To-day zoologists include extinct as well as living animals in their lists. Before Darwin classification was a mania, since Darwin zoologists persistently endeavour to bridge gaps.

FIG. 12.—Young kangaroo hanging on the teat by its lips. (Museum, Royal College of Surgeons.)

Hunter's fossils turned Owen's thoughts to palaeontology and led men to take an interest in animals, huge and weird, that once moved about the earth and then passed into the twilight and silence of the past.

THE ORATION.

A man who achieves greatness in any calling inspires others to follow his example. No man retains prominence unless he has impressed others to believe in him and magnify his name. Those who have been closely associated with a masterful teacher and speak well of him are often mockingly called disciples by his contemporaries. Many who during the lifetime of a great investigator or a reformer were detractors are often loudest in appraising him when dead. When our friends are alive we hesitate to say much about them in their presence—except in after-dinner speeches. As soon as they are dead we are apt, in a paroxysm of sympathy, to overpraise their work. Hunter was in advance of his time; his contemporaries could not appreciate the value of his work, and some of his later admirers overrate it.

The delivery of the Oration is justified. It is necessary to remind men of their benefactors; even the holiest saints require to have their names preserved by shrines, chantries,

cathedrals, or festivals. Are there not saints' days in the calendar of every church—Protestant, Greek, or Roman?

Aesculapius had two famous sons: of these Machaon healed injuries, and Podalirius could recognize what was not visible to the eye and tended what could not be healed. They served with the army in the Trojan war.

Podalirius, returning from the war, was wrecked at Caria, Asia Minor. He had the good luck to cure a princess of falling sickness (probably hysteria), and in consequence acquired a great reputation. The Carians, after his death, built him a temple and paid him divine honours. This temple has long since disappeared, but his effigy survives on the College seal.

FIG. 13.

The essential work of Hunter's life was the useful specimens he prepared and left for successors. These specimens, safeguarded by faithful Clift, catalogued by sagacious Owen and Paget, and such able curators as Flower and Shattock, are now in the care of Keith, who lacks none of Hunter's enthusiasm but totally eclipses him in the art of exposition. The Museum was never in safer custody.

If I could believe the soul of man survives the dissolution of his body, I would believe the spirit of John Hunter haunts the galleries of this wonderful Museum, but I do believe his influence is a quickening spirit among surgeons to-day.

THE PROPERTIES OF CERTAIN "COLLOIDAL" PREPARATIONS OF METALS.

BY

A. J. CLARK, M.C., M.D., F.R.C.P.

(From the Pharmacological Department, University College, London.)

CONSIDERABLE attention has been paid during the past decade to the therapeutic action of metals in the colloidal form. The clinical literature associated with this subject is very extensive, and the results recorded are extremely remarkable; indeed, a cursory survey of the subject leaves the impression that colloidal metals act as specific cures for every known disease. The full claims of colloidal therapy will be found in the works of Searle.^{1,2} Unfortunately the quality of this literature does not correspond to its quantity. Dale,³ in a review of Searle's book, points out that the claims made there regarding the action of colloidal metals violate most of the known laws of physiology. The *Journal of the American Medical Association*¹⁷ criticized Searle's report as follows:

"In a style as bombastic and verbose as the usual house-organ write up, the report recklessly details all sorts of conditions in which the so-called colloids—and particularly the Collosol brand—have been recommended, but derogatory findings are conspicuous by their absence."

An examination of the clinical literature further shows that the great mass of it is wholly uncritical, and that the few animal experiments and therapeutic observations which have been made with proper controls have mostly given negative results. Since the "scientific" literature on this subject is so uncritical, it is only natural that the manufacturers of colloidal preparations should have made rather startling therapeutic claims in advertising these preparations.

The author, at the invitation of the BRITISH MEDICAL JOURNAL, has investigated the properties of certain of the colloidal preparations advertised. The preparations investigated were certain of the collosols (The Crookes' Laboratories) and of the oscols (Messrs. Oppenheimer and Son, Ltd.). The preparations were bought in the open market, but care was taken to ensure that they had come recently from the manufacturers. The retail price of collosols varied from 2s. to 6s., and that of oscols from 2s. to 15s., a 4-oz. bottle.

Chemico-physical Properties.

The preparations contain in most cases 1 in 2,000 of metal, together with 0.6 per cent. of sodium chloride, and from 0.5 per cent. to 5 per cent. of organic matter. The organic matter in collosols is in some cases stated to be arabinic acid derived from gum arabic, and in other cases to be glutaminic acid derived from gelatin; in the patent specifications peptones are said to be used as the suspending agent. The organic matter acts as a protective to the colloidal metal and keeps it in suspension. Ultrafiltration showed that the organic matter was partly in colloidal form and partly in true solution, for the greater part of it passed through collodion membranes, but a part of it was retained.

