maniacal condition, and he was certified as dying of acute delirious mania, which accorded with his symptoms. I found that his blood and fluid both gave a positive reaction, and there was an abundant lymphocytosis of the fluid. There were scarcely any naked-eye signs of general paralysis; in fact, there was nothing which could be asserted positively as evidence of the disease—a circumstance which accorded well with the history, that just prior to the accident he had been discharged from the navy and had passed as a taxi driver. I found a definite scar of a chancre on the penis. Examination of several regions of the brain were made, but only in one region examined were there the histological appearances characteristic of the disease—namely, increased vascularity, well-marked infiltration of the small vessels of the cortex with plasma cells and lymphocytes, also the membranes, proliferation of the glia cells, absence of the tangential fibres, distortion of Meynert's columns, and atrophy of the constituent ganglion cells; lastly, the existence of the "rod cells of Alzheimer." All these conditions showed that this man was suffering with acute mania of general paralysis in its earliest stage; it is, therefore, highly probable that the severe injury had been the exciting factor in the production of the disease. We are able to decide two points by this examination—namely, that the man had general paralysis, a disease that is invariably fatal; that he had syphilis, which is an essential cause. That the evidence *post mortem* was to the effect that it was in its earliest stage, and might therefore never have occurred if he had not had the severe accident. The fact of the existence of the scar of the chancre and antecedent syphilis should not weigh in the minds of the jury if they were satisfied that the man in all probability was not suffering with general paralysis prior to the accident, for only a very few syphilitic subjects die of general paralysis.

Another case has recently occurred which, from a medico-legal point of view, is of interest in showing how necessary it is to examine various parts of the brain histologically to confirm the diagnosis of general paralysis. Dr. Bond, of Long Grove Asylum, recently gave evidence in a trial in which the wife of one of his patients alleged that traumatism was the cause of her husband's mental breakdown. Dr. Bond considered that the case was clinically one of general paralysis of the tabetic variety, although he said there were certain anomalous bodily symptoms. He sent me the central nervous system of this patient when he died. I found a typical tabetic lesion of the posterior columns of the spinal cord. Examination of the prefrontal and central convolutions did not show the typical lesion of general paralysis. The tip of the first temporal convolution, especially on one side, showed all the characteristic lesions which I have just described. I will show photographs illustrating these points.

In conclusion, I beg to thank you for so kindly listening to me so long, and yet I feel there are many things left unsaid which I might have said; however, many eminent authorities are about to follow who will be able to fill up the gaps, and very probably also from their wide experience modify and correct some of the statements I have made. Finally, I wish to acknowledge my indebtedness to my assistants, Dr. Candler and Mr. Sydney Mann, who have carried out the researches on the blood and cerebro-spinal fluid to which I have referred, and upon which I have based my opinion as to the value of the reaction. These were published in the *Lancet* recently by Dr. Candler.

THE Council of the Central and Associated Chambers of Agriculture at its meeting on October 31st decided to ask the President of the Board of Agriculture to issue regulations for the sale of condensed machine-skimmed milk, and requiring that every tin should have printed upon the label "Unfit for infants and invalids."

A MEETING of the Medico-Psychological Association of Great Britain and Ireland will be held at the house of the Medical Society of London (Chandos Street), under the presidency of Dr. W. R. Dawson, on Tuesday next, at 3 p.m. After the transaction of formal business, papers will be read by Dr. Geoffrey Clarke on sterilization from the eugenic standpoint, and by Dr. C. T. Ewart on amenorrhoeal insanity.

CHOLERA AT PALERMO:

FURTHER EXPERIENCE IN THE TREATMENT OF CHOLERA BY INJECTIONS OF HYPERTONIC SALINES AND PERMANGANATES INTERNALLY AMONG EUROPEANS AT PALERMO.*

By LEONARD ROGERS, M.D., MAJOR I.M.S.

It is impossible, as it is unnecessary, in such a paper as this, to give a complete account of all the details of the system of treating cholera which I have worked out during the last few years in Calcutta, as they are fully recorded in my recently published work on the disease,¹ while a summary appeared in a paper in the *BRITISH MEDICAL JOURNAL*.²

PATHOLOGICAL PRINCIPLES.

