May, 1920.

needling done by native physicians in the veins for the purpose of letting out the "toxic blood," the vein passing over the internal malleolus on the inner side of the foot could always be found.)

Secondly, that relapses were the rule; 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, that 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 for six days. The only remedy seemed to be the use of almost continuous "cupping," usually by means of 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 Stump's methods. A large supply of half-and-half suspension was placed near the patient and the nurse was told to encourage the patient to take as much as possible. At the commencement large quantities could be tolerated, but as the vomiting and diarrhoea ceased the liquid was refused. In all cases food was withheld for 18 to 24 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 none was returned. Later on much was retained. If the condition of the patient was precarious on arrival at hospital, it was found that subcutaneous bilateral infusion usually restored the patient sufficiently to take kaolin by the mouth. In desperate cases hypertonic salt solution was given intravenously (Rogers), but no 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 so good as those obtained with kaolin alone.

Advantages of Kaolin Treatment.

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

In the lighter cases 12 hours saw the cessation of diarrhoea and 24 to 36 hours the passage of urine. 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 were commenced at once and had a marked 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 which vomited it was felt that some kaolin had been deposited on the walls of the stomach which began to absorb the toxic products of the cholera vibrio; the second administration of the kaolin suspension by the mouth was frequently retained or only partially returned.

So the most marked advantages of the kaolin treatment were: (1) simplicity of method; (2) absence of relapse; (3) cessation of loss of fluid; (4) great improvement in the condition of the patient from the absorption 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 cases treated in St. Luke's Hospital, Hing Hwa, we had a series of 75 cases from one village, situated two hours' journey from hospital, with no fatal results, and this result was obtained in spite of the fact that many of the patients arrived at hospital 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 owing to the absence in China of any registration of deaths.

Laboratory Experimental Work on the Action and Effect of Kaolin.

In a rabbit fed with 20 c.cm. of a 50 per cent. kaolin suspension, on chloroforming 18 hours later, well-marked traces of kaolin were found 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.

In a rabbit fed with 20 c.cm. of a 50 per cent kaolin suspension, and also 20 c.cm. of a 50 per cent. kaolin suspension rectally, chloroformed 42 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 faeces mixed.

A further experiment was done to show the microscopical appearance and position of the kaolin in the intestinal tract. A rabbit was fed at 9 A.M. with 20 c.cm. 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, 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 had torn away, adherent to the kaolin layer in process of preparation.

Cultures of cholera vibrios 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

TABLE I.

Kaolin suspension strength.	Agar plate after 24 hours' growth.	Result.
1.8 per cent.	—	++
2.5 " "	—	++
5.0 " "	—	++
10.0 " "	—	++
20.0 " "	—	++

TABLE II.

<i>V. cholerae</i> through silk.	Filtrate grown on agar.	Result.
1.0 c.cm. of 5% kaolin suspension	—	++
2.5 c.cm. " " "	—	++
5.0 c.cm. " " "	—	++
7.5 c.cm. " " "	—	++
10.0 c.cm. " " "	—	++
20.0 c.cm. " " "	—	++

virulence. The resulting cultures gave typical pure cholera reactions and were those used in the following experiments. To broth cultures of *V. cholerae* varying strengths of kaolin were added. Later, agar plates were planted from this mixture, and the results given in Table I. were obtained, thus showing that the presence of kaolin in cultures of *V. cholerae* had no bactericidal effect.

Filtration of suspensions of *V. cholerae* were then made through varying thicknesses of kaolin deposited on silk, as given in Table II., 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.

As far as the above experiments go, it is clear that the presence of kaolin in the bowel can have no other than a merely mechanical effect on the cholera vibrio itself. This mechanical effect, however, may be instrumental in sweeping out a very large quantity of active cholera 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 4, 6, or 14 days. The above medium was 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 tested as follows:—

Pulp was spread thinly over a perforated plate and 100 c.cm. of a 10 per cent. kaolin suspension poured over this bed. The above liquids were filtered through by means of a vacuum pump. It was found that no indol reaction was obtainable with the filtrates obtained. Commercial indol, on the other hand, filtered through this bed. Tests were made as shown in Table III.

TABLE III.

