COLLOIDS IN HEALTH AND DISEASE

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THE USE OF COLLOIDS IN HEALTH AND DISEASE

BY

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WITH FOREWORD
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FOREWORD

BY SIR MALCOLM MORRIS, K.C.V.O.

THE subject with which this book is concerned is one of vast extent and enormous importance. It covers wide tracts of territory in physiology and medicine. "All life processes," as Prof. Wolfgang Ostwald has summarily said, "take place in a colloidal system," and that is true both of the normal fluids and secretions of the organism and of the bacterial toxins, as well as, in large measure, of the reactions which confer immunity. If this is so, it would seem to be an obvious *desideratum* that the drugs employed to combat disease should be in the colloidal state, i.e. in a form in which they may be isomorphic and isotonic with the elements of the body. Only so can they be expected to exert their full potency. The task of thus bringing their remedial virtue to its highest point is not an easy one, for colloidal substances, unless prepared with consummate skill and meticulous care, lack stability, and are prone to precipitation when brought into contact with the electrolytes normally present in the body tissues and fluids. That it is not beyond the resources of scientific chemistry is clearly shown in this book. A measure of success has, in fact, been achieved which leaves no doubt of the brilliant future which lies before drugs in the colloidal form.

To the study of colloids, both in health and disease, some of the world's greatest investigators have devoted and are devoting their genius for research. Much that was mystery has already been elucidated. A very considerable body of literature has accumulated, and the time is ripe for such lucid expositions of ascertained results as will be found in these pages, written by an acknowledged master of the subject.

AUTHOR'S NOTE

THE present volume is based on a lecture delivered at the request of the Chadwick Trustees, under the chairmanship of Sir William Collins, K.C.V.O., and forms one of a series of works published under their auspices. Some of the information also appears in the author's contribution to the British Association Report on Colloids, viz. *The Administration of Colloids in Disease*, published by the Department of Scientific and Industrial Research, and obtainable from H.M. Stationery Office.

A. B. SEARLE.

THE WHITE BUILDING,
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THE USE OF COLLOIDS IN HEALTH AND DISEASE

CHAPTER I

NATURE AND PROPERTIES OF COLLOIDS

THE difference between a healthy and a diseased organism is so important, and the necessity for improving the health of the nation is so urgent, that any application of knowledge to this end is worth very serious consideration. Consequently it is necessary that any possible use of discoveries in branches of science, other than medicine, should be brought to the attention of all concerned with the least possible delay. This application of knowledge gained in various fields of investigation to the improvement of health and the reduction of disease was one of the foundation principles of Sir Edwin Chadwick, whose generosity made the present publication possible.

The study of hygiene and of many diseases has been enormously facilitated by the discovery that many of the ills that flesh is heir to, and many others which it is unnecessary to suffer, are due to the influence of bacteria and their products. There is, however, a still wider cause of disease, of which bacteria form only a part, which is due to the peculiar structure of the essential organs of all animals and vegetables—a structure which has long been recognised in certain ways, though some of its properties have only been realised within the last decade or two.

We are all aware that living organisms are composed of a number of cells consisting of an external envelope, or membrane, and an enclosed fluid. Even the most complex animal structure can be shown to consist of a vast number of such cells, differing enormously in their shape and functions, but all possessing certain well-defined characteristics. The membranes or envelopes of these cells possess the peculiar property of allowing certain substances to pass through them quite readily whilst others cannot do so, and on this property depend many of the most complex functions of the whole organism. The processes of digestion and assimilation and the oxygenation of the blood are well-known examples of the selective passage of certain substances through the membranes concerned. Some investigators, including Moore and Roaf,[1] do not accept the idea of membranes of selective permeability, but consider the phenomena usually attributed to them as being due to selective absorption. This appears to be specially applicable to living cells, as several colloids behave differently in these from what they do in synthetic, or " dead," membranes.

It is well known that if a mixture of sand, gelatin, salt, and water were to be filtered through cotton wool, paper, or other recognised filtering medium, the sand would remain on the filter, but the salt and gelatin would pass through in solution in the water. It is not

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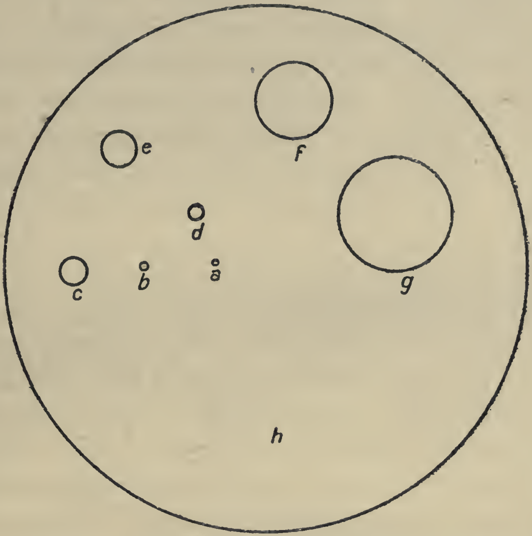
[1] Hober, *Arch. ges. Physiol.*, 1913, **150,** 15; Moore and Roaf, *Koll. Zeits.*, 1913, **13,** 133.

so well known that if such a solution of salt and gelatin is placed in a parchment or collodion cup, and the latter partially immersed in a vessel of water, the salt will pass into the water, but the gelatin will remain behind in the cup. By repeatedly changing the water in the outer vessel the whole of the salt may be removed from the gelatin solution. This distinctive property of salt and gelatin was investigated by Thomas Graham, who found that all those substances which pass readily through a filter, but not through a membrane, had certain other resemblances. He also found that some substances could exist in such a state that they would pass either through a membrane or not, according to their method of preparation. Faraday extended this investigation, prepared a number of substances in this state, and found that they had properties quite different from those ordinarily possessed by them. Thus, metallic gold, which is peculiarly insoluble and resistant, could be obtained in so fine a state of suspension that it passed readily through all ordinary filters and behaved as a solution. At the same time its colour was entirely different from that characteristic of the metal, being red or blue instead of yellow, and its other properties were changed to a correspondingly great extent.

When Thomas Graham, in 1861, found that certain solutions would pass through a membrane, whilst others did not do so, he little realised how great a discovery he had made. He had, in fact, found, and was able to describe, a state of matter of which little or nothing was realised at the time, though many industries, and indeed life itself, were and are dependent on it. Graham's chief discovery in this connection was that substances may enter into solution in such a manner that they exhibit characteristics which are quite different from those of a true solution. To this intermediate state he applied the term "colloidal" (from *Kolla*=glue), as glue, gelatin, and allied substances were most readily recognised by him as being in the colloidal state. Since Graham's time it has been found that most substances can be obtained in the colloidal state, their occurrence being sometimes due to reactions which are specially characteristic of animal or vegetable organisms and sometimes to purely inorganic changes.

The colloidal state may be defined as a physical condition of matter consisting of at least two parts or phases, one of which is the active substance and the other the one in which it is distributed. The former is termed the *disperse phase ;* it is the active agent and may consist of either solid or liquid particles which are so minute that they remain for an indefinitely long period in suspension. The second phase is either a liquid or an otherwise homogeneous complex material ; it is known as the *dispersion medium.* Such a definition does not, however, give any clue to the peculiar properties of substances when in the colloidal state, and it might be applied with accuracy to any turbid fluid. In a colloidal solution—which not being a true solution is preferably termed a *sol*—the dispersed substance is able to react in a manner quite different from what would ordinarily be anticipated. The dispersed or suspended particles are not merely so minute that the effect of gravity on them is counterbalanced by other forces which keep them in suspension (though they are often only one-thousandth part of the size of average bacteria), but they are in a state of unordered oscillation which gives rise to the well-known Brownian movement. They behave in a liquid in a manner very similar to the molecules and atoms of a gas, and are in constant movement, travelling at a high velocity and repeatedly colliding with each other. There is no group of substances which are invariably colloids. Thus soaps dissolve in alcohol and behave as true



a. Hydrogen molecules. *b.* Chloroform molecules.
c. Hæmoglobin molecules. *d, e, f, g.* Particles of colloidal gold.
h (large circle). Particles which precipitate from gold suspensions.

FIG. I. RELATIVE SIZES OF COLLOIDAL PARTICLES AND MOLECULES

(*Scale* 1 : 1,000,000)

crystalloids ; in water they behave equally characteristically as colloids. Common salt, on the contrary, behaves as a colloid in relation to benzole, but as a crystalloid when dissolved in water. Von Weimarn and others have shown that so many substances can be obtained in the form of colloidal solutions that it is probably correct to regard colloids as substances which are in a particular state rather than as forming a distinct group of substances. Colloids are readily divisible into two fairly well-defined groups to which various names have been given by different investigators, the most generally accepted being *emulsoid* (fluid particles) and *suspensoid* (solid particles), as suggested by Wo. Ostwald. The colloids in the first group have many of the properties of gelatin or glue ; they swell when immersed in a suitable fluid (water), absorbing a large quantity of it, and gradually become so dispersed as to possess many of the properties of a solution. The apparently solid particles have many of the properties of a liquid, and for this reason the term emulsoid is very aptly applied to them. The behaviour of emulsoids towards electrolytes is so complex that their classification on an adequate, yet simple, scale is, at present, impossible. The second group of colloids contains substances which are much more sensitive to small traces of added substances, and the electric charge acquired by them is much greater. They appear to consist of extremely minute particles of solid matter, though this adjective must not be applied too rigidly in this connection.

There are many well-known organic substances which occupy an intermediate position between colloids and crystalloids, and are conveniently termed *semi-colloids.* Casein, soap, many degradation products of albumen, peptones, and other constituents of animal organisms, and several dyes belong to this class. Thus albumen is a true emulsoid, but the protalbic and lysalbic acids derived from it diffuse through the parchment and behave in other ways as crystalloids, whilst at the same time having several properties (such as opalescence, viscosity, and "protective action") which are characteristics of colloids. Semi-colloids, such as soaps, may not be colloids under ordinary conditions, but form colloidal sols when in contact with certain liquids; they are sometimes termed *colloidogens.* Other semi-colloids are clearly electrolytes, but their boiling points and vapour pressures are approximately the same as those of water; these and other properties are so abnormal that such substances must be classed among the semi-colloids.