The chief point to be determined was whether all or any of the active principles in the various preparations were in true colloidal suspension. The following are the chief tests by which colloidal solutions are distinguished from true solutions:

1. *Ultramicroscopic Examination*.—The ultramicroscope shows colloidal solutions to be full of microns, which appear as bright points undergoing rapid Brownian movement.
2. *Tyndall's Beam*.—A beam of light passed through a colloidal solution illuminates its path, just as a beam of sunlight in a darkened room is visible when the air contains dust or smoke.
3. *Kataphoresis*.—An electric current passed through a colloidal solution contained in a U tube causes the solution to move towards one of the electrodes.
4. *Dialysis and Ultrafiltration*.—Colloidal particles do not pass through such membranes as parchment or collodion.
5. *Diffusion*.—Colloidal particles diffuse into water much more slowly than do molecules or ions. Colloidal particles do not diffuse into gelatin.

These tests can easily be applied to pure solutions of colloidal metals, but the presence of a considerable quantity of organic matter in the preparations tested made them much more difficult to test.

The manufacturers apparently rely upon ultramicroscopic examination for determining the state of suspension of the metal, for they emphasize in their advertisements that the preparations show Brownian movement under the ultramicroscope, and state that this is evidence of the colloidal nature of the preparations. The absence of particles on ultramicroscopic examination is evidence of the absence of colloidal

matter; on the other hand, most forms of colloidal matter will show visible particles under the ultramicroscope. For instance, the ultramicroscopic examination of soapy water shows an extremely brilliant picture of microns in active Brownian movement. The ultramicroscope cannot therefore give any reliable evidence as to whether metals mixed with an excess of organic matter are in a colloidal state, for the particles seen may be metallic or organic; evidence may be obtained that probably some of the metal is in colloidal form, but it is not possible under these conditions to estimate how much of the metal is in colloidal suspension.

Kataphoresis also is of little value as a test for the physical state of these solutions. The passage of an electric current through these solutions caused a movement of the solution towards the anode, but this may have been due to the colloidal organic matter present.

Dialysis through parchment thimbles was next tried. The solutions were placed in parchment thimbles and were dialysed for six days. The results are shown in Table I. This test showed that oscol ferrum and oscol argentum were true colloidal solutions, for none of these metals passed through the parchment. In all the other cases examined a considerable proportion of the metal passed through the parchment. This suggested doubts as to whether these preparations were colloidal, but the test is open to the objection that the solutions may have oxidized on exposure to the air.

Külz⁴ examined a preparation of colloidal arsenic and found that on exposure to the air free arsenious acid was liberated slowly; with a solution of 0.1 per cent. of arsenic in colloidal form, after three days' exposure to the air, 0.07 per cent. of free arsenious acid was liberated.

Ultrafiltration Experiments.

Since dialysis was inconclusive, ultrafiltration was employed. Colloidion membranes were used. At first membranes were made from 7 per cent. colloidion dissolved in equal parts of ether and alcohol, the membranes were made to fit Buchner funnels, and fluid was driven through under a pressure of two atmospheres. In later experiments colloidion thimbles were made from 9 per cent. colloidion in equal parts of ether and alcohol; the thimble was fixed to a rubber cork through which passed a glass tube, and a pressure of 100 c.cm. of water was used to drive the fluid through the thimble. In all cases the membranes employed were tested by filtering through them solutions of Congo red or haemoglobin, and only those membranes were used which retained 99 per cent. of these substances. About 5 c.cm. of fluid could be filtered in from one to three hours by these methods.

The colloidal preparations were tested by taking 20 c.cm. of the preparation, filtering through 10 c.cm., and then estimating the amount of metal in the filtrate and in the residue.

Iron preparations were estimated colorimetrically with ferricyanide. Arsenic and antimony were estimated gravimetrically by precipitating as the sulphide; in some cases arsenic was also estimated quantitatively by Marsh's test. Quinine was estimated by extracting the solution with chloroform and then estimating the residue obtained from the chloroform volumetrically by using Mayer's reagent as

described by Schmidt.⁵ Silver was estimated volumetrically with cyanide solution. The results of these experiments are shown in Table I.

The results shown in Table I indicate that the whole of the metal present in oscol ferrum and oscol argentum is in a colloidal form, and that it does not pass into true solution on exposure to the air. Collosol antimonium and arsenicum and oscol arsenicum and stibium all appear to contain a mixture of colloidal and non-colloidal metal, but on exposure to the air the metal tends to pass into true solution. Very little of the quinine in collosol quinine appears to be in colloidal form, and no demonstrable quantity of the iron in collosol ferrum appears to be in colloidal form.