It will, however, be advisable briefly to recapitulate the principles on which it is based, so as to allow of what I have to say regarding my recent very instructive experience of cholera among Europeans at Palermo being more readily followed.

The Blood Changes in Cholera as a Scientific Basis for its Treatment.

In the first place my researches³ have shown that in the collapse stage of cholera, from one-half to two-thirds, or even more, of the fluid of the serum has been lost to the system, while in the most severe cases a still greater proportion of the chlorides may be lost, and the serum may even be haemolyzed. These observations indicate the necessity of rapidly replacing the lost salts as well as the lost fluid, and of raising the salts in the blood somewhat above the normal point, so that the osmotic currents will tend to cause fluid to run into the blood rather than out of it, and thus the diarrhoea will be checked, instead of increased, as it is by the use of normal salines. For this purpose I use the following hypertonic saline solution:

Sodium chloride	...	...	...	120 grains.
Potassium chloride	...	...	...	6 "
Calcium chloride	...	...	...	4 "
Aqua	...	...	...	ad 1 pint

As this formula contains 1.35 per cent. of sodium chloride it is twice as strong as formerly used as normal saline, and half as strong again as the amount of salts now given as the normal amount by physiologists. The last two chlorides are added to make the proportion of the three approximate to Ringer's solution, which, when perfused through an animal's heart, will keep it beating very much longer than sodium chloride alone. Messrs. Parke Davis make hypertonic tablets of the above composition such that four to one pint make my hypertonic solution, while three in the same amount make an approximately normal saline. I used them with marked success at Palermo. I have, however, used 2 drachms to the pint of sodium chloride alone in very many cases, with successful results. I may take this opportunity of pointing out that the solution advised for intravenous injection in the article on cholera in the last edition of Allbutt's *System of Medicine*, consisting of 0.4 per cent. sodium chloride and 0.2 per cent. sodium carbonate, is dangerously hypotonic; in fact, I found it haemolyzed a little of my own blood nearly completely in about two hours, so that its use in large quantities would probably have most disastrous consequences.

Blood Pressure and Specific Gravity Estimations as a Guide to Transfusions in Cholera.

The degree of collapse may be accurately measured by taking the blood pressure with one of the numerous modifications of the Riva-Rocci mercury manometer. Observations on several hundred cases of cholera have shown that if the blood pressure has fallen to 70 mm. or less in natives of India, or to 80 mm. or less in Europeans—which means a serious degree of collapse—it is necessary to give intravenous injections, but if above these points, saline injections are readily absorbed when given subcutaneously as hypertonic solutions, or by the rectum as isotonic ones. Of even greater value is the estimation of the specific gravity of the blood by means of a series

* Read before the Clinical Section of the Royal Society of Medicine.

of twelve small bottles of glycerine and water of each two degrees from 1048, 1050, etc., up to 1070. A small drop of blood from the finger is blown gently from a capillary tube into the middle of a bottle, and if it sinks it is heavier than the solution, and a higher bottle is tried until it just floats for a few seconds, which is the point required. If it sinks in one and rises in the next, the point is between the two. This estimation can be easily made by the bedside in two minutes, and it furnishes invaluable information as to the degree of concentration of the blood, and the necessity for an intravenous injection, as well as an indication of the quantity required. The normal specific gravity being about 1056, if it is raised to 1063 or over it is safe to inject intravenously 4 pints in an adult male, and $3\frac{1}{2}$ pints in a female. If the blood is very greatly concentrated, as shown by a specific gravity of from 1066 to 1070 or over, as much as 5 or 6 pints may be used, the last one or two being given slowly. The rate of injection can be readily controlled by means of the graduated glass bulb and stopcock cannula made for me by Messrs. Down Brothers. The fluid may be run in at the rate of 4 oz. per minute until a full pulse has returned, and then more slowly, especially if there is headache or oppression of the chest. It is advisable to dilute the blood to several points below the normal specific gravity, so as to allow a reserve of fluid for any further diarrhoea and for excretion through the kidneys, whereby toxins will be removed from the blood. The latter effect will be greatly facilitated by the fully normal blood pressure which will usually be obtained by the injection of the large quantities advised above. In addition to the intravenous injections, whenever the blood pressure falls to 80 mm. or less in a European, half to one pint of normal saline is also injected high up into the rectum every two to four hours in all cases to keep the blood fully diluted, and this measure is continued until at least 2 pints of urine are passed in the twenty-four hours.