Each colloidal particle also carries a characteristic definite charge of electricity, some colloids being electro-positive and others electro-negative. Usually, when any given substance is in the colloidal state it has the same electric sign, but by adopting special methods of preparation it is possible to produce some substances in a colloidal form in which the particles may have either a positive or a negative electric charge. The electrification of colloidal particles may be compared with that of a piece of glass suspended by a thin silk thread and rubbed with a piece of amalgamated silk. If a second piece of glass similarly electrified by rubbing is brought near to the first there will be a mutual repulsion. On the other hand, a piece of ebonite which has been rubbed with fur will attract the glass because it carries an electric charge of the opposite sign. The electric charge is not the total amount of electricity which the body possesses, but only the excess or deficit of that which it carries compared with the neutral electrical condition.

It is important to note also that the chemical composition, and often the physical appearance of a substance, gives no indication of the electric charge which it has acquired, so that unless the charge is definitely investigated its existence may be overlooked. This has to a large extent been the case in the study of many drugs and other remedies.

Substances such as glass and ebonite are most easily charged electrically as the result of friction, but this is by no means the only or even the most important cause of excitation. If two different metals are moistened and brought into contact, a feeble but observable electrification is produced. This is easily shown by holding a silver and copper coin edgewise on the tongue. So long as the coins are separate no electrification results, but directly they touch each other at some point away from the tongue the taste produced by the electrification becomes apparent. If two dissimilar metals are partially immersed in a liquid which can chemically react on one of them, a simple voltaic cell or battery unit is formed, the electric current produced depending on the sizes of the pieces of metal and on the nature of the fluid used. Chemical action and electric phenomena are, indeed, so closely related that in many instances one cannot occur without the other. In fact, many phenomena which are generally regarded as chemical are largely electrical in character, or at least may be helpfully considered as such.

For example, the dissociation of a compound into its elements or into two distinct groups of ions is frequently accompanied by the assumption of definite electric charges by each of the groups. Thus, when a solution of common salt in water is made sufficiently dilute, the salt is dissociated into positively charged sodium and negatively charged chlorine particles, or ions. Sulphuric acid—a more complex substance—is dissociated into positive hydrogen ions and negative SO_4 ions. Even a partial dissociation of the fluid in which the substance is dissolved or suspended may cause the colloid to acquire an electric charge. Thus, water ($H^+ \cdot OH^-$) can form two classes of colloids the particles of which are respectively positively and negatively charged, and it is suggested that in many cases there is a chemical combination with the liquid

$$aPt + H^+ \cdot OH^- = (Pt_a\, H^+) + OH^-,$$

or

$$aPb + H^+ \cdot OH^- = (Pb_a\, OH^-) + H^+.$$

The charge on a sol is very much less than on an equivalent amount of the corresponding ion, and, therefore, a larger amount of sol will be required when it is used as a reagent.

Burton has estimated a charge for a single particle of gold and silver sols on the assumption that the amount of Al in aluminium salts which just precipitates the gold or silver has acquired the same amount of positive electricity as that amount of negative electricity acquired by the precipitated particles.

The volume of a particle is 2×10^{-4} cc., so that

100 cc. of a sol with 6·5 mgms. silver contains 3×10^{10} particles. This volume of sol required $3 \cdot 0 \times 10^{-5}$ and $2 \cdot 6 \times 10^{-5}$ gms. of $Al_2(SO_4)_3$ for precipitation, from which the charge on a particle is $2 \cdot 8 \times 10^{-2}$ electrostatic units, and the charge on one gram-equivalent of silver in a sol is 4 per cent of the charge on one gram-equivalent of silver ion. This dissociation on solution with the assumption of an electric charge is well known to chemists, though it is not so obvious to others on account of the minuteness of the particles and of the charges which they carry. There is a general agreement among those who have studied the subject that colloidal sol particles are enclosed by a double electric layer, as suggested by Quincke and Helmholtz; when a particle is negatively charged there is a negatively electrified layer on its surface, whilst in the liquid immediately surrounding the particle is a corresponding layer which is charged positively. Burton has shown that there is a layer of hydroxide, or hydride, on the colloidal metals which may affect the external change on these sols. It is not definitely known how this double layer is formed, and for most purposes it is sufficient to regard the particles as positively or negatively charged, the effect of the double layer being neglected.

Any substance which conducts an electric current, and is decomposed thereby into separate groups of ions, is known as an electrolyte. The terminals, or plates, by which the current is passed through a liquid are known as electrodes, the one by which the current is supposed to enter being termed the positive (+) electrode, or anode, and the other, the negative (−)

electrode, or kathode. When a current of electricity is passed through the solution the positively and negatively charged groups tend to collect at the opposite ends of the solution, i.e. they tend to travel to each electrode respectively, and are in this way separated from each other, though they lose their characteristic charge as soon as they come into contact with the electrode. Thus, if a current of electricity is passed through water containing sufficient acid to render it a conductor, the oxygen atoms will pass to the anode and the hydrogen to the kathode, each escaping from the solution in the form of a gas without any electric charge. Between the electrodes, however, the oxygen ions have their distinctive charges and are able thereby to act very differently from the electrically neutral gases bearing the same names. When a liquid is contained in a porous vessel or membrane, which is partially immersed in a second liquid, and a current is passed from one liquid to the other, the membrane plays an important part. It prevents the liquids from mixing rapidly, whilst it allows them to come into contact with each other, so that by arranging the electric current to pass in a suitable direction one substance may be passed through the membrane and thus separated more rapidly than by the slow process of unaided dialysis or diffusion, whilst its separation from other substances in solution is effected more easily and with less general disturbance than if purely chemical methods are used. The chief investigations of the movements of colloidal particles under the influence of an electric current are based on the work of

Linder and Picton,[1] who with other observers have found that the substances mentioned in Table I move to either the positive or the negative electrode, as shown, when suspended in pure water. In dilute solutions of salts, alkalies, or acids, entirely different characteristics may be observed with the same colloidal particles.

Thus, some colloids such as globulin and silicic acid are negatively charged in alkaline solutions and positively charged in acid solutions.

TABLE I

ANIONIC (negatively charged and moving to the positive pole)	CATHONIC (positively charged and moving to the negative pole)
Antimony sulphide	Hydroxides of
Arsenic sulphide	Iron, Chromium
Cadmium sulphide	Copper, Aluminium
Platinum sol	Zirconium, Cerium
Silver sol	Thorium
Gold sol	Bredig sols of
Mercury sol	Bismuth, Lead
Silver chloride	Iron, Copper
Silver bromide	Hoffmann violet
Silver iodide	Magdalene red
Vanadic oxide	Methyl violet
Tin oxide	Rosaniline hydrochloride
Silica	Bismarck brown
Aniline blue	Methylene blue
Indigo	Albumen
Molybdene blue	Hæmoglobin
Soluble Prussian blue	Agar
Eosin	Titanic oxide

[1] *Journ. Chem. Soc.*, **61,** 148 ; **67,** 63 ; **71,** 568 ; **87,** 1906.

ANIONIC

(negatively charged and moving to the positive pole)

Fuchsine
Iodine
Sulphur
Selenium
Shellac
Resin
Starch
Mastic
Caramel
Lecithin
Chloroform
Oil emulsions
Amœbæ and animal organisms

CATHONIC

(positively charged and moving to the negative pole)

Diatoms
Unicellular algæ
Vegetable organisms

The electric charges on gelatin, agar, and silicic acid are very small and difficult to observe.

The rate of movement of a particle in an electric field is independent of the size of the particle, but is affected by the viscosity of the fluid and the potential of the current.

The employment of electricity remedially for effecting the movement of the colloidal substances in the living cells is, however, extremely limited, especially with regard to animal organisms, as a separate electrode would require to be introduced into each individual cell—a hopelessly impracticable condition. The result of applying an electric current to a large area is entirely different from that which occurs during the electrolysis of a single cell. When two sols of the same sign are mixed they not only do not precipitate each other, but the mixed sol acquires the stability of the more stable component. No adequate explanation of this fact has yet been published, though the fact itself is indisputable. When two particles of *opposite sign* come within a suitable distance of each other they are mutually attracted and, if sufficiently free, will eventually touch and discharge each other. The product will then be electrically neutral unless one of the particles carries a larger charge than the other, when the product will carry the balance of the charge or will decompose, forming an electrically neutral substance—which settles more or less rapidly—and a negatively charged product.

Substances in the colloidal sol state have corresponding electric charges and therein bear a very close resemblance to substances which become ionised in solution. They attract particles of opposite sign and repel those of like sign which come within the sphere of their influence, and when two colloidal sol particles of opposite sign come into contact with each other they are mutually discharged, and the combined product settles more or less rapidly. Thus, the effect of discharging two colloidal sol particles is to remove them from the active colloidal state and to form a precipitate or even a coagulum. This may, under some conditions, retain a certain amount of chemical activity, and being then in an intermediate state between a sol and a precipitate is conveniently known as a *gel*. Gels are usually obtained when emulsoid sols are cooled or evaporated; they may be regarded as composed of two liquid phases, whereas a sol bears a closer resemblance to a solid phase dispersed in a liquid one. Gels have characteristic optical properties, such as double refraction.

Agglutination, or the precipitation of colloids of like sign, occurs in some cases, e.g. with toxins and bacteria sols. Though extensively used by some pathologists as the basis of treatment of diseases due to toxins, bacteria, etc., the precise nature of the phenomena which produce agglutination are by no means well understood. Lottermoser, in 1901, found that when a positive sol precipitates a negative one, the precipitate contains both colloids.

The amount of one sol required to precipitate another varies with the nature of the sols, and the precipitate contains both colloids, though, owing to the difficulty of filtration without adsorption, the liability of the excess of colloid in the sol to precipitate, and the slowness of the reaction, it is often difficult to determine the amount of each colloid in a precipitate.