Diffusion Experiments.

Further experiments were made to measure the rate of diffusion into water. Tubes 27 cm. long, with a diameter of 6 mm., were closed at one end and filled with water; the tubes could be inverted without the water escaping. A solution of collosol was put in a small bottle, a tube was dipped into the solution, the bottle closed with a rubber ring, and then left to stand in a dark cellar for sixteen days. At the end of this period the metal content of the solution within and without the tube was estimated. This method is a rough one for measuring diffusion, but control experiments showed a well marked difference between colloidal and non-colloidal substances. The results are given in Table II, and it will be seen that with non-colloidal substances the concentration inside the tube is about one-seventh that of the outside solution, whereas with colloidal substances the concentration inside the tube is only about one-seventieth that of the outside solution.

Oscol ferrum behaved like a colloidal solution, but collosol ferrum and oscol iodine behaved like non-colloidal solutions. The iodine content of collosol iodine was so low that it was impossible to measure it exactly.

Further experiments were made to test the rate of diffusion of collosol ferrum and other iron solutions into gelatin. A tube was half filled with 10 per cent. gelatin, and 5 c.cm. of solution were poured on top of the gelatin; at the end of a week the distance the colour had diffused into the gelatin was noted, and the quantities of iron in the fluid and in the solution were estimated. These results are shown in Table III, and it will be seen that collosol ferrum diffused into the gelatin like a non-colloidal solution of iron.

The results of the diffusion experiments confirm the previously expressed opinion that the iron in collosol ferrum is in a non-colloidal form; they suggest also that the iodine in oscol iodum either is not in colloidal form or else passes into true solution very readily. Collosol iodine is advertised as "Crookes' Colloidal Iodine," and the statement is made²⁰—"Collosol iodine consists of a 0.2 per cent. colloidal solution of iodine." In a more recent publication²¹ the statement is made—"Collosol iodine is a 0.05 per cent. colloidal solution of iodine suitably protected," and "Collosol Iodine Aqueous (Crookes)" is described as 1 in 500 (0.2 per cent.).

I have received the following report from the analyst selected by the BRITISH MEDICAL JOURNAL.

Analytical Report on Collosol Iodine.

I beg to report that I have analysed samples of collosol iodine, with results which show that it consists essentially of an aqueous solution of iodine with sodium chloride and gelatin.

The quantitative composition was found to vary in three bottles purchased on different occasions, but in no case was the iodine found to exceed that which could be dissolved by water containing the sodium chloride alone without the gelatin. The iodine, therefore, is present in the form of a plain aqueous solution of simple character; the addition of gelatin is without influence on its molecular nature or activity. Therefore the iodine is in no sense colloidal, nor indeed is there any colloidal quality in the preparation except the colloidal attribute of the dissolved gelatin.

The most notable effect of the gelatin in this composition is to reduce a part of the iodine to hydriodic acid, which becomes neutralized by the gelatin. The effect is visible as a loss of colour. Reference is made to the loss of colour in a separate label on the bottle, which states—

"If exposed to light collosol iodine becomes lighter in colour. The clinical efficiency is not affected, but for the sake of uniformity keep in a cool dark place."

TABLE I.

Preparation.	Amount of Active Principle stated to be present in—	Amount of Active Principle found on Analysis in—	Portion of Active Principle present which passed—	
			Colloidion Membrane in Ultrafilter.	Parchment Dialysing Thimble (6 days' Dialysis).
Collosol antimonium...	Per cent. 0.01	Per cent. 0.09	Per cent. 25	Per cent. 20
Collosol arsenicum ...	0.1-0.2	0.15	47	60
Collosol ferrum...	0.05	0.05	100	93
Collosol quinine ...	1.0	0.9	80	85
Oscol argentum...	0.05	0.06	nil	nil
Oscol arsenicum ...	0.05	0.05	25	80
Oscol ferrum ...	0.05	0.05	nil	nil
Oscol stibium ...	0.05	0.04	23	75

The following are the analyses:

I.					
Free iodine ...	...	...	...	...	0.021
Iodine as iodides ...	...	...	...	...	0.009
Sodium chloride ...	...	...	...	...	0.737
Gelatin ...	...	...	...	...	0.315
Water ...	...	...	...	...	98.918
					100.000
II.					
Free iodine ...	...	...	...	...	0.023
Iodine as iodides ...	...	...	...	...	0.002
Sodium chloride ...	...	...	...	...	0.65
Gelatin ...	...	...	...	...	0.327
Water ...	...	...	...	...	99.483
					100.000
III.					
Free iodine ...	...	...	...	...	0.012
Iodine as iodides ...	...	...	...	...	0.014
Sodium chloride ...	...	...	...	...	0.215
Gelatin ...	...	...	...	...	0.213
Water ...	...	...	...	...	99.546
					100.000

These figures agree closely with my own figures. I tested three samples, and the highest figures I found on analysis were 0.025 per cent. of free iodine with 0.015 per cent. of combined iodine. This concentration was too low to allow its rate of diffusion to be tested with any certainty.