1. Formalin and strong sulphuric acid	No colour with filtrate.
Filtered commercial indol solution and above reagent	Blue colour.
With unfiltered toxin solutions	Blue colour.
2. Glyoxylic acid } and filtrate	No reaction.
Strong sulphuric } and indol solution	Red.
" " and toxin solution	Red.
3. Nitric acid and filtrate	No reaction.
" " " indol solution	Red.
" " " toxin solution	Red.
4. Sod. nitro-prusside (fresh sol.) and filtrate	No colour.
" " " (fresh sol.) and indol solution	Violet, changing to green-blue.
" " " (fresh sol.) and toxins	Violet on addition of acetic acid.
5. Filtrate extracted with benzol and No. 4 test applied	No colour.
Toxin extracted as above gave characteristic indol reactions.	
6. Paradimethylamido-benzaldehyde	
Alcohol	
HCl.	
Potass. persulph. (equal parts)	
" " and filtrate	No colour.
" " and indol sol.	Pink.
" " and toxin	Pink.

The above series of tests were made as the fact of the "toxin" being held back by the filter bed while indol solution came through pointed to the possibility that the toxin giving indol reactions is not a true indol, but a larger molecule which is held back by the China clay filter, while the commercial indol, which has a small molecule and is in solution, can get through.

A further series of experiments was made to test the absorptive power of kaolin for "indol," as found in the *V. cholerae* toxin-peptone water culture fluid. Week-old *V. cholerae* toxin was taken and well mixed with equal weights of kaolin. Of this mixture 1 c.cm. was withdrawn every five minutes for an hour and a half and tested with Ehrlich's indol reagents. A standard colour series was made with commercial indol solutions of dilutions up to 0.0001 g. per c.cm. added to Ehrlich's reagents, and it was found that after centrifugalising 1 c.cm. of kaolin and toxin suspen-

sions at five minute intervals no variation in the indol colour index was obtained, thus showing that the suspension of kaolin in *V. cholerae* toxin cultures had no absorptive action on the indol in the culture.

A further series of experiments was made to test the action of kaolin on ferments. Rennet and trypsin were used. (Table IV.)

TABLE IV.

	Result.
Rennet and milk	Coagulation.
Rennet centrifugalised and milk	Coagulation.
Rennet shaken with kaolin and milk	Some delay in action.
Rennet and kaolin shaken at intervals for half an hour. Centrifugalised: clear liquid added to milk.	Considerable delay in action.
Rennet filtered through kaolin bed and filtrate added to milk.	No action.

The same experiments were performed with trypsin, and the digest of gelatin plates used as indication of action of ferment. The same results as above were obtained and it was found that trypsin filtered through kaolin beds had no digestive action on the gelatin plate. It was found that 3 c.cm. of a 10 per cent. kaolin suspension caused rapid death in a rabbit if injected intravenously: Death was caused by deposit of kaolin on valves and walls of the heart and subsequent clotting of the blood. Six c.cm. of a 1 per cent. suspension had no apparent effect on the rabbit. On post-mortem examination 24 hours later no kaolin could be detected in the blood. Intraperitoneal injections of 10 c.cm. of a 20 per cent. kaolin suspension in a guinea-pig caused death in 20 hours. Post mortem: signs of peritonitis. Masses of kaolin were present everywhere in the abdomen. The lower surface of the diaphragm and the omentum were thickly plastered with kaolin. Slide preparations were made of the mesentery and omentum, but it could not be demonstrated that the lymphatics were packed with the salt, though its presence, adherent to the cells, was obvious everywhere.

Toxins.

The culture used in the experiments given in Table V. was one from a fatal case of cholera in India. The vibrio was non-hæmolytic, agglutinated well, and gave typical reactions of a cholera vibrio. Half-litre flasks of alkaline peptone water were used. These were sterilised three times with an interval between sterilisation to remove all spore-bearing bacilli. The resulting toxins were examined at 4, 6, and 14-day growths. It was found advantageous to have wide-necked flasks so that as large a surface area as possible might be presented to the air. The resulting bacillary growth was moved each day by shaking, when it fell to the bottom of the flask and a new growth appeared. To obtain a virulent culture for growing the following method was adopted.

A rabbit was inoculated intra-peritoneally with one tube of 24 hours' growth of the strain mentioned above. On chloroforming in three hours' time it was found that all signs of the cholera vibrio had disappeared, and no growth was obtainable. Therefore passaging was then done through a series of five rabbits, each being killed two hours after infection, the growth cultivated on agar for 24 hours and the whole culture injected again. By this method a more virulent organism was obtained, a tube culture of which would kill a rabbit in 20 hours. One loop of culture killed in five days with progressive wasting.