Control of the Temperature Reaction.

There is always a rise of temperature in the reaction stage of cholera, even when no salines have been used, and older Anglo-Indian writers regard this as the most dangerous stage of the disease. After an intravenous injection a similar marked febrile reaction occurs, often accompanied by a rigor, and it may sometimes run on into a dangerous hyperpyrexia, if not detected in time, and controlled by cold sponging and iced water rectal injections. A temperature of from 101° F. to 103° F. is a good sign, and if it rises to 104° F. or over, it should at once be reduced by the above measures. I have observed that dangerously high reactions occur most during hot damp weather, and especially in patients whose rectal temperatures were above normal at the time of the injection, although the surface heat may have been much below normal. In such cases the salt solution should be injected at below blood heat. Instances in which 4 pints of hypertonic solution were successfully given intravenously at a temperature of only 86° F. in patients whose rectal temperatures were 105° F. and 106° F. are given in my book.

The Prevention of Uraemia.

The greatest danger after recovery from the collapse stage of cholera is the continued deficiency of the renal secretion, terminating in fatal uraemia and toxæmia. I have shown experimentally that this is due to renal stasis from continued subnormal blood pressure and concentration of the blood, which can be readily detected by blood pressure and specific gravity estimations two or three days before the onset of grave symptoms. Further, provided the kidneys were previously healthy, and the patient is not very old, the onset of uraemia may nearly always be prevented by diluting the blood to at least the normal point by isotonic salines, either subcutaneously or intravenously at a slow rate; and by the use of blood pressure raising drugs, such as digitalin, strophanthin, caffeine, and the vaso-constrictors, adrenalin and pituitrin. A number of illustrative cases are given in my book, so I need only mention here that in Calcutta the deaths from uraemia have been reduced by these methods to one-half their former numbers, and that too in spite of so many grave cases of cholera being tided over the

collapse stage by hypertonic injections intravenously to face the dangers of later failure of the renal secretion.

Permanganates Internally to Destroy the Cholera Toxins in the Bowel.

Although a great reduction in the mortality of cholera resulted from the use of hypertonic salines, yet some of the more severe cases died of toxæmia after being rescued from the dangers of collapse. It thus became clear to me that any further progress must depend on the destruction of the toxins in the body. In the absence of any specific serum of proved potency, I experimented to see if the toxins are readily destroyed by any substance which could be safely introduced into the gastro-intestinal tract in sufficient quantity to be likely to be of service, for as the cholera organisms are practically limited to the interior of the bowel, the toxins must be elaborated there, and absorbed into the blood. As bacterial poisons are mostly albumoses and closely allied unstable albuminous compounds, I tested the action of oxidizing agents, such as I had previously shown readily destroy all kinds of snake venoms, which are also albumoses. I found that cholera toxins are rapidly rendered completely inert by the action of permanganates, so I commenced giving these drugs in the following ways. A solution of calcium permanganate (which is somewhat less astringent than the potassium salt and at the same time stronger, as it is divalent) is given to drink *ad lib.* in a solution of 6 grains or more to the pint. It is usually advisable to dilute it further at first until the patient gets accustomed to the taste, and then gradually increase it as much as possible. In addition, the potassium salt is given in pills, being more convenient for this purpose, as it is much less hygroscopic than the calcium one:

Potassium permanganate	...	...	2 grains
Kaolin	...	...	q.s.

Make a pill and coat with salol or keratin, so that it will pass through the stomach and dissolve in the small intestine, where the action is desired. Two pills are given every quarter of an hour for the first three hours, and then two every half-hour until the stools become green and less copious, which usually occurs within about twelve hours. The pills are then discontinued, but a course of eight pills is given at the beginning of the second and third days under treatment, to prevent relapses. In children smaller amounts must be given. Any pills which are vomited are replaced by others.

Results Obtained in India.