The equivalent amount of sols required to cause precipitation is not a chemical equivalent, but an electrical one; usually the maximum precipitation occurs when the positive charge on one cell exactly equals the negative charge on the other, but the number of particles, their size, and the rate of mixing affect the results.

Substances in colloidal solution behave quite differently from those which are merely in suspension. Thus, coarse suspensions are not affected by electrolytes and they do not usually bear a definite electric charge, whereas colloidal sols—unless protected—are very sensitive even to traces of electrolytes, and readily migrate towards one pole when an electric current is passed through them. It is a mistake to regard them merely as fine suspensions, as the properties of a substance undergo considerable change when it is converted into the sol state. They do not behave precisely the same as either suspensions or solutions, but occupy an intermediate position for which the term " sol " is preferable. It was at one time thought that colloidal substances could be defined as those which appeared to be in suspension but do not pass through a parchment or collodion membrane into an external volume of water. This is by no means always the case, as Graham soon found, and since his time more anomalies have been discovered. It is scarcely possible, therefore, in simple terms to say precisely which substances are colloidal and which are not, though for most practical purposes the distinction is readily appreciated. Like " life," we may have a fairly clear concept, but cannot express it in mere words.

The difficulty of finding a clear line of demarcation between colloidal and other substances is greatly intensified when living organisms are studied, as reactions take place in these which do not occur in the dead organism. For example, the peptones are a class of nutritive substances which are in many respects typically colloidal, and in the laboratory their solutions do not pass through animal or vegetable membranes. In the *living* organism, on the contrary, peptone solutions pass readily through certain membranes and owe their nutritive power to this property. Hæmatin, on the other hand, is a typical crystalloid substance which might be expected to pass readily through the blood vessels, yet it does not do so as long as the organism is alive. Here are two typical substances, both acting precisely contrary to the general behaviour of the groups to which they belong, whilst in the living organism, but behaving normally when removed from the organism and studied *in vitro*. This difference in behaviour impels all investigators who are aware of it to pause ere they draw conclusions from laboratory experiments and apply them to the living subject. Even in so apparently simple a phenomenon as the passage of a substance through a membrane, the effect of "life" may be to upset all prognostications from the tests on dead or synthetic materials. This fact needs specially to be borne in mind when dealing with the introduction of drugs and other substances into the living subject, or seriously erroneous conclusions may be drawn.

Turning again to the characteristics of colloidal substances, it should be observed that they are most remarkably active, an apparently minute proportion of a suitable colloid frequently effecting the precipitation of many times its weight of another substance from "solution." In this respect, many colloids resemble enzymes, or so-called vegetable ferments, and bacteria, though they do not reproduce themselves like living organisms. They owe their activity to their minuteness and to the fact that substances when in the colloidal state have an enormous surface area as compared with their volume or weight, and as chemical reactions depend on the amount of contact between two or more particles these reactions will proceed the more rapidly and completely when the substances have a large surface area and are in a state of oscillation. It is well known that chemical reactions can only occur when two or more substances are in direct contact, and as the completeness of the reaction depends on the amount of contact, colloidal substances are very powerful because of the enormous area they possess.

On the other hand, mass plays an important part in all chemical reactions and largely regulates their intensity. The mass of colloidal sol particles is so minute that the objectionable effect of *intense* reactions on the human subject are largely avoided, whilst the advantages of rapid and complete reaction are secured. For this reason, certain medicines administered in the colloidal form are not merely more active and possess greater penetrating power, but they are free from the poisonous effect of the same substances when given in the form of tincture or solution. The difference in behaviour of a solution of iodine in alcohol or aqueous potassium iodide, when compared with that of colloidal sol iodine, is most impressive. The forms of iodine usually employed induce pain and other symptoms of iodism, whereas large doses of colloidal sol iodine (if the preparation has been properly prepared) are quite free from this risk. A colloidal preparation of iodine in petroleum or other mineral oil can be rubbed into the skin without leaving any stain, the iodine being absorbed more readily than the oil. A solution of commercial iodine in alcohol or in potassium iodide leaves a characteristic stain when applied to the skin.

The precise reason for this rapid absorption and non-staining action has not been definitely ascertained, but it has been repeatedly demonstrated in a variety of cases.

The action of radiations on sols.—The γ-rays of radium and the X-rays have no action on colloidal sols. The positively charged α-rays of radium have not sufficient penetrating power for any action they may have to be important. The β-rays of radium, which are negatively charged, hasten the coagulation of the positively charged particles and increase the stability of the negatively charged ones. A sample of hæmoglobin was coagulated by the rays in several hours by Hewin and Mayen.[1] Some albumen sols when exposed to the ultra-violet light are rapidly coagulated. These reactions partially explain some of the remedial effects of various radiations on the human system. It is clear that such effects are limited by the permeability of the skin, and that for deep-seated affections better results may be anticipated from the introduction of suitably charged particles (colloidal sols) into the blood stream.

The colour of colloids.—The colour of the colloids depends chiefly on the size of the particles, and only to a small extent on their composition. Thus, the smallest particles of colloidal gold, when seen by transmitted light, are red and the larger ones are blue.[2] The colour is, in each case, dependent chiefly on the scattering effect of the particles on the light transmitted through the liquid. In accordance with Rayleigh's & Thompson's calculations, the intensity

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[1] CR., 138, 1904, 521 ; CR. *Soc. de Biol.*, 57, 1904, 33.

[2] Mee found the relation of the size to colour reversed in some cases.

of the scattered light varies directly as the sixth power of the diameter of the particles and inversely as the fourth power of the wave-length. Hence, the intensity of the scattered light and the absorption are both greatest with the smallest particles. Stebbing found that very little light leaves a colloidal liquid, most of it being absorbed. Svedberg found that colloidal sols are often more highly coloured than a true solution of the same element at the same concentration, but that the absorption spectra of the colloidal sols and solutions do not differ essentially. W. Ostwald [1] has enunciated the law that " with decreasing size of the particles the absorption band of any colloidal solution moves to the shorter wave-lengths."

Mayer, Schäffer, and Terroine [2] have shown that traces of alkali increase the size of the particles if the colloid is positive, and reduce it if the colloid is negative. Traces of acid produce the reverse effect. The change in the dispersion thus effected varies with the colour of the sols. Zsigmondy[3] and Gutbier and Resenschack[4] found that, on adding coagulating reagents, the colour of gold sols changes consecutively from red to purple-red, red-violet, blue-violet, and deep blue, the colloid eventually separating as flakes of powder or gel.

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[1] *Koll. Chem. Beiheft.*, 2, 1910 ; 11, 409.

[2] *Comptes rendues*, 1907, **145,** 918.

[3] *Zier, Erkentniss der Koll.*

[4] *Z.f. anorg. Chem.*, 1904, 39, 112.

CHAPTER II

ANIMAL AND VEGETABLE FLUIDS

THAT animal and vegetable fluids are largely colloidal in character is a fact which is now unquestioned, but little is known as to their precise nature. Thus, the particles in cow's milk can be demonstrated under the ultra-microscope, but those in human milk are too minute. This suggests that in adapting cow's milk for feeding infants, it is not sufficient to endeavour to match the ordinary chemical analysis of human milk, but that cow's milk should be treated in such a manner that the product is in a similar colloidal state to that of the human milk. The valuable superiority for infant use of milk to which barley water, gruel, or other starchy solution has been added has long been known, but few have, as yet, realised that it is due to the protective action (in a colloidal sense) of the added substance. Gelatin, gum-arabic, or preferably gum-acacia, have an even stronger protective action, and they possess the further advantages of being easier to prepare and of altering the composition of the milk to a less extent, whilst making it physically much more like human milk.

In human milk the protective colloid is lact-albumen, which is present to the extent of 1·3 per cent (i.e. equal to the casein present), whilst cow's milk contains only 0·5 per cent of lact-albumen and over 3 per cent of casein. Of all the domestic animals, asses' milk bears the closest resemblance to human milk, both in chemical and colloidal properties.

The coarse particles of curd which are formed when cow's milk is coagulated by acids or rennet may be replaced by finer, more flaky, and more porous curds by diluting the milk with water, by adding lime-water (though this tends to prevent the coagulation altogether and so may unduly delay its digestion or even cause it to be passed out of the body of an infant in the undigested state), and by the use of one of the protective colloids previously mentioned.

Bearing in mind its colloidal nature, human milk can best be imitated by using cow's milk as the basis and adding the following: (*a*) cream sufficient to raise the total fat present to 3·8 per cent (about 3 per cent of the final mixture being required usually); (*b*) milk sugar to raise the total sugar content to 6·2 per cent (about 3 per cent of the total mixture being usually required); (*c*) about 1 per cent of lactalbumen, or 2 per cent of gelatin, or a considerably larger percentage of starch in the form of barley water, etc., as the protective colloid; and (*d*) sufficient water to effect the solution of the protective colloid and the sugar. If there is any risk of the cow's milk not being quite fresh, part of the added water may wisely be replaced by a tablespoonful of lime-water, which will neutralise any trace of acidity in the milk and will therefore increase its keeping power.

In the same way chemical analysis alone does not determine the value of even the essential properties of a foodstuff; its physical condition—particularly if it is a colloidal substance—is of at least equal and sometimes greater importance. Thus, cheese cannot be digested by some people as it is too densely coagulated to be readily converted into a colloidal fluid. By preparing it under conditions which will facilitate its resuspension, its high value as a food material may be utilised. The various preparations of casein which are at present so popular as recuperatives depend largely on the fact that they are colloidal substances, which can be resuspended or converted into colloidal fluids more easily than ordinary cheese or dried milk. Indeed, the chief test of such a preparation may usefully consist in an examination of its properties when mixed with water or other suitable fluid.