TABLE II.—The Amount of Metal which Diffuses in Sixteen Days into a Tube of 6 mm. diameter filled with Water.

Solution.	Concentration of Active Principle in Original Solution in—	Concentration of Active Principle after Diffusion in Fluid outside Tube in—	Concentration of Active Principle after Diffusion in Fluid inside Tube in—	Relative Concentrations inside and outside of Tube after Diffusion.
	Per cent.	Per cent.	Per cent.	
<i>Non-colloidal Solutions:</i>				
Potassium ferricyanide ...	0.1	0.072	0.01	1 to 7.2
Ferric ammonium sulphate ...	0.01	0.0083	0.0015	1 to 6
Ferrous ammonium sulphate ...	0.1	0.09	0.016	1 to 5.6
Iodine ...	0.127	0.09	0.013	1 to 7
<i>Colloidal Solution:</i>				
Dialysed iron ...	0.2	0.2	0.003	1 to 70
<i>Solutions Tested:</i>				
Collosol ferrum ...	0.05	0.047	0.006	1 to 8
Oscol ferrum ...	0.05	0.05	0.0005	1 to 100
Oscol iodum ...	0.16	0.09	0.0124	1 to 7.5
Collosol iodum ...	0.024	0.014	About 0.005	—

TABLE III.—The Diffusion of Iron Salts into Gelatin.
(5 c.cm. of a solution containing 2.5 mg. iron were in contact with gelatin in a tube 5 mm. in diameter for seven days.)

Solution.	Iron Remaining in Solution in—	Iron Diffused into Gelatin in—	Depth in mm. at which Colour was Visible in Gelatin.
Ferric ammonium sulphate...	1.25 mg.	0.85 mg.	5
Ferrous ammonium sulphate	1.75 mg.	0.7 mg.	7
Dialysed iron ...	2.25 mg.	nil	nil
Collosol ferrum ...	1.75 mg.	0.43 mg.	15*

* This colour was, I believe, largely produced by the organic matter present.

PHARMACOLOGICAL ACTION OF COLLOIDAL PREPARATIONS.

A certain number of pharmacological tests were made to determine the action on living tissues of some of the preparations already mentioned.

Collosol Iodine.

The literature supplied by Messrs. Crookes suggests that the iodine in collosol iodine has an action on the body different from that of ordinary iodine. They state:

"The iodides have the disadvantage that being rapidly excreted they must be exhibited in large doses which often cause sickness, a foul taste in the mouth, and later, iodism with skin eruptions . . . collosol iodine is free from these defects."

C

Collosol iodine is, of course, very unlikely to cause iodism, for according to the analysis given above a litre of collosol iodine only contains 6 grains of iodine (free and combined), and the dose recommended by mouth of collosol iodine is from 2 to 8 c.cm.

I determined the smallest amount of iodide and of iodine which, when taken by mouth on an empty stomach, would cause the appearance of a demonstrable amount of iodine in the urine, and then determined the effect of corresponding amounts of the colloidal preparations of iodine. The results are given in Table IV. It will be seen that collosol and oscol iodine apparently suffer exactly the same fate in the body as does ordinary iodine.

TABLE IV.

Drug Administered.	Quantity of Iodine Administered.	Amount of Iodine Appearing in the Urine in Four Hours.
Sodium iodide ...	Gram. 0.008 0.016	Presence just demonstrable. Presence clearly demonstrable.
Iodine ...	0.02	Presence just demonstrable.
Collosol iodine (50 c.cm.)...	0.012	Presence just demonstrable.
Oscol iodum (5 c.cm.) ...	0.008	None demonstrable.
" " (10 c.cm.) ...	0.016	Presence just demonstrable.

Colloidal Antimony and Colloidal Arsenic.

Cawston⁶ and Wildish⁷ claim to have cured leprosy with oscol stibium, and the total quantities of the preparation which they found effected a cure varied from 15 to 40 c.cm. These results are very remarkable, for 40 c.cm. of oscol stibium only contains 0.02 gram (1/3 grain) of antimony, and the quantity of antimony found necessary to produce cures in other diseases has been from 5 to 40 grains. Rogers,¹⁸ who used colloidal antimony sulphide, recommended 2/3 grain antimony intravenously as a single dose.

Messrs. Crookes claim for collosol arsenicum that¹⁹ "it is entirely non-irritant and does not cause any symptoms of arsenic intolerance; it has a very low toxicity while remaining therapeutically active."