A. Toxins were grown from cholera vibrio	No passage.
B. " " " " "	3 passages.
C. " " " " "	5 "

Finally:

D. Toxins were grown from the five passages *V. cholerae* injected into a rabbit, with the addition of some of the four-day toxins grown from the five passages *V. cholerae*.

The four strengths of "toxic fluids" were then investigated as follows:—

1. The toxic fluid was filtered through a porcelain candle by means of an exhaust pump. The filtrate, which was clear, was injected intravenously and intra-peritoneally into two rabbits with no fatal results. Amounts up to 4 c.cm. were used.

TABLE V.—Culture Medium—Alkaline Peptone Water.
(2 c.cm. injected intravenously in each case as recorded below.)

—	Days' growth of culture.	Peptone medium filtered through porcelain candle.		Bacillary deposit of last column ground in bacillary mill, picked up in saline, and refiltered through candle.		Fatal fluids of above experiments filtered through kaolin filter-beds and filtrate injected.	Above fluids shaken with kaolin, centrifugalised and injected.	2 oz. kaolin placed in ½-litre flask of peptone culture medium.	Control without kaolin.
		Filtrate.	Bacillary deposit.	Filtrate.	Deposit.				
A. Toxins grown from V.C., no passage.	4	—	+ 24 hrs.	—	—
B. Toxins grown from V.C., 3 passage.	4	—	+ 12 hrs.	—	+ 12 hrs.	—	—
	6	..	+ 12 hrs.	—	+ 12 hrs.
	14	..	—	—	—
C. Toxins grown from V.C., 5 passage.	4	—	+ 8 hrs.	+ 8 hrs.	+ Under 8 hr.	—	—
	6	..	+ 8 hrs.	+ 8 hrs.	+ Under 8 hr.	—	—
	14	..	—	—	—
D. Toxins from 6 passage (being 5 passage V.C. injected with four-day-old toxins added).	4	—	+ 8 hrs.	+ 8 hrs.	+ Under 8 hr.	—	—	—	+
	6	..	+ 8 hrs.	+ 8 hrs.	+ Under 8 hr.	—	—
	14	..	—	—	—

+ Fatal. — Not fatal.

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) heat at 60° C. for an hour; (b) Finsen light, one hour exposure; (c) chloroform added to the solution in sufficient amount to leave a clear layer of chloroform showing. After shaking the mixture, five minutes killed the *V. cholerae*. (The method of killing the *V. cholerae* appeared to have no marked effect on the results obtained—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.cm. 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, and after mixing with 0·8 per cent. saline, was again filtered through the porcelain candle.

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

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

I am greatly indebted to Prof. J. W. H. Eyre, of Guy’s Hospital, for his kind assistance in the above experiments.

General Conclusions.

The action of kaolin is two-fold: (1) Mechanical; (2) adsorptive.

1. *Mechanical.*—The administration of 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. It has, however, no bactericidal effect, and this fact calls for energetic action in the destruction of faeces 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, due to the adsorptive properties of kaolin for ferments.

2. *Adsorptive.*—This, the chief function of kaolin, is very marked; its extremely fine state of division lends itself to 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, and general toxic conditions, kaolin has a wide range of use. In 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 cessation of diarrhoea and consequent loss of fluid which is 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 would appear to act partly as a filter-bed and prevent the transmission of toxins to the patient. The adsorptive action of kaolin does not appear to be chemical.

Professor Bayliss has pointed out that kaolin is an electro-negative colloid, which sign may become changed by allowing it to adsorb ions of opposite sign to itself (Bayliss, p. 72); this, I take it, occurs in the small intestine.

I am indebted to Professor Russ and Mr. Clark (of Middlesex Hospital Cancer Research Department) for the following fact (experiments were made after Hardy’s method, *Journal of Physiol.*, xxxiii., p. 289): Cultures of cholera vibrio in an alkaline medium gave a definite electro-negative sign. So 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 electro-static 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’s principle; this may be the explanation of the marked difference in treatment of cases of cholera which have had saline injections preceding the kaolin treatment, to those treated only by kaolin.

THE LATE DR. VICTOR DONALD ORR LOGAN.—Dr. Logan died at St. Mary’s Hospital, London, last week from injuries received through being knocked down by a motor cycle in Bayswater-road. He graduated M.B., Ch.B. Edin. in 1909, and was a temporary Captain, R.A.M.C. Formerly he was resident medical officer at St. Mary’s Hospital, Plaistow, to the Sussex County Hospital, Brighton, and to the Prince of Wales Hospital, Tottenham. At the time of his death he was in practice at Liverpool.