The cell-structure of animal and vegetable organisms closely resembles the cellular structure of the synthetic cells. The walls of such cell-structures are really emulsoid gels, the cell-fluid being an emulsoid sol. The gels which form the cell-walls and membranes of the body contain albumen- and gelatin-like substances which swell in water and to a varying degree in solutions of acids, alkalies, and salts. In other words, living protoplasm is essentially a complex liquid; the presence of a network, observed in protoplasm which has been killed or "fixed" by various reagents, is not apparently seen in the living material. The so-called cell-wall of the protoplasm of some low forms of life appears to have both the properties of a solid and of a liquid substance, and in this respect resembles the film of a soap bubble. For example, Chambers has recently (1917) found that a needle can be repeatedly passed into living protoplasm without injuring it in any way and without leaving any trace of its track. Bacteria, etc., penetrate the cell-wall in a similar manner without damaging it, just as well as through a soap-bubble. The outer layer of protoplasm is not, however, identical with the membrane to which the cells owe their semi-permeable properties.

When a cell dies it passes from an emulsoid sol into an emulsoid gel state and thereby changes its character and reactions, one of the most remarkable differences being that the liquid of the dead cell freely mixes with the surrounding watery solution, whilst the contents of the living cell do not escape in this manner. Under normal conditions living cells are non-conductors and are largely impermeable, but under the influence of certain ions they become permeable and allow electrically charged particles to pass freely through them. When certain cells are immersed in a saline solution the sodium ions present increase their permeability; the addition of calcium ions restores them to their normal condition. Hence simple solutions of salts do not form an efficient substitute for the blood or for the sea-water in which marine creatures live; a small but significant proportion of calcium salts is essential unless a colloid, such as gelatin or gum-acacia, is added in sufficient proportion to give the saline solution an osmotic pressure as high as that of the blood. The selective permeability of living cells is very remarkable. Acids which are soluble in the cell or in the analogous liquid bodies readily penetrate the cells, but other acids and strong bases do not. Weak bases (including ammonia and the amines) penetrate the cells without difficulty.

Although sodium hydroxide does not enter the living cells it greatly increases the rate of oxidation processes in the cells. This is due to the fact that the cell-wall is really a concentration of the components of the protoplasm of the cell, and in the presence of sodium hydroxide the normal equilibrium is upset, and this produces marked changes in the cell, notwithstanding the fact that the sodium hydroxide does not penetrate into it.

The cell materials, whilst being typical emulsoids, behave in a far more complex manner than the synthetic emulsoid gels or the natural or synthetic suspension sols. Thus, albumen is electrically neutral and is precipitated by basic emulsoids (as histone) and basic sols, which are positive sols. It is also precipitated by acid emulsoids, such as silica sol and acid dyes, which are negative sols. Tannin and gallic acid behave similarly. Perrin[1] has suggested that primary cell growth and cell division are essentially colloidal in nature, an idea which is, to some extent, supported by galvanotropism in microscopic animals.[2] If this is the case—and there is much evidence in support of it—a study of the changes in the viscosity of the body fluids under certain circumstances,[3] the influence of certain salts on the properties and action of the blood,[4] and the laws regulating the permeability of the cell-walls for salts and colloids in the human body are bound to

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[1] *Journ. Chim. Phys.*, 1904, II, 607.

[2] Miller, *Journ. of Physiol.*, 1907, 215. Buxton and Rahe, *Zs. f, D. Ges.*, Bischam, XI, 11 to 12, p. 479.

[3] Rachlmann, *Berl. kln. Wochensch*, 1904, *Heft.* 8; *Deutsche Med. Wochensch*, 1904, *Heft.* 29.

[4] Nanes, *Chem. Beih. Physiol.*, 1910, 40, 327.

advance our knowledge of the normal action of the body and to increase our power of treatment when it is diseased. As an instance of the advance which has been made since the colloidal nature of animal and vegetable substances has been appreciated, it may be noted that when investigating albumens and their digestive products, students of physiological chemistry have long been puzzled by the complexity of the mixtures precipitated by various reagents, such as ammonium or zinc sulphate. It has been impossible to effect really satisfactory separations of such substances by ordinary chemical processes, but their strikingly different behaviour towards colloidal metals has opened out a new field of research which it is anticipated will have far-reaching results. Another interesting result of the recognition of the colloidal nature of blood may suitably be mentioned here. For many years it has been held that the oxygen in the blood was in the form of a compound of oxygen and hæmoglobin, but in 1907 Wolfgang Ostwald pointed out that all the available data may be arranged to form graphs or curves which are typical of adsorption and there can be little doubt that both the oxygen and the carbon dioxide in the blood are in an adsorbed condition.

Red blood-corpuscles are negative, but can be precipitated by both positive and negative sols. Henri[1] assumes that they are surrounded by a pellicle which can adsorb salts, such as magnesium and calcium sulphate. These salts act on any precipitable sol, producing a coagulum around the corpuscles;

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[1] *Compt. Rend.*, 1904, 138, 1461.

they can be removed by diffusion into an isotonic sugar solution, after which blood-corpuscles are much less susceptible to precipitation by sols.

Blood-corpuscles which have been soaked in solutions of salts—especially chlorides and sulphates—are made more easily precipitable by sols, especially ferric hydroxide sol.

The fact that the blood is a typical complex colloidal fluid is now accepted, and this is the basis of the treatment of numerous diseases, though many physicians have scarcely recognised it. The colouring matter—*hæmoglobin*—is definitely colloidal, and hence it is not surprising that the colouring matter obtained from different animals differs both in its composition and properties. In red corpuscles from the human subject, the hæmoglobin is associated with a complex of various substances, some colloidal and others crystalloidal, and with a liquid which is isotonic with a solution of nine parts of common salt in a million parts of water. If the red corpuscles are immersed in a more dilute solution than this they swell, and hæmoglobin gradually passes from them to the external solution (*hæmolysis*). The importance of this phenomena—which is characteristic of colloidal gels—will be appreciated when considering the effect of colloidal substances in diseased conditions of the human subject.

The characteristic behaviour of some of the waste products of the human organism is also due to their colloidal character. Thus, urine contains colloidal substances which normally prevent the uric acid from separating. This colloid may be removed by dialysis or precipitated by alcohol; it appears to be a derivative of nucleinic acid. Urines which are deficient in this protective colloid may be prevented from depositing uric acid on cooling by adding to them a suitable colloid. Unfortunately, those colloids, such as gelatin, which are most successful *in vitro*, are absorbed by the alimentary tract and therefore do not reach the bladder in sufficient quantity to admit of their being used in certain urinary diseases. Experiments with other colloids are now being made. In this connection, it should be noted that alcohol reduces the rate of diffusion of salts in gels, whilst urea, chlorides, and iodides increase it.

CHAPTER III

THE HYGIENIC USES OF COLLOIDS

The important part played by colloidal sols and gels in the maintenance of hygienic conditions is seldom realised by those whose attention has not been called to this aspect of the subject. The removal of harmful impurities in water, the disposal of sewage in an innocuous manner, and the effective disposal of " dirt " are all largely dependent on some colloidal properties, the precise nature of which is by no means well recognised by many of those engaged in the purification of water, or sewage, or who are habitual users of soap and other detergents.

The study of colloids in relation to these subjects is comparatively new, and much has yet to be learned. On the other hand, it is interesting to note how much of the best modern practice and use of colloidal properties has been reached by persistent investigation on the lines which had little or no bearing on the recognition of the real nature of colloids. Now that the importance of the colloidal state has been recognised in other branches of industry and science, it is surely not too much to hope that it will lead to equally striking improvements in the sphere of hygiene. A few words on each of the important subjects of sewage, water, and soaps must, however, suffice.

Sewage.—Sewage consists essentially of water contaminated with excrement, kitchen- and other domestic refuse, and matter washed from roads ; in some areas it may be further contaminated with other waste products from factories, or other industries. This contaminated matter is in three forms : (*a*) in suspension, as silt, sand, paper, rags, fæces, vegetable and animal matter, etc. ; (*b*) colloidal matter in solution or pseudo-solution ; and (*c*) in true solution. In purifying sewage the chief purpose is to separate the matter in suspension and to render harmless that in colloidal and in true solution. The chief difficulty in dealing with sewage is that the matter in colloidal solution prevents the effective removal of the coarse material in suspension, as well as assisting in keeping it in suspension in larger proportions than would otherwise be the case. Hence, if the colloidal matter can be precipitated in a suitable form the most serious difficulty in sewage treatment is overcome.

The complex nature of sewage is such that it is impossible to treat each of its constituents separately, and this adds to the difficulty of purification. It is, however, recognised that the most difficult constituents are the colloidal sols, and these can be precipitated in accordance with the recognised methods for precipitating other colloids. The most successful chemical methods of treatment depend on a recognition of this colloidal character and on the coagulation of the colloidal sol by the addition of some other substance carrying an electric charge of the opposite sign. Ferric and aluminium hydroxides have been largely used for this purpose, and they are quite efficient. Their great drawback is the cost of treating such enormous volumes of liquid by any process of sedimentation and filtration to remove the precipitated colloid and the difficulty hitherto experienced in converting this colloid into a useful material. The method which appears most likely to prove of value consists in utilising the fact that water which has been violently agitated with, or has fallen through, air may become positively charged, and these electrically positive particles then effect the coagulation of the negatively charged colloids in the sewage. Hence, by agitating the sewage with air, under suitable conditions, a complete coagulation of its colloidal content is rapidly effected at a low cost, and the precipitate is one which settles with extraordinary rapidity. In the well-known "activated sludge" process, air is blown through the sewage, the inventors of this process having apparently failed to realise that the electric charge of the water particles is at least equally as important as the oxidising power of the air. A modification of this process, in which the water is charged positively by agitating it superficially with air, offers still greater prospects of success, as it avoids the use of "chemicals" and the costly supply of large quantities of air. In this connection it is interesting to note that beneficial action of the air at the seaside is probably due more to the particles in it which have been positively charged by the violent beating of the waves on the shore, than to the ozone to which this action is usually attributed. These positively charged particles, reacting with the negatively charged bacterial and other undesirable colloids, precipitate them and render them harmless.