Experiments were made, firstly to determine the minimal lethal dose of these colloidal metals, and secondly to determine the minimal dose required to exert a trypanocidal action. The minimal lethal dose and the minimal trypanocidal dose were determined by intravenous injection into mice. In case the protective colloids should have any toxic action on intravenous injection the minimal lethal doses on intramuscular injection in rats also were determined. These results are shown in Table V.

TABLE V.—The Minimal Lethal Doses of Antimony and Arsenic Preparations.

Drug.	Animal.	Mode of Injection.	Minimal Lethal Dose in Grams of Metal per kilo Body Weight.
<i>Antimony Preparations:</i>			
Tartar emetic ...	Rat	Intramuscular	0.012
Tartar emetic ...	Mouse	Intravenous	0.015
Oscol stibium ...	Rat	Intramuscular	0.02
Oscol stibium ...	Mouse	Intravenous	0.015
Collosol antimonium ...	Mouse	Intravenous	0.02
<i>Arsenic Preparations:</i>			
Arsenious acid ...	Rat	Intramuscular	0.006
Arsenious acid ...	Mouse	Intravenous	0.007
Collosol arsenicum ...	Rat	Intramuscular	0.017
Collosol arsenicum ...	Mouse	Intravenous	0.007
Oscol arsenicum ...	Mouse	Intravenous	0.01

The minimal lethal doses of non-colloidal arsenic and antimony agree with the results of other workers. Voegtlin and Smith⁸ found, by intravenous injection into rats, that the minimal lethal dose of antimony given as tartar emetic was 0.018 gram per kilo, and that the minimal lethal dose of arsenic given as arsenious acid was 0.0053 gram per kilo. Fargher and Gray⁹ found that the minimal lethal dose of arsenic injected as arsenious acid intravenously into mice was 0.0057 gram per kilo.

Külz⁴ found, however, that the toxicity of a purified preparation of colloidal arsenic was far less than that of arsenious acid. The minimal lethal dose of arsenious acid injected intravenously as arsenious acid in a rabbit is 0.005 to 0.007 gram per kilo, but Külz found the minimal lethal dose of his preparation under these conditions was 0.03 to 0.035 gram per kilo. These results lead to the conclusion that colloidal arsenic is about one-sixth as toxic as arsenious acid.

Table V shows that the collosol and oscol arsenic and antimony were nearly as toxic as non-colloidal solutions on intravenous injection, but that the former were about one-half as toxic as the latter on intramuscular injection. The results with intramuscular injection may be due to the organic matter in the colloidal preparations hindering absorption. These results confirm the conclusion that a considerable proportion of the arsenic and antimony present in these preparations is in true solution, and suggest that the remainder is rapidly converted in the body into true solution.

The trypanocidal action of these substances was tested upon mice infected with *Trypanosoma equiperdum*. The trypanosomes were kindly supplied by Dr. C. M. Wenyon of the Wellcome Research Laboratory. The mice were infected with 0.1 c.cm. of the blood of a heavily infected mouse; this infection produced in most cases a trypanosome count of from 100,000 to 300,000 trypanosomes per cubic millimetre of blood after three or four days. Untreated controls died in all cases within ten days, and usually within seven days of the infection.

The minimal dose of arsenic or antimony which cleared the blood of trypanosomes after four days was determined. The results are shown in Table VI.

TABLE VI.—The Trypanocidal Action of Antimony and Arsenic Preparations Injected Intravenously into Mice Infected with *T. equiperdum*.

Drug.	Minimal Curative Dose in Grams of Metal per kilo Body Weight.	Minimal Lethal Dose in Grams of Metal per kilo Body Weight.	Ratio M.C.D. to M.L.D.
Antimony Preparations:			
Tartar emetic	0.003	0.015	1 to 5
Oscol stibium	0.0076	0.015	1 to 2
Collosol antimonium ...	0.01	0.02	1 to 2
Arsenic Preparations:			
Arsenious acid	0.006	0.007	1 to 1.2
Collosol arsenicum ...	0.005	0.007	1 to 1.4

The results in Table VI show that in mice tartar emetic is superior to either collosol antimonium or oscol stibium as a trypanocidal agent, and that there is no pronounced difference between the activity of arsenious acid and collosol arsenicum.

The minimal curative doses obtained for tartar emetic and arsenious acid agree fairly well with those obtained by Voeghtlin and Smith.⁸ These workers used rats infected with *T. equiperdum*, and obtained ratios $\frac{\text{M.C.D.}}{\text{M.L.D.}}$ of 1/4 for

tartar emetic and 1/1 for arsenious acid. These results show that these special preparations of arsenic and antimony have much the same trypanocidal action as non-colloidal arsenic and antimony.