Such is a brief outline of my methods, and I venture to claim that they amount to a complete system of treatment, based on scientific investigations, and affording means of accurately estimating the exact condition of the patient at any stage of the disease and for correctly meeting the indications furnished by the blood pressure and specific gravity estimations. The results obtained during the last four years in India may be summarized by saying that by the use of the hypertonic saline solution intravenously the death-rate in almost 300 cases, during two years, was reduced to 32.6 per cent. from the previous rate in the same hospital during eleven years of 59.6 per cent. Further, during a complete year, with the addition of the permanganates internally, the death-rate was further reduced to 23 per cent. Moreover, I have been informed by Major Megaw, I.M.S., that this last result has been well maintained during the present year; while Capain Rutherford, I.M.S., in an epidemic in the Central Provinces in 1910, also obtained 77 per cent. of recoveries, his death-rate being little more than one-third of that of cases in the same outbreak treated by other methods.

THE TREATMENT OF CHOLERA AT PALERMO AMONG EUROPEANS AND ITS LESSONS.

The above-mentioned results were obtained in natives of India, but in Europeans in Calcutta the disease is more severe, the mortality among them during thirteen years having been no less than 81.6 per cent. With the new treatment the recovery-rate in Europeans in Calcutta has risen from 18.4 to between 50 and 60 per cent., which still leaves room for further improvement. The number of cases of cholera among Europeans in Calcutta are fortunately few, so I was anxious to take advantage of the

prevalence of the disease in Europe this year to obtain a larger experience of the disease among them. Thanks to the very kind help of Professors Marchiafava and Bastianelli in Rome, and of Professor Romano, the Director of the Lazaretto at Palermo, I obtained permission to live at the Palermo Cholera Hospital for three weeks during August, and to demonstrate and practise my methods, with the cordial assistance of the able staff of doctors residing there, who showed me the greatest kindness and did all in their power to make my efforts a success. The difficulties were great, owing to my ignorance of the language, while, until the staff had learnt the details of my methods, the cases were too numerous to allow of the intravenous injections being used as frequently as was desirable, while it was only towards the end of my visit that it was possible to arrange for their being given at night. Moreover, as much of the nursing was done by relatives admitted to look after the patients, it was not possible to ensure for those who had been rescued from very serious collapse the degree of skilled attention which is supplied by the English system of nursing, and which is essential to obtaining the best results in such an exhausting disease as cholera. For these various reasons a number of patients were eventually lost who might have been saved under more completely favourable conditions of work. Nevertheless, the Palermo medical authorities were rapidly convinced of the great advance in the treatment of cholera afforded by my system, while as the results were even better than had previously been obtained among Europeans in Calcutta, I have good reason to be satisfied with them. Moreover, thanks to the great advantage of living at the hospital, and the large number of serious cases I was able to closely watch, I have been fortunate enough to very greatly add to my previously extensive knowledge of cholera in all its rapidly changing phases; with the important result that I am not only fully confirmed as to the great value of the new system of treatment but I am convinced that even still better results will be obtained in the near future by yet earlier and more frequent hypertonic injections. I will therefore first briefly record the results obtained at Palermo, and then detail the lessons I have learnt from my experience there, and point out their bearing on further improvements in the treatment of this justly dreaded disease.

Some idea of the extent of the work at Palermo may be formed from the statement that eighty-four intravenous injections were carried out in 67 patients in twenty-two days, almost all of which I was present at, having on several days spent at least twelve hours in the wards, the temperature throughout having been at a point which would have ensured the use of punkahs in India. In estimating the results I have divided my stay into two portions, as during the first ten days the difficulties already mentioned were particularly great, while during the last twelve days the Italian doctors had learnt my methods and carried them out enthusiastically as far as was possible, and I was able to make daily observations on the blood pressure and specific gravity of the blood in all the more serious cases, and generally carry out my system in a more satisfactory manner than at first. It is also necessary to say a few words on the condition of the cases treated, for it is well known that towards the end of an epidemic the disease is less severe than at first, while there may be much difference of opinion as to what should be clinically classed as cholera. In the first place, as many as twenty patients were admitted on some days; while there was no lack of nearly moribund cases, so there was no evidence of any decline in the virulence of the disease. On the other hand, a number of cases of diarrhoea were admitted as suspected cases, some of which did not present the typical symptoms of cholera during their detention. Professor Romano informed me that during my stay the death-rate to total admissions was under 20 per cent. This is striking testimony, but I would not lay undue stress on it, for the reason just mentioned, that a few non-choleraic diarrhoeas were probably included in the numbers.