The purification of sewage is complicated by the fact that the precipitation of the colloidal and suspended material is not sufficient to remove all the putrefactive constituents: though the greater part is so removed. The remainder appears to be most advantageously treated by bacterial action, especially by the activated sludge, or similar process, and, as it happens, the two processes of precipitation of the colloids and the development of bacterial action can in most cases be carried on simultaneously. The action of bacteria alone (as in a septic tank) does not appear to affect the proportion of colloidal matter to any serious extent, so that where the purification is confined to bacterial treatment the precipitation is more prolonged, and the final purification of the liquid is much less complete than when the colloids are precipitated in the presence of, or prior to, the action of the putrefying bacteria.

The sludge produced by the precipitation of the colloidal matter by electrically charged air, with or without the action of the activated sludge, is a fairly stiff material which settles rapidly and is easily filtered, whereas the ordinary sewage sludge is largely liquid. The sludge may suitably be subjected to anærobic bacterial action, whereby it is converted into a more dense and granular material which is free from the objectionable qualities of the untreated sludge.

The purification of water.—The artificial purification of water is effected by colloids:

(1) A colloidal coating on the grains of sand in the filter retains (by neutralising the charge) all the bacteria, etc., but not the colouring matter.

(2) Aluminium sulphate, or ferric sulphate (with or

without alkali), is added to the water, and causes a precipitation of the positively charged alumina, or ferric oxide, which reacts with the negatively charged bacteria, clay, etc., and precipitates them. Simultaneously, the positively charged colouring matter is precipitated by the negatively charged SO_4 ions, whilst any true colouring matter is adsorbed by the precipitated hydroxides. Any excess of alumina, or ferric oxide, is precipitated by agitation.

Sometimes it is best to add the alkali first ; sometimes only after the aluminium or ferric sulphate. The latter is preferable when there is much colouring matter to be removed.

The natural purification of muddy water is largely dependent on its colloidal character. Thus Skey[1] has shown that suspended mud is precipitated by electrolytes, including those in sea water. Hence, when a muddy river flows into the sea the proportion of mud which settles out, owing to the slower current in the mixed water, is insignificant compared with that which is precipitated by the electrolytes in the salt water. Schloesing[2] has shown that deltas are chiefly due to this cause.

Soaps.—Sir Edwin Chadwick was a firm believer in the idea that the effectual preventative of all forms of epidemic, endemic, and most other diseases, is the entire removal of all conditions of dirt, including foul air, defective drainage, and dirty surfaces of all kinds. He was most emphatic as to the necessity of personal cleanliness, and on one occasion he declared that if a

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[1] *Chem. News*, 1868, **17**, 160.

[2] *Journn. Chem. Soc.*, 1874, **30**, 37.

great epidemic were to occur he would proclaim and enforce the active application of soap and water as the chief preventative. In any consideration of the subject of colloids in relation to health and disease, under the auspices of the Chadwick Trustees, it is, therefore, desirable to point out that the detergent action of soap to which Chadwick and his colleagues attached such importance is almost wholly due to its colloidal character, by means of which it is able to reduce the surface tension between other solids (" dirt ") and water, and to effect the removal of the former by a process of colloidal solution. It is a striking fact that a 1 per cent solution of soap will reduce soot to so fine a state of subdivision that it will pass completely through any filter, and will remain suspended indefinitely. In a 2 per cent solution of soap, on the contrary, the soot will be deposited almost as rapidly from pure water! In a similar manner a solution of soap in water will " disperse," or bring into " colloidal solution," a sufficient proportion of " dirt " adherent to any cleansable surface to enable the whole of the " dirt " to be removed in suspension in the fluid. The addition of any abrasive or scouring material—such as finely ground sand or silica flour—may aid the cleansing process, but the chief feature of it is, nevertheless, the production of a colloidal solution of a sufficient proportion of the " dirt " to enable the remainder to be removed readily.

The peculiar behaviour of soap has puzzled many investigators, some of whom have doubted its colloidal character yet have failed to find a complete explanation in a purely chemical conception. The true nature of soap is most probably shown by Bancroft, who has suggested that undissociated soap appears to be almost wholly present in colloidal form, but in the presence of water the sodium palmitate, or corresponding compound, is hydrolised, the OH ions being largely adsorbed by the undissociated soap, the adsorbing substance then becoming an anion.

CHAPTER IV

MICRO-ORGANISMS AND DISEASE

THE microbic origin of many communicable diseases is now generally recognised, and it is reasonable to presume a similar cause in many other diseases with which no specific micro-organism has been identified. Many of the disease-producing bacteria are sufficiently large to be readily visible under a powerful microscope, but others, such as those relating to yellow fever, foot-and-mouth disease, and tobacco disease, are too small to be directly visible. Their existence has been discovered indirectly by means of the ultra-microscope—an instrument which is described later.

Whilst recognising the remarkable advances in the treatment of many diseases which have resulted from the recognition of their bacterial or protozoal origin, the fact still remains that by far the most marvellous preventatives of disease are contained within a normal, healthy body, in which, as Lister has clearly demonstrated, bacteria can only establish themselves when conditions have arisen which create a state of unhealthiness.

The period in which all zymotic diseases were attributed solely to the introduction of bacteria, or protozoa, into the otherwise healthy subject is, happily, passing away, and pathologists and others are increasingly recognising as a fact the necessity for the bodily conditions being suitable before the disease germs can multiply extensively in it. As a result of the wide recognition of this fact—originally pointed out, though expressed in different terms, by Sir Edwin Chadwick and his colleagues—it is now seen that attention should be concentrated on the state of the body fluids and cells as well as on the invading micro-organisms. Now that the colloidal nature of the body fluids and cells has been recognised, it is possible to make considerable progress in maintaining them in, or restoring them to, a suitable condition on purely chemical or physio-chemical lines. The subject is too vast to discuss in detail in the present volume, but briefly it is now admitted that if the normal colloidal condition of any of the more important body fluids, or cells, is disturbed by the advent of undesirable electrolytes, salts, or colloids of the " opposite " sign, conditions are produced which provide a suitable nutrient medium for many of the disease-producing germs which are constantly coming into contact with the body. If the altered body fluids or cells can be restored to their normal colloidal state without seriously damaging any other portion of the subject, the invading germs will soon perish and will be removed from the body by the normal processes of life. If this view of the matter is correct, it is of far greater importance to restore the disarranged colloidal state to its normal condition than it is to endeavour to kill the invading germs without otherwise altering the state of the diseased or altered cells or body fluids. In the latter event it will only be a question of time before the patient is attacked by further organisms, and these attacks will be continued until, by some means or other, the diseased organs regain their normal colloidal state, or until they are atrophied or have been removed by means of a surgical operation. If, on the contrary, the normal colloidal state of the diseased organ can be restored, the body as a whole is well able to effect a complete recovery without any serious risk or delay. The importance of the influence of the "soil" upon the "seed," and the predisposition of the individual body to attacks by germs, has been established by Sir Wm. Collins in an essay published in 1884, dedicated to Herbert Spencer, who "regarded it as opening the way to a considerable reform in pathology." If his theory (as to underestimated influence of evolution on the specific disease-producing effects of organisms whose cycle may be only a few hours or even less than one hour, and whose rate of propagation is incalculable) is approximately correct the necessity of maintaining the body fluids in the correct colloidal state must be obvious. The rational treatment of *zymotic* disease must not depend solely on the destruction of the germs by means of which the disease is propagated; the requisite attention must also be paid to the "soil," or medium, in which the germs exist in the body.

This is readily understood when it is realised that emulsions of bacteria may be regarded as suspensoids protected by an emulsoid sol. They are precipitated by definite amounts of electrolytes, such as acids, heavy metal ions, and by aluminium and ferric ions, as are ordinary suspensions. Emulsions of bacteria are not precipitated by alkalies and are not protected from precipitation by other emulsoids, such as gelatin, as are many negative colloids. The addition of an immune serum to a bacteria sol greatly increases the sensitiveness of the latter to electrolytes, and apparently destroys the protecting part of the bacteria sol, which thus becomes a suspensoid sol.

Unfortunately, the colloidal characteristics of fluids containing bacteria are highly complex. Many of their reactions appear to be partly of a colloidal and partly of a chemical nature. Thus, the reaction between bacteria and agglutinins, including emulsin and gelatin, resembles an adsorption, but as sols of any one kind of bacteria are affected only by the agglutinin produced in the serum by the injection into the animal of the same kind of bacteria, this fact seems to imply the existence of definite chemical properties. On the other hand some bacteria sols are definitely affected by inorganic colloids in a manner which suggests both a colloidal and a chemical action.

Toxins and anti-toxins.—Toxins are the products of bacterial life, and are to some extent analogous to the excreta of the higher organisms. They are decomposed and rendered harmless by a number of substances, of which special interest attaches to those other products of bacterial life (such as immune serum) known as anti-toxins. Thus, when a suitable immune serum is added to the corresponding bacteria sol, the latter does not coagulate, even after dialysis, but it becomes so sensitive to electrolytes that the latter coagulate it easily. This is explained by the suggestion that the agglutinin in the serum destroys a protecting agent which is assumed to be present in the bacteria sol.

A mixture of the corresponding agglutinin and bacteria sol is not precipitated by OH ions, but readily so by acids and salts of the heavy metals. The addition of salts precipitates the colloids if there is an equivalent of agglutinin to bacteria sol. If either colloid is greatly in excess of the other no precipitation occurs.

Both toxins and anti-toxins are colloidal, particularly the latter. Thus, when a diphtheria toxin is treated with its anti-toxin, the reduction in toxicity depends on the manner of administration. If the anti-toxin is added in small quantities at long intervals much more anti-toxin is needed.

Field and Teague[1] found that both toxin and anti-toxin migrate distinctly in an electric field. There may be a chemical compound between the toxin and the anti-toxin, but more probably there is a mutual adsorption, the reaction being wholly colloidal. A difficulty exists with both explanations, inasmuch as diphtheric anti-toxin is the only one which will neutralise the diphtheria toxin, and, at present, both these substances appear to possess both chemical and colloidal properties.