Toxicity of other Collosol Preparations.

The minimal lethal dose to mice on intravenous injection of various other colloidal preparations was tested. The results are shown in Table VII.

TABLE VII.—Minimal Lethal Doses in grams of Metal or Alkaloid per Kilo Body Weight on Intravenous Injections into Mice.

Non-colloidal Preparations.		Collosol.	
Substance.	M.L.D.	Substance.	M.L.D.
Quinine HCl	0.015	C. quinine	0.015
Mercuric chloride	0.01	C. hydrargyrum ...	0.02
Ferrous ammonium sulphate	0.05	C. ferrum	0.022
		C. argentum	0.015

The results in Table VII show that the collosol preparations tested have nearly the same toxicity as non-colloidal preparations of the same substances.

Heubner¹⁰ found that with intravenous injection into rabbits the minimal lethal dose of the non-colloidal silver thiosulphate was 0.01 to 0.03 gram per kilo, while the minimal lethal dose of colloidal silver was 0.065 gram per kilo. That is to say that colloidal silver was less than one-half as toxic as an ordinary silver salt.

The Pharmacological Action of Colloidal Metals.

The facts as to the pharmacological action of colloidal metals have been obscured by various effects having been ascribed to them without adequate evidence, and also because many workers have used preparations which were to a large extent non-colloidal.

Metals in the colloidal form appear to exert only a feeble disinfectant action *in vitro*.

Marshall¹¹ prepared pure colloidal solutions of silver, and found that when tested over a period of ten minutes the colloidal silver had a disinfectant action only one-tenth as strong as silver nitrate. Marshall and Killoh¹² found that after *B. coli* had been covered with undiluted collosol argentum (1 in 2,000 silver) for ten minutes a vigorous growth resulted when the solution was removed; on the other hand, silver nitrate killed *B. coli* in five minutes at a dilution of 1 in 2,000,000. These results tend to show that colloidal metals will not exert a rapid disinfectant action.

Colloidal metals, if left in contact with bacteria for prolonged periods, will, however, act as efficient antiseptics. Simpson and Hewlett¹³ found that on a twenty-four hour exposure collosol argentum acted as a disinfectant at a dilution of 1 in 200,000. This action of colloidal metals is, I think, probably due to their slowly breaking down and liberating free ions. Since metals in the colloidal form are non-irritant, this slowly exerted disinfectant action may be of considerable therapeutic value.

Fate of Colloidal Metals in the Body.

The suggestion is often made that metals in the colloidal form will continue to circulate for a long time in the blood; this is incorrect, as several workers have shown. Duhamel¹⁴ found that when colloidal silver was injected into a rabbit 60 per cent. of the metal injected was fixed in the liver within fifteen minutes. Voight¹⁵ in similar experiments, found that after three hours 81 per cent. of the silver was fixed in the liver, and that none remained in the blood. It appears from these experiments that colloidal metals will not circulate in the blood and act there as a disinfectant for more than a few minutes.

The results recorded in this paper concerning the action of collosol and oscol antimony and arsenic lead me to conclude that these are not superior as trypanocides to non-colloidal preparations; these results are inconclusive as regards the relative merits of colloidal and non-colloidal preparations because the proportion of colloidal metal in these preparations is uncertain. Külz⁴ found that arsenic in purely colloidal solution was not superior to arsenious acid as a trypanocide in rats.

The chief therapeutic action of colloidal metals when given intravenously appears to be that they produce a general reaction similar to that produced by the injection of peptones or non-specific vaccines. Petersen¹⁶ classes colloidal metals amongst the agents which produce "protein shock," and considers their use as a particular example of non-specific protein therapy. Since many of the collosols and oscols contain breakdown products of proteins in considerable amount as protective colloids, the injection of such preparations is particularly likely to produce the reaction known as protein shock. Unfortunately our present information as to the value of non-specific protein therapy is so vague that the knowledge that colloidal preparations may belong to this class of preparation gives little exact guidance to their therapeutic value.

Summary.

The physico-chemical tests employed indicated that the active principles of some of the "colloidal" preparations investigated were entirely in the colloidal form; in other cases the active principles were partly in colloidal form and partly in true solution; whilst in some cases the whole of the active principle appeared to be in true solution. Previous criticisms of the physico-chemical properties of some of these preparations have appeared in the *Journal of the American Medical Association*.¹⁷

The pharmacological tests employed failed to show any marked difference between the action of the "colloidal" preparations tested and the action of the same substances in true solution.

Note.—The expenses of this research were defrayed by a grant from the British Medical Association.

REFERENCES.