Fortunately the difficulty in accurately estimating the results is easily overcome by only considering the markedly collapsed or otherwise very serious cases requiring intravenous saline injections. As I have estimations of the blood pressure and specific gravity in this series, the necessary data are available for com-

paring them with the results I obtained in India in exactly similar cases. I found, however, that a blood pressure of about 70 mm. in a native of India represents a similar degree of collapse to one of about 80 mm. in a European, whose normal point is about 20 mm. higher than that of an Indian. I therefore took the blood pressure of 80 mm. or less as an indication of a degree of collapse necessitating an intravenous injection at Palermo, and my experience showed that even this is too low a point for complete safety. Moreover, Calcutta experience shows that such a degree of collapse in a European suffering from cholera was formerly very rarely recovered from, not more than 10 per cent. of such cases being cured under former modes of treatment. Yet among 27 cases treated by intravenous injections during my first ten days at Palermo, there were 14 recoveries, or 51.8 per cent., representing a probable fivefold reduction in the mortality in these very grave cases. This result was all the more satisfactory because four very old patients were included who were hopeless from the first—a much larger proportion than I have met with in India. Moreover, during this time it was usually only possible to transfuse the worst patients.

During the second period of twelve days no less than 40 patients were given intravenous injections, a number of whom had more than one. There were 24 complete recoveries, or 60 per cent., thus amounting to a probable sixfold reduction in the mortality of these serious cases. Figures, however, convey but a feeble impression of the remarkable nature of the cures resulting from this treatment, while words can do little more. It is necessary to see patients brought in a moribund condition, and rescued from certain death by the intravenous injections and restored to health within a very few days. It will therefore be well to quote from a generous letter Professor Romano gave the day I left, with permission to publish it. The following is a literal translation by a friend who has long lived in Italy:

Palermo, Lazaretto Guadagna,
August 25th, 1911.

I, the undersigned Director of this Lazaretto, do declare that Professor Leonard Rogers lived in this hospital from August 4th of this present month until to-day, in order to practise and demonstrate his method of treatment of cholera. The results obtained have been more than satisfactory, they have been surprising, seeing that many of the patients who were admitted at the point of death regained their health and were discharged cured.

It will be well here to refer to the treatment in vogue on my arrival. I am very glad to be able to say that, short of the use of the methods recently introduced by me, the treatment at Palermo was excellent. Sterile normal saline solutions in sealed glass vessels of half a litre capacity were used for repeated subcutaneous injections, with good results in many patients coming under observation before serious collapse had ensued. The injections were given every few hours until the patient had not only passed the stage of acute diarrhoea, but were also continued until a free secretion of urine was obtained. The results were particularly good in very young children, in whom intravenous injections are very difficult, a point I shall return to presently. Careful attention was also paid to dieting and disinfection, and the whole institution was excellently administered. I made full use of the subcutaneous injections to supplement the intravenous ones, only adding some further salt to raise the strength to the hypertonic point during the acute evacuation stage, and I am of the opinion that some part of the improved results over those obtained in Europeans in Calcutta was due to these subcutaneous injections. They were used in all patients admitted with a blood pressure of over 80 mm. in the earlier stages, and proved efficient in preventing collapse in a number of them. Nevertheless, no less than 15 of my intravenous cases had been admitted with a blood pressure of over 80 mm. and treated by subcutaneous injections of as much as one litre at first and half a litre every four hours subsequently, but became much worse and passed into severe collapse, requiring an intravenous injection, 10 of whom ultimately recovered. It is thus clear that the intravenous method will save a large proportion of the cases in which the subcutaneous one has signally failed to avert the progress of the disease. The fact that the former method of treatment at Palermo was very good as far as it went, certainly better than I have seen in India antecedent to recent

improvements, makes the further marked decrease in the mortality due to my methods, to which the Italian doctors have borne such generous testimony, all the more satisfactory.

Lessons Learnt from my Palermo Experience.

Striking as are the successes with the new methods of treatment, yet it is the failures which teach us most, so a study of the cases in which we did not succeed in rescuing the patients from the deadly grip of severe cholera will be most helpful in the quest for still better results. The following table shows the causes of death in the cases treated by intravenous injections. The figures in parentheses indicate the number of cases which I think might probably have been saved under completely favourable conditions and with my present knowledge and experience.