In addition to the difficulty of treating such complex substances in accordance with general principles, there is the further disadvantage that, whilst blood serum has normally a positive charge, most of the sols of the pathogenic bacteria are not coagulated by fluids with such a charge. This remarkable behaviour may

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[1] *Journ. Exp. Med.*, IX, 86.

be due in part to the presence of a powerful protecting agent, but if this is correct it only transfers the difficulty without eliminating it. The value of a suitable immune serum lies in its power of increasing the sensitiveness of the bacteria sols to electrolytes, and thus facilitating their precipitation. Much work is now being done in the endeavour to ascertain the chemical or colloidal nature of the various agglutinins, and until the results of this work have been published judgment on this matter must be deferred. The fact that so small a quantity of the agglutinins has such far-reaching effects is highly confirmatory of their essentially colloidal character, and their peculiar specificity may ultimately be found to be due to the simultaneous production by the bacteria of a specific protecting agent which, in its turn, may be decomposed by the elementary colloidal sols, though it resists the attack of compound sols.[1]

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[1] Further information on the current views of the reactions between agglutinins and bacteria will be found in :

Immuno-chemistry, S. Arrhenius (Macmillan and Co.).

Le mechanisme de l'agglutination, J. Bordet. *Annales de l'Inst. Pasteur*, 13, pp. 225 to 272.

" Mechanism of the Agglutination of Bacteria by Specific Sera," W. J. Tulloch, *Biochem. Journ.*, 8, pp. 294–319.

CHAPTER V

POISONING—DIGESTION AND COLLOIDS

THE similarity between the poisoning of animals and the stoppage of the reaction of certain metallic sols by small quantities of well-known poisons is very striking. Thus, the presence of a trace of prussic acid will reduce the speed of reaction of platinum sol on hydrogen peroxide to half the normal rate, and a somewhat larger proportion will cause the reaction to cease. Enzymes and ferments are " poisoned " in a similar manner.

This great similarity between animal "poisoning" and a stoppage of a relatively simple chemical reaction is very important, as it suggests many other points of possible resemblance which are worth further study and opens out large fields of chemical research in connection with biological and physiological problems. Moreover, the relative ease with which the effect of metal and other sols on chemical reactions can be studied and controlled, suggests that similar reactions —equally well controlled—may be effected in the human subject with far-reaching results.

Digestion and colloids.—The reactions which occur in normal digestion result in the production of substances which are able to pass through the membrane of the alimentary canal into the blood stream. At the first glance, it may be supposed that such a passage would exclude all colloidal sols, though precisely the opposite is the case. It has been found that in the presence of a crystalloid, such as common salt, the passage of colloidal sols through the membranes is considerably increased, thus showing the importance of the salt to the animal and human organism. The advisability of eating salt with so typical a colloidal gel as a boiled egg is thus seen to be based on a physiological requirement, and not merely on a matter of taste.

It is important to observe that the products of digestion, and some other colloidal substances occurring in the animal organism, consist of much smaller particles than artificially prepared colloids. Thus hæmoglobin will pass through much less permeable membranes than colloidal metals, and serum, albumen, and protalbumoses are correspondingly finer in the order given. This may partially account for their ability to pass through certain membranes. Donnan has shown that the permeability of a membrane to a simple ion is greatly affected by the presence of a colloid. In some cases the colloid is hydrolised by some unknown means in the presence of an inert membrane and an electric potential is created. In both these cases the difference between a living and a dead organism must not be overlooked, though its importance should not be exaggerated.

The nature of materials used for food is so varied and the products of their digestion are so numerous that for anyone who realises their essentially colloidal nature, it is easy to see that any change of state may produce a profound disturbance in the whole system, and that such a disturbance may appear to be quite out of proportion to the chemical activity of any compound or element which may be present. For this reason there can be no general cure for all forms of indigestion, as each has its specific cause. If any such general remedy could exist it would be a substance which would effect the conversion of any food substance into a colloidal sol of a nutritive and non-toxic character.

Similarly, it is possible to see that improper food, unsuitably prepared, the absence of sufficient air, and the neglect of sanitary and hygienic precautions may effect changes which are quite disproportionate to the actual weight of " dirt " or other objectionable matter present. The normal state of the body fluids is easily disturbed, and whilst it is almost as easily restored under healthy conditions of life, restoration is made difficult or even impossible if the conditions are unsuitable.

CHAPTER VI

USE OF COLLOIDS IN MEDICINE

COLLOIDS have long been used more or less unwittingly in medicine, the colloidal state being the only one in which certain medicaments can be administered, whilst others—exhibited as tinctures—are converted into colloids on dilution. Such crude forms are necessarily subject to many disadvantages, and the true significance of their colloidal nature not having been recognised it is only natural that they should not be either as certain in action nor as free from objectionable properties as colloids which have been specially prepared so as to secure the maximum colloidal efficiency. Thus, tincture of podophyllin and other resinous substances are precipitated on diluting them sufficiently with water, with the consequent formation of a small proportion of colloidal sol. This sol is the most active therapeutic constituent, and the remaining material is only useful medicinally when it has been converted by the action of the body fluids into an assimilable form. This conversion is accompanied by a serious loss of material, both directly, by its conversion into inert or undesirable substances, and indirectly by its transport to portions of the organism where it cannot exercise the desired effect. Consequently, the accidental production of therapeutic agents in colloidal form results in uncertainty of action, the production of undesirable side reactions, and necessitates the administration of large doses, the greater part of which is inert, or, in some cases, somewhat harmful to the patient. These disadvantages were unavoidable so long as no satisfactory colloidal preparations were available, but with the increase in the number and efficiency of the latter, the science of pharmacology and the practice of medicine will, it is anticipated, make rapid progress.

The most widely-used preparations of a highly colloidal character are the embrocations and liniments used externally or those administered internally in the form of emulsions of cod liver oil, petroleum, etc. These have proved a convenient and satisfactory means of introducing certain liquids in varying degrees of dilution, under conditions in which ordinary solvents are inadmissible.

Such emulsions are truly colloidal in character, the active liquid being usually present as the disperse phase, whilst the continuous phase is of a different character, such as water to which a small proportion of an emulsifying agent—usually albumen or a soap—is added. Other active therapeutic agents may usually be present in solution in the aqueous phase, it being an additional advantage possessed by emulsions that they permit the simultaneous exhibition of two or more active agents in any desired degree of concentration.

Emulsions of the kind just mentioned must not be confused with the colloidal sols described later. Even the most elegant emulsions are very coarse compared with the sols, and the penetrating power and general activity of the latter are correspondingly greater than that of emulsions.

The customary administration of any remedy—quite apart from the particular substance or drug which it may contain—is primarily based on the assumption that such a remedy has a specific reaction either with a substance in the body (such as the action of pepsine on the undigested food) or an equally definite, but less understood, reaction whereby certain organs are stimulated to unusual effort, as in the administration of emetics or purgatives. It is generally supposed that the effect is roughly proportional to the dose administered, though it is recognised that the optimum dose differs with different patients. In some cases—particularly in the administration of mercury compounds—it is also realised that minute quantities administered frequently have an effect which is entirely different from that of the same substance administered in a single and large dose. Still more striking is the fact previously mentioned, that with some remedies the changes are out of all proportion to the dose which may be administered. The great changes which occur in certain diseases are prevented, and the normal state is restored by quantities of chemical agents which appear ridiculously small when regarded as definite reagents. But such a condition is a well-known characteristic of colloidal fluids, in which even a few drops of solution will effect a solidification of a large volume of material. The coagulation of milk by rennet or acid, and that of blood after a short exposure to air, are typical illustrations of such a change. The extraordinarily rapid action of minute doses of some poisons is probably a similar effect. Bearing in mind these great changes in condition which result from the action of small amounts of active agents, it is easy to see that a slight excess or deficiency of some element present in minute proportions in the organism may effect a profound change in the action of that organism. The deficiency of phosphorus in certain nervous diseases is well recognised, and various methods of supplying it have met with encouraging results. There is, however, a curious idea extant, that an element in which there is a deficiency should be administered in the same form as that in which it exists in the body. For instance, there is a popular idea that glycophosphates are superior to any other phosphorus compounds, because the phosphorus in the brain is chiefly found as a glycophosphate. This is quite a mistake, as will readily be seen if other analogous cases are considered. For instance, sugar is stored in the liver in the form of glycogen, but to administer glycogen orally would be useless, as it is destroyed in the stomach. It is essential that any medicine should be administered in such a form that its essential constituent will travel through the body until it reaches the part where it is required, and that it shall arrive at that organ in such a state as to be used to the greatest advantage. To administer lecithin because lecithin has been isolated from the brain substance is to misunderstand the chemical changes which take place in assimilation, and to supply the subject with a material in a form from which it has to be converted to something more suitable. The fact that this conversion occurs merely shows how marvellous an alchemist is the human organism ; it is no reason for the administration of chemical agents in unsuitable forms.

The principle underlying the treatment of disease by the administration of chemical compounds is much more easily understood when it is realised that the reactions deal largely with colloidal materials, and that they may be effected most efficiently and with a minimum of disturbance to other organs by basing the treatment on this principle.

This fact has been recognised in a half-hearted way for some years, but its implications were scarcely realised until a few years ago. This was due to a number of causes, of which the two most important were the difficulty of studying the special properties of substances in the colloidal state with the appliances then at hand, and the difficulty experienced in obtaining active colloidal fluids which were isotonic with and therefore stable in the body fluids to which they were applied. The work of Ehrlich and others may, in certain respects, be regarded as attempting to supply elements of a highly toxic character, such as arsenic, in such a form that they would affect the disease-creating germs without harming the patient or host. Such methods suffer from obvious drawbacks, such as the caustic, irritant, or even toxic effect of the stabilising organic compound, and as the complexity of the compounds was increased, their essentially colloidal character gradually receded into the background of the minds of the investigators until it was wholly overlooked.

Colloidal fluids only retain their characteristic properties so long as their active ingredient is in a properly dispersed and suitable colloidal state. In the presence of very small quantities of certain salts, the ions or ultimate particles of which have an electric charge which is opposite in sign to that of the active colloid, the latter will be coagulated and rendered inactive, unless they have been protected by some other colloid. In the latter case, coagulation or precipitation can only occur when the protective agent has been destroyed or removed.