- ¹A. B. Searle: The Administration of Colloids in Disease. Report of the British Association for the Advancement of Science, 1918, 155. *The Use of Colloids in Health and Disease*, London (Constable), 1920. ²J. Laumonier: *La Colloidothérapie*, Paris (Félix Alcan), 1920. ³Dale: *Journ. of the Soc. of Chem. Industry*, 21, 39, 1920. ⁴Kütz: *Arch. f. Exp. Path. und Pharm.*, 111, 9, 1921. ⁵Schmidt: *Alkaloide, Handbuch der Biologischen Arbeitsmethoden (Abderhalden)*, I, 9. ⁶Cawston: *BRITISH MEDICAL JOURNAL*, 1920, II, 855, and 1921, I, 419. ⁷Wildish: *Ibid.*, 1922, I, 55. ⁸Voeghelin and Smith: *Journ. of Pharm. and Exp. Ther.*, 457 and 476, 15, 1920. ⁹Fargher and Gray: *Ibid.*, 541, 18, 1921. ¹⁰Heubner: *Arch. f. Exp. Path. und Pharm.*, 370, 56, 1906. ¹¹Marshall: *Proc. Roy. Soc. Edin.*, 39, 145, 1919. ¹²Marshall and Kiloh: *BRITISH MEDICAL JOURNAL*, 1915, I, 102. ¹³Simpson and Hewlett: *Lancet*, 1914, II, 1359. ¹⁴Duhamel: *C.R. Soc. de Biologie*, June 21st, 1919. ¹⁵Voight: *Biochem. Zeit.*, 409, 63, 1914. ¹⁶Petersen: *Protein Therapy and Non-specific Resistance*, New York, 1922. ¹⁷*Journ. Amer. Med. Assoc.*, 841, 69, 1917; 1634, 72, 1919; and 1218, 73, 1919. ¹⁸Rokers: *Lancet*, 1919, I, 555. ¹⁹Crookes' *Colloids*, fifth edition, p. 17. ²⁰*Colloidal Iodine*, p. 7. ²¹Crookes' *Colloids*, fifth edition, p. 41.

FIVE CASES OF DIABETES MELLITUS IN YOUNG CHILDREN.

BY

F. JOHN POYNTON, M.D., F.R.C.P. LOND.,

PHYSICIAN TO UNIVERSITY COLLEGE HOSPITAL AND THE HOSPITAL FOR SICK CHILDREN, GREAT ORMOND STREET.

THE occurrence of five cases of diabetes mellitus in young children admitted within a short interval to one ward in a hospital leads me to think that at the present juncture in the history of this disease their publication may be of value. It is clear from the present literature that, for those who have few opportunities of studying a malady which is fortunately rare in childhood, it will be of importance to recognize the symptoms and, above all, the course of the disease at this early age, in order to obtain a correct perspective of the value of treatment by pancreatic extracts. It is in childhood that we see the pure type of virulent diabetes, and if very different results from those recorded in this series are obtained in the future there must be conviction that a great step forward has been made in medical knowledge. These cases were treated upon what until recently was considered to be the modern lines, and with the assistance of Dr. Spence and Dr. Donald Paterson, good medical clerks and devoted nurses, a whole-hearted attempt was made to study the effect of dietetic treatment and of such pancreatic extracts as were then available. The first case was an example of the type of problem that confronts us in hospital, and it will serve as an introduction to the main subject.

CASE I.

A boy aged 7 years was admitted on September 5th, 1920, in a state of coma. He had suffered from diabetes for eleven months, and for four months had been under "a specialist," and was sent to us when comatose. If we turn to this boy's history we find it is a characteristic one. An only child of healthy parents, he had been for the first time attending school. For two weeks, though complaining of headache and thirst, he tried to do his work and then had to stop. For six months these two symptoms remained the prominent ones, but later others were added—hunger, irritability, constipation, and polyuria (5 to 6 pints per diem). His weight at first hardly altered. The final symptoms were increasing thirst; emaciation, some vomiting, abdominal pain, and fleeting pains in the limbs. Finally drowsiness and coma.

On admission he smelt strongly of acetone and was comatose. The action of his heart was feeble and his face grey. The abdomen was scaphoid, and the urine contained 2.2 per cent. of sugar. Death was sudden.

Among these symptoms I should dwell upon irritability as one which repeatedly appears in the young when the disease is making headway, and upon abdominal and other pains as occurring just before the onset of the coma.

There was no necropsy, and a more unsatisfactory case than this for all concerned can hardly be imagined. The second case was much more instructive.

CASE II.

C. N., a boy aged 5½ years, was admitted on December 11th, 1919, with a history of symptoms of two months' duration. These symptoms were thirst, nocturnal enuresis, and occasional pain in the upper part of the abdomen. The sugar had been detected three weeks before admission, when the boy was attended by a doctor for colic due to eating green apples. Unless an attack of measles

in June, 1919, could be claimed as a factor in causation, there was not a single event in the boy's history to suggest a cause for the diabetes.