Cause of Death.	First Series.	Second Series.	Total.
Collapse	10 (4)	5 (2)	15 (6)
Hyperpyrexia	0	2 (1)	2 (1)
Uraemia	1	6 (2)	7 (2)
Lung complications ...	2	0	2
Asthenia	0	1 (1)	1 (1)
Total	13 (4)	14 (6)	27 (10)

The largest number come under the head of collapse, but it will be observed that they were much more numerous in the first series, when time did not permit of the intravenous injections being given as early and as often as was advisable. Six fatal collapse cases are placed in parentheses as possibly preventable deaths. Of these, two were patients who collapsed fatally during the night, when it was not possible to give a second injection, while one should have had a second injection late at night, but it could not be given owing to another more urgent, and ultimately successful, case requiring one at the same time. Of still greater interest and importance are the remaining three cases, as these patients were admitted with a very fair pulse and a blood pressure between 80 and 100 mm., so that an intravenous injection was not considered necessary on their arrival. One later on the same day and the other two on the following morning were found to be collapsed in spite of having been treated with repeated hypertonic saline solutions subcutaneously. An intravenous injection was now given in each, but proved to be too late to save the patients. It is the not infrequent occurrence of such cases which makes one often regret having withheld an intravenous injection at the time of the admission of a patient, and necessitates a careful reconsideration of the rules I have adopted regarding the use of this life-saving measure.

The next largest class is the deaths from uraemia, and here again the two patients who are entered as possibly preventable deaths were admitted with a fairly good pulse and a blood pressure between 80 mm. and 100 mm., but subsequently had to be given intravenous injections, owing to the supervention of serious collapse, in spite of repeated subcutaneous injections. I feel convinced that both of these patients would also have been saved had an intravenous injection been given at the time of their admission. The other two preventable deaths were from hyperpyrexia and asthenia respectively. Had all the probably preventable deaths been averted, no less than 70 per cent. of the very serious intravenous transfusion cases would have been saved.

THE TREATMENT OF CHOLERA IN CHILDREN.

Another aspect of the successful treatment of cholera with regard to which I learnt much from my experience at Palermo relates to the disease in children, who formed a much larger proportion of the cases than in Calcutta. The successful treatment of cholera in young children requires much watchfulness, yet there is no class in which constant care is more fully rewarded by the saving of valuable lives. I have already mentioned that hypertonic salines subcutaneously were often efficient in the pre-collapse stage of cholera in children, while they occasionally were successful even after collapse had occurred. The most striking example of this was in a child, aged 3,

admitted with scarcely any pulse at the wrist, cold and restless, while the specific gravity had reached the very high point of 1067. I considered that the only chance was an intravenous injection, which is a difficult procedure at such a low age. As the transfusion apparatus would not be ready for an hour, I first gave half a litre of the hypertonic solution subcutaneously, and at the end of an hour the pulse had distinctly improved, so the injections were ordered to be continued every four hours, with complete success. In several other less grave cases, in children of from 2 to 7 years of age, the occurrence of serious collapse and the consequent necessity of an intravenous injection was averted by the use of subcutaneous injections. On the other hand, in three boys of from 7 to 11 years, subcutaneous hypertonic salines failed, and the occurrence of grave collapse necessitated the intravenous injection of from three-fourths to one litre of the hypertonic solution, with success in two of them. Altogether, intravenous injections were given in ten children from 6 to 11 years old, with recovery in seven of them, while one was lost of preventable hyperpyrexia when apparently doing well, and one died of collapse, namely a boy, who was moribund on admission. It is thus clear that the intravenous method is eminently satisfactory in children, in whom the use of a small glass cannula (which is readily made from glass tubing with a blowpipe or the flame of a spirit lamp) is often necessary for this purpose. If the elbow veins are too small the large vein which crosses over the internal malleolus usually suffices, or the internal saphenous vein in the thigh may be used, as has been done in Calcutta. From dissections I have made I am convinced that in this way intravenous injections could even be given in an infant, with the aid of one of the small glass cannulas used by physiologists.

THE ADVISABILITY OF STILL EARLIER AND MORE FREQUENT INTRAVENOUS INJECTIONS.