Medical possibilities of colloids.—From what has already been stated it will be seen that the application of colloidal sols to diseased conditions of the human body is distinctly encouraging, but like all other new ideas it has had its share of drawbacks and discouragements, due in almost every instance to ignorance. Among other causes the premature supply of improperly prepared and unstable colloids has been one of the most serious sources of trouble.

Shortly after the definite recognition of the colloidal nature of the chief body fluids was effected, the enormous possibilities which might result from the application of colloidal disinfectants and medicines were rapidly recognised by German investigators; a number of colloidal substances was placed on the market and their therapeutic properties were carefully and vigorously "boomed" in this country and elsewhere.

It was soon found, however, that most of these preparations rapidly deteriorated in value; some of them were so unstable that they contained no active colloid at the time when they were used, and others—

not being isotonic with the physiological fluids in the diseased organs to which they were applied—were coagulated immediately after their administration to the patient.

Many attempts to secure stability by means of organic compounds were made, and eventually the main difficulties were overcome—especially with regard to certain colloidal elements. One of the chief causes of trouble was due to the fact that if a colloidal substance is prepared in the purest possible state in a disperse medium (such as water) of great purity, the product will be highly unstable. Even a trace of material of the opposite electric sign will cause the precipitation of the colloid. If, on the contrary, the substance is converted into the colloidal state in the presence of certain other colloids and of certain salts, the desired colloid will not have its activity impaired in the least degree, but it will be quite stable and can be mixed with normal blood or other body fluids without being rendered inactive by them. The salts and additional colloids exercise a protective action on the colloid chiefly under consideration, and so enable it to be used under circumstances which would otherwise be impossible. The therapeutic action of the protective agent must not be overlooked ; usually it appears to be negligible, but occasionally it has been observed to be of considerable importance.

Failure to realise the necessity for stabilising the remedial colloids by rendering them isotonic with the blood serum, and protecting them against precipitation by undesirable agents, was thus one of the chief causes of failure of the earlier investigators, but it has been entirely overcome in the case of a large number of colloidal sols mentioned later, and these are quite stable and effective. Yet in consequence of the failure which resulted from such ignorance of the essential properties of all colloidal fluids, British medical men were at first rightly averse to using colloidal preparations, and the subject remained in a parlous state for some time. In fact, it so remained until suitable methods of preparing stable and isotonic colloidal sols were discovered in 1910–1913 by the late Henry Crookes—a son of Sir Wm. Crookes—and were extended and improved by his colleagues and successors, as well as by other investigators.

CHAPTER VII

PREPARATION AND ASSAYING OF COLLOIDAL SOLS

ANY substance can be obtained in the colloidal state if the conditions under which it is prepared are suitable. All colloidal sols are prepared by either

(1) Dispersing or breaking down the larger particles in the presence of a suitable fluid; or

(2) By "condensing" particles in solution until they form larger suspensoid particles.

The dispersion may be effected—

(*a*) Mechanically, as by grinding the substance and fluid together;[1]

(*b*) By dilution, as when a gum is dissolved in alcohol solution and the solution poured into a large volume of water;

(*c*) By using electrodes of the substance to be dispersed immersed in a suitable liquid and passing an electric current through them;

(*d*) By the addition of a suitable electrolyte (such

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[1] Colloidal solutions must not be confounded with the suggestions made by homœpathists with respect to prolonged trituration of a solid material or to the administration of small doses at regular intervals.

No trituration, however prolonged, will convert some materials into a colloidal sol state, and even those which can be converted are too much contaminated with non-colloidal material and are too unstable to be of much service. As regards dosage, it is a well-known characteristic of all colloidal reactions that if the whole of the reagent is added rapidly its effect is much greater than if it is added in small quantities at a time.

as an acid or alkali) to a colloidal gel. From the analogy between this process and that of animal digestion it is frequently termed *peptisation*.

The condensation may be effected by chemical reduction, oxidation, hydrolysis, or double decomposition. Thus, colloidal gold sol is readily obtained by reducing a dilute solution of gold chloride, formic aldehyde, or phosphorus in the presence of potassium carbonate. Colloidal sulphur sol may be obtained by adding a solution of sodium hyposulphite drop by drop to a dilute solution of sulphuric acid, heating the mixture to 80° C. for a short time, filtering off any insoluble sulphur and neutralising with sodium carbonate.

Although many colloidal sols are made by hydrolysis (i.e. by the action of water on them) this is seldom used as a method of preparation. The methods of preparation just indicated do not as a rule yield colloids which are stable in the presence of serum. For this purpose they must be modified so as to produce a stable fluid. It is most important to observe that it is relatively easy to produce a colloidal sol of low stability and containing a considerable proportion of impurities ; it is peculiarly difficult to prepare pure sols which remain stable when mixed with the blood-serum and other physiological fluids. Yet the use of impure and unstable sols is so serious that no pains must be spared in ensuring the purity and stability of the sols used for remedial purposes, and particularly those which are administered by intravenous or intramuscular injection. For these reasons, the remedial colloidal sols prepared by the amateur should not be used until exhaustive tests have proved their efficacy and stability. The author is aware of a number of severe cases of poisoning which were due solely to the use of impure colloids with a very low degree of stability. As many colloidal sols of high stability and suitability for administration either orally or hypodermically can now be purchased, there is little or no advantage to be gained by medical men preparing these sols.

The *stabilising* or protecting of a colloidal sol depends on its being in a state of equilibrium between the forces tending to cause these small particles to coalesce (surface tension) and those tending to cause dispersion of the colloid throughout the medium. Stability appears to be due, in most cases, to a union of the particles to be stabilised with those of the protective colloid or with ions which have a stabilising action. Zsigmondy maintains that stability is wholly due to the equilibrium between the adsorption and dissociation of ions by colloidal particles. The instability which is most serious in colloidal sols used as medicines is that which results in coagulation.

Stability is secured in a variety of ways, including the following :

(*a*) Preparing the sol in the presence of those substances in which it is required to be stable, i.e. by substituting an appropriate fluid for water as a solvent for the various substances from which the colloid is produced. Thus colloidal sulphur, prepared in a solution in which water is replaced by a physiological salt solution, is much more stable after injection into the blood than colloidal sulphur prepared in pure water. On the other hand, the former is liable to set up undesirable reactions within the body unless special precautions are taken to remove the undesirable salts by a process of selective dialysis.

(*b*) Adding a protective agent such as gelatin or protalbinic acid prior to producing the sol.

(*c*) Preparing the sol so that all the dispersed particles are of the same size and without any appreciable surface tension in the dispersing fluid.

(*d*) The presence of chlorine or of other characteristic ions appears to be essential to the stability of positive sols. If these ions are removed the sols are unstable.

(*e*) Removing the greater part (but not the last traces) of electrolytes. This method is inapplicable to colloids used for medical purposes.

Assaying sols.—It is of utmost importance to determine the activity of a sol just prior to its use unless it is definitely known that it is sufficiently stable for its activity to be relied on implicitly.

The percentage of active colloid cannot be determined by any of the ordinary chemical methods as the colloidal state is physical rather than chemical in character. Thus, a colloidal solution of silver gives no precipitate with a solution of a chloride, a colloidal solution of iodine does not produce a blue colour with starch solution. Hence, it sometimes happens that a chemist may report that a certain solution does not contain a particular element or compound if the latter is in a colloidal sol state. By appropriate treatment—usually by converting the substance into the crystalloid state—the ordinary methods may be applied, but they do not differentiate between the proportions of colloidal and crystalloidal substance when both are present.

The chief methods of determining the activity and therefore the value of the sol are :

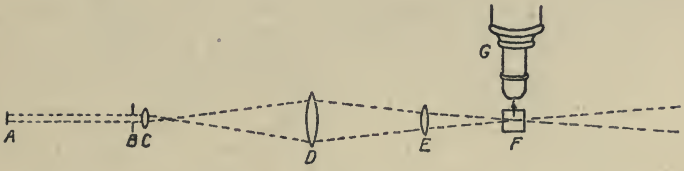
(*a*) Observation of the movement of the particles by means of an ultra-microscope.

(*b*) Observation of the intensity of the Tyndall phenomena.

(*c*) Determination of the gold number.

(*d*) Observation of the time taken for a deposit to form.

(*e*) Observation of the effect of the addition of the solution to serum or other characteristic physiological fluid.



A. Arc Lamp. B. Slit. C. Primary Lens. D. Secondary Lens.
E. Condenser (1in. objective). F. Cuvette. G. Microscope.

Fig. 2. Diagram showing Action of Ultra-microscope

(*a*) The *ultra-microscope* affords the simplest and most rapid means of ascertaining the activity of the colloidal particles in a sol. When properly prepared, colloidal sols are transparent or slightly opalescent, coloured or colourless, pass readily through a filter paper, are apparently homogeneous in chemical behaviour but under the ultra-microscope are seen to contain minute particles in a state of rapid motion, the particles being comparable in size to those of molecules in crystalloid solutions. In some colloidal sols the particles are too small for their movements to be observed in the ultra-microscope (i.e. they are less than about 30 $\mu\mu$ in diameter). The ultra-microscope is based on the fact that the existence of particles which are quite invisible to direct vision may be readily recognised by passing a beam of light across the space in which they occur. The beam of light from a lantern is in itself invisible, but the particles of dust present in the air—which are also invisible—reflect the light in various directions, so that we recognise the presence of these particles by their action on the light.