I dwell for a moment on the symptom of nocturnal enuresis. We see many cases of this disability, but very few are due to diabetes. It is, then, very unfortunate if one should overlook testing the urine thoroughly in a case of nocturnal enuresis and happen upon a diabetic child. This boy was well nourished and walked into hospital. His skin was dry and his tongue beefy. The knee-jerks were present but difficult to obtain; the fundi were normal. The urine had a specific gravity of 1042, was acid, contained 6 per cent. of glucose, and also acetone and diacetic acid.

Treatment.

His appetite was poor. He was placed on a low diet of tea, bovril, two eggs, and some minced meat. The calorie value of this diet was about 250, and in four days the urine was free from sugar, acetone, and diacetic acid.

We then started to test his carbohydrate tolerance, and by December 30th we had reached a diet of calorie value 914, which contained 78 grams of carbohydrate. The weight of the boy was 18 kilos, and accordingly the calorie value per kilo was $\frac{914}{18} =$ practically 50 calories per kilo. Authority has stated that 40 are sufficient to maintain weight, but this boy barely held his own when in bed on 50 per kilo.

On January 1st we let him get up on the same diet for three days, and his weight increased, but a slight trace of sugar appeared in the urine. He returned to bed, whereupon the sugar disappeared, but his weight began to fall again.

By January 18th we had increased his carbohydrate tolerance to 86 grams, but after four days there was a slight trace (under 0.5 per cent.) of glucose. We accordingly decided that his carbohydrate tolerance was about 80 grams.

We then turned our attention more particularly to the fat tolerance, which we raised to the limit of 110 grams. During the next month we made tentative experiments in dieting, with these obvious points in view:

1. To obtain a diet which his parents could give him when he left hospital—one, that is to say, not too expensive for their resources, and fairly satisfactory for the boy.
2. A diet which, while keeping him sugar-free, maintained his weight.

This, whatever may be the opinion of others, is, I am convinced, very essential. We must try and maintain the weight in children. "Keep them thin" may be a motto for adults, but not for children. His diet finally had a calorie value of 836, but this would only admit two small slices of bread and two tablespoonfuls of milk pudding.

We failed—though the value of 46 calories per kilo body weight was attained—to maintain his weight in hospital, and after a long stay we sent him out with a fair diet. On admission he had weighed 2 st. 11 lb.; on February 15th, 1920, he weighed 2 st. 9 lb.

The diet for guiding his parents when he was at home was:

- Breakfast.*—One egg, one buttered rusk, and an ounce of bacon.
Lunch.—Clear broth, one buttered rusk.
Dinner.—Mince 2 oz., cabbage 6 oz., potatoes 2 oz.
Tea.—One orange, one cup of milk, one buttered rusk.
Supper.—One buttered rusk, one cup of cocoa.

This was the skeleton outline—fish and other vegetables could be substituted—and it was useful as a working basis.

Three weeks later he was readmitted, with urine specific gravity 1039, glucose 3.9 per cent., and a faint trace of acetone. We ascribed this to eating too many vegetables. He had gained weight.

Once again in hospital we had difficulty in getting him to maintain weight, but on a diet of 926 calories he just held his own. In a month, however, he was able to take 122 grams of carbohydrate and a diet of 1,124 calories, on which he had gained a pound. The urine (specific gravity 1014) was free from sugar and ketone bodies.

From March 31st to August, 1920, he lived at home and kept well but did not gain weight. Then he broke down with hunger, thirst, irritability, and polyuria. There was sugar but no acetone in the urine. He was admitted on August 28th, when only a trace of sugar was demonstrated. This time the specific gravity of the urine was never above 1026, and only traces of sugar and acetone appeared when we were building up his diet. The result on this occasion was encouraging, and he left the hospital in October, 1920.

About Christmas he became thirsty, lost strength, and suffered from polyuria. Alarm was aroused three days before he came to the hospital by a "bilious" attack and drowsiness.

On admission he looked ill and drawn, and his urine was loaded with ketone bodies and sugar. There was general abdominal tenderness. In spite of intravenous alkaline injections he died that night in severe convulsions.

The *post-mortem* examination naturally interested me greatly, for I had never had an opportunity of seeing one in a child after so protracted an attack of diabetes. His illness had extended over almost three years. As usual there was very little to see and no long description is needed. The liver was large, pale, and flabby; the kidneys appeared natural. The pancreas was small and soft, and microscopy showed no increase of fibrous tissue but atrophy of cells. The gland looked exhausted, and the cells of the islands of