This is the most important lesson I have learnt at Palermo, and is based on the following considerations. I have never seen any harm result from an intravenous injection of hypertonic solution in the acute stages of cholera, with the sole exception of excessive temperature reaction, which is preventable if the precautions I have advised are strictly carried out. On the other hand, I have often had to regret the decision not to give an intravenous injection in a cholera patient coming under observation with a fairly good pulse and a blood pressure of over 80 mm., but who subsequently required one owing to the supervention of collapse, and was ultimately lost. Several such cases at Palermo have already been referred to. This shows that I have not hitherto used the intravenous method as often as is advisable, and the rules I have laid down regarding them require to be reconsidered in the light of my further recent experience. It has been shown above that the patients in whom a reliance on subcutaneous injections proved disastrous all had blood pressures between 80 mm. and 100 mm. on admission, so that it is clear that withholding intravenous injections when the blood pressure is over 80 mm. is not an altogether satisfactory rule. Fortunately we have an additional guide in the specific gravity of the blood, and it is of great interest and importance to note that in all the patients admitted with a fairly good pulse, but who collapsed fatally later, the specific gravity of the blood was 1063 or over on their arrival, which means that they had already lost three or four pints of fluid from their blood. Now with such high specific gravities, continued copious diarrhoea is almost certain to produce collapse within a few hours, while the blood is already concentrated to such a degree as to make the intravenous injection of three to four pints at a not very rapid rate a perfectly safe and highly beneficial procedure in cholera. Again, we have seen that once serious collapse has taken place, although death in this stage can in the great majority be averted by one or more intravenous injections, yet a considerable proportion of such grave cases will ultimately be lost from one or other of the later complications, such as severe reaction, uraemic or lung complications or asthenia. The further diminution of these still not infrequent causes of death can only be accomplished by anticipating and preventing the occurrence of serious collapse by replacing the great loss of fluid as early as possible; or in other words by intravenous injections as soon as the blood has become markedly

concentrated, as shown by a specific gravity of 1063 or over, even though the strength of the pulse may only have fallen a little below normal, as indicated by a blood pressure of not much below 100 mm. I have previously advised that intravenous injections should always be given if the specific gravity is extremely high, such as over 1065, but I would now go further and recommend this treatment to be adopted as soon as the specific gravity has risen to 1063 or over in the stage of acute copious diarrhoea, in order to avert the nearly inevitable collapse if they are withheld. If, however, the acute diarrhoea stage is passed, and the reaction stage with a rise of temperature has commenced, the blood pressure being over 80 mm., an intravenous injection is not necessary, while it is more likely to produce an excessive febrile reaction at this stage.

THE PREVENTION OF URAEMIA.

I have little to add under this heading, except to repeat that the further reduction in the death-rate from this complication must mainly depend on the earlier use of intravenous injections to prevent the onset of collapse with the accompanying stasis of the renal circulation, which is the essential cause of the subsequent deficient renal secretion. It has long been known that the frequency of uraemia is in proportion to the duration of the collapse stage. This point is further illustrated by the fact that all the fatal uraemic cases at Palermo were admitted on the second and third days of the disease, while all also showed a specific gravity of 1063 or over. Several patients admitted after two or more days' complete suppression of urine, and with a high specific gravity and threatened uraemia, were treated by slow intravenous injections (isotonic solutions being used if the blood pressure was nearly normal and the diarrhoea stage past), with the result that the urinary secretion was rapidly re-established and recovery from a very grave condition followed. If in this stage the specific gravity is not above normal, intravenous injections might produce oedema of the lungs, so in that case only subcutaneous and rectal salines should be given. If the respirations continue to be frequent and laboured after urine is being freely passed, oedema of the lungs should be sought for, and if present all saline injections should be stopped.

Such are the lessons I learnt at Palermo, and I venture to hope that their application in the future will do something to still further lessen the death-rate of cholera. That cases will still be met with of too virulent a nature, or coming too late under observation to be saved from a fatal termination, it is useless to deny. Nevertheless, these should be quite exceptional in previously healthy subjects, who are neither old nor extremely young, and who come under treatment at a fairly early period of the disease. In such I think the recovery-rate should be fully 80 per cent. However that may be, the results already obtained furnish a remarkable example of the successful application of modern methods of research, in discovering a life-saving method of treatment of one of the worst scourges which humanity is heir to, and one which should go far towards robbing the disease of much of its terrors in countries adequately provided with skilled medical men.

ADDENDUM.

Since the above sanguine estimate of the probable further reduction of the death-rate in cholera by the still earlier and more frequent use of the hypertonic saline treatment, as advised in the foregoing paper, was written, a report has reached me from Palermo which has more than fulfilled it. Professor Romano has sent me notes with blood pressure and specific gravity estimations of 54 severe cholera cases, all with specific gravities on admission of 1063 and over, which were treated by hypertonic intravenous injections during the month after I left Palermo, with only 8 deaths, or 15 per cent., two of the fatalities having been due to late pulmonary complications. After making every allowance for any possible decrease of the virulence of the disease, these are most remarkably successful results. The impression made by them on Professor Romano and his assistants may be gathered from the opening sentence of his letter, a translation of which reads as follows:

"I have the honour to inform you of the marvellous progress made by the patients whom you left under treat-

ment here at the time of your departure. I have delayed writing in order that I might further communicate, by means of the accompanying letter and forms, the results obtained from a large number of patients who were brought here since then in a hopeless condition, and who have been almost all saved through your valuable and miraculous method of treatment." The Professor goes on to say that he and his assistants hope to be permitted to go to Tripoli to spread the use of my methods there. This generous testimony can leave no possible doubt as to the value of the treatment advocated in this paper.

REFERENCES.

¹ *Cholera and its Treatment*, Oxford Medical Publications. ² *BRITISH MEDICAL JOURNAL*, September 24th, 1911. ³ *Proc. Roy. Soc.*, 1909. ⁴ *Indian Med. Gaz.* December, 1910.

THE PHYSIOLOGICAL ACTION OF AMORPHOUS DIGITOXIN (DIGALEN).

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IN 1904 Cloetta¹ described a product obtained from digitalis leaves which he regards as amorphous digitoxin, and which is now in the market under the name "digalen." I am indebted to the manufacturers of this substance for samples for the purpose of physiological experiment.

Cloetta's own physiological work on digalen dealt chiefly with the question of cumulation. He confirmed Fraenkel's statement² that crystalline digitoxin may give rise to cumulative effects in cats, and added that animals which had exhibited cumulation with this drug showed none even with larger doses of digalen.³ Cloetta also found that digalen appears unchanged in the urine.⁴ Sasaki,⁵ testing digalen on the frog's heart, by subcutaneous injection and by directly douching the ventricle, observed characteristic digitalis effects.

Neave⁶ tested digalen, by perfusion, on the heart and blood vessels of the frog, and by intravenous injection on the rabbit. He also observed characteristic digitalis effects, adding that digalen is less active and also less irritant than either crystalline digitoxin or the B.P. tincture of digitalis. Worth Hale⁷ examined digalen toxicologically and physiologically. He found it less poisonous, and (on the circulatory system) less active than crystalline digitoxin. The lack of uniformity in his results emphasizes the desirability of obtaining digitalis preparations from manufacturing chemists rather than from drug stores. Both Neave and Hale employed doses which, judged by the following observations, were of toxic rather than of therapeutic order.

The present paper deals with two main sets of observations: (a) By intravenous injection, on fully anaesthetized cats; and (b) by perfusion, on the surviving heart of the frog.

Observations on the Cat.

In these anaesthesia was induced and maintained throughout the experiment by ether.

The solution supplied in "ampoules," which contains 0.3 mg. of digalen and 70 mg. of alcohol per c.cm., was (unless otherwise stated) diluted ten times with normal saline and injected slowly into the saphenous vein, whilst blood pressure was recorded either by a mercurial or by a membrane manometer. Urine was collected and measured, both before and after the injections, at intervals of ten minutes, by means of a catheter left continuously in the bladder.

Intravenous injections, containing 0.1 to 0.4 mg. of digalen, produce characteristic digitalis effects—namely, slowing of the pulse, augmentation and prolongation of the systolic wave, increase of arterial pressure, and increased secretion of urine. Such effects usually commence to subside about half an hour after the injection.

The slowing of the pulse by such doses is rarely great, occasionally zero. The normal pulse of etherized cats (200 to 250 a minute) is generally slowed by 10 to 30 beats