Zsigmondy applies the same principle to colloidal particles by passing a very concentrated and powerful beam of light horizontally through the liquid to be examined and then views the liquid against a black background through an ordinary microscope. If the liquid consists of a solution of a crystalline salt the field of the microscope remains dark, but if an active colloidal substance is substituted the field is at once occupied by minute specks of light which dart hither and thither in a wholly irregular manner. The ultra-microscope consists of a powerful source of light—an arc lamp or the sun—which sends a beam of light through a suitable slit 0·002 to 0·02 in. wide and 0·004 to 0·08 in. high, the light being focussed by a telescopic objective of about 0·4 in. focus. A second similar lens of about 3 in. focus forms an image of the slit in the plane of a condenser, the latter consisting of a microscope objective, whereby a reduced image of the slit is thrown into the solution to be examined. A polariser may be inserted between the slit and the second lens if polarised light is desired, and all extraneous light may be cut off by suitably disposed diaphragms. The solution to be assayed is contained in a specially shaped glass vessel termed a cuvette, which consists of an accurately shaped rectangular cell with a small tube at each end to form an outlet and inlet respectively. By passing a current of specially distilled water through the cuvette it is readily cleaned and the colloidal solution can be admitted, discharged, and the cell washed as required.

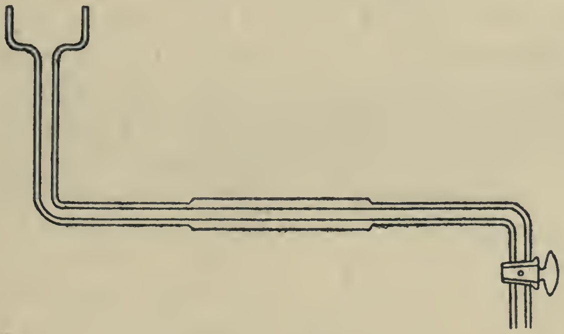


FIG. 3. CUVETTE.

The light passing horizontally through the solution is reflected by suspensoid particles, and if an ordinary microscope is used to examine the solution in the cuvette the field will be illuminated by brilliant specks of light if a colloidal sol is being examined, but will be dark if a crystalloid solution is used. If the cuvette is filled with an active colloidal sol, the movements of the particles are readily observable, and then if to this active liquid is added another containing either a colloid of opposite electrical sign or some other substance on which the active colloid can exert itself, the field rapidly darkens because the active colloid and the reagent combine and settle to the lower part of the cell and so out of the beam of light.

An active colloid which has, for any reason, become unstable will show very few specks of light in the ultra-microscope, and their movement will be slow and wholly different from a freshly prepared colloid. By this simple means, the activity of a colloidal fluid may be ascertained in a few minutes and all uncertainties in this respect at once removed. Without such an instrument, useless, inactive, and unstable colloidal preparations might be administered instead of active ones. The use of an ultra-microscope was particularly necessary when the uncertain colloids prepared by electrical methods or by reduction from unsuitable solutions were used, but at that time, unfortunately, such instruments were not available in this country. During the past five years, perfectly stable colloidal preparations have been available in this country, and as they can be relied upon, if prepared by a good firm, the general use of the ultra-microscope is no longer necessary.

Incidentally, it may be mentioned that the ultra-microscope has been invaluable in recognising the dissimilarity between normal and infected serum and the effect of prepared colloids upon the characteristic colloidal eccentricity of such substances as syphilitic serum. Normal serum is a saline colloidal solution of insoluble protein protected by soluble protein (aliphatic amino-acids). In syphilis, the proportion of colloidal matter in the serum is supernormal, and especially in the cerebro-spinal fluid, and the charge carried by the protein is positive.

(*b*) The *Tyndall phenomenon* first investigated by John Tyndall,[1] who found that light passed through a gas or liquid containing particles in suspension—even when these are so small as to be ultra-microscopic—produce a delicate blue colour the intensity of which is roughly proportional to the number of particles. Larger particles produce a white tint as they are not small enough to scatter only the shortest waves of light.

If a concentrated beam of light from an arc lamp is passed through a slit placed in its focus, next through the solution in a rectangular vessel and then observed with a mounted Nicol prism, it will be found that the polarisation of the light is affected by the colloidal particles. If these are less than 100 $\mu\mu$ in diameter the polarisation is complete, and the Nicol must be turned through 90° to depolarise it. For larger ones, a lesser angle will suffice. If a selenite plate is substituted for the Nicol prism, the light which has been polarised almost completely by the solution will produce vivid colour effects. These coloured rings form an extremely delicate means of estimating the number of particles in suspension in the solution, the diameter of the beam of light required to produce the rings being inversely proportional to the number of colloidal particles in the solution. Thus, a large beam of light is needed for distilled water, whilst with a good colloidal solution so small a beam as to be scarcely visible will produce vivid colours with selenite.

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[1] *Proc. Roy. Soc. Lond.*, 1868, 17, 223; *Phil. Mag.*, 1869, (4), 37, 384–388.

A true solution devoid of all colloidal particles does not show the Tyndall effect, though it is extremely difficult to obtain any liquid which does not give at least a faint indication. Fluorescent solutions (such as quinine disulphate, dilute eosin solution, etc.) which might otherwise be mistaken for colloidal sols, do not show this effect.

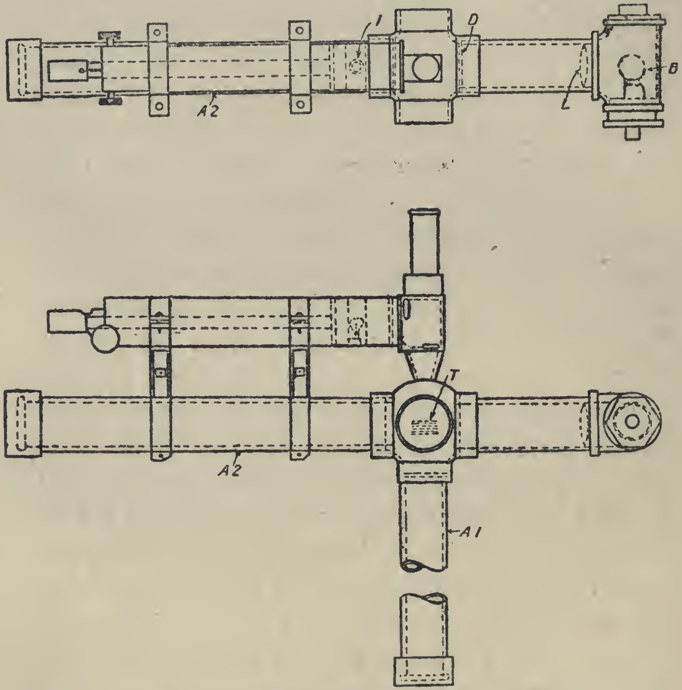

FIG. 4. TYNDALLMETER (Vertical Section and Plan).

A convenient arrangement for applying the Tyndall beam to colloidal liquids is that devised by Tolman and Vliet. It consists of an electric light bulb B, a condensing lens L, giving a beam of parallel light which passes through the diaphragm D, and a Macbeth illuminator for measuring the intensity of the Tyndall beam T. A cylindrical tube is introduced at T through which the liquid to be examined is admitted and discharged. The tubes A_1 and A_2 are provided to absorb the beam after it has passed through the colloidal liquid, and also to serve as a dark ground on which to view the Tyndall beam. The central chamber in which the colloid to be examined is placed is about 1 in. diameter and 4 in. long, and the tubes A_1 and A_2 are about the same diameter and 12 in. long. The illuminator is an electric lamp of about 30-candle power at 6 to 8 volts, capable of adjustment so that the apparatus may be standardised, the light being usually adjusted so as to give a brightness of 22·5 foot candles, though any convenient figure may be used. The intensity of the Tyndall beam is fairly proportional to the concentration of the colloid when the dispersion is great, but when the concentration is much higher than 0·5 gm. per litre the intensity is not proportional as the increased turpidity of the sol prevents the light passing through the liquid. It should be noted that the size of the particles must be taken into account, as in the following formulæ :

$T=knd^6$ for small particles
$T=k^1nd^6$ for large particles

where T is the intensity of the beam, k and k^1 are constants ; n is the number of particles per cb. cm., and d is the diameter of the particles.

(*c*) The *Gold number* is a measure of the protective power of a colloid against the tendency of other colloids, etc., to effect precipitation; it is also a measure of the stability of the colloidal sol. The gold number is defined by Zsigmondy[1] as the weight in mgms. of colloid which just fails to prevent the change from red to violet in 10 cc. of gold solution (containing 0·0053 to 0·0058 per cent of gold) when 1 cc. of 10 per cent solution of sodium chloride is added to the sol. Hence, the lower the gold number the greater the protective effect of the colloid or the greater the stability of the sol examined.

The gold number is found as follows: Three portions, *a*, *b*, and *c*, containing 0·01, 0·1 and 1 cc. of a suitable protecting colloid such as gelatin and 1 cc. of the colloid to be tested, are placed in three small beakers and well mixed with 10 cc. of gold collosol. After three minutes 1 cc. of 10 per cent solution of sodium chloride is added to each and mixed. Assuming there is a colour change in *a* but not in *b* the gold number lies between 0·01 and 0·1. For a more accurate determination, repeat with a fresh series, using 0·02, 0·05, and 0·07 cc. of colloid. The following gold numbers are useful:

		Class of protective colloid.
Gelatin and glues	0·005–0·010	I
Isinglass	0·010–0·020	
Casein	0·010	
Good gum arabic	0·150–0·250	II
Dextrin	6·000–20·000	III
Potato starch (about)	25·000	
Silicic acid	∞	IV

The *stability number* is a useful modification of the test, as applied to the determination of the stability

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[1] *Zeits. anal. Chem.*, 1902, **40**, 697.

of a colloidal sol. It is found by first selecting a substance which will decompose the colloidal sol, preparing a suitable solution of this substance, and then adding it to a known volume of the sol to be examined. The amount of substance required to just destroy the activity of 1 c.c. of the colloidal sol, as observable under the ultra-microscope, is the stability number.

(*d*) The *time required* before a colloidal sol will form a deposit is a crude, but useful, measure of its stability. With sols of poor quality the time is very short, but properly stabilised sols are remarkably durable. The author kept a sample of colloidal iodine dispersed in 33 times its weight of mineral oil for three years and found that it was as active and free from deposit as when first prepared. Great care is needed when making comparisons of colloids on a time basis, as so many variable factors may occur. The influence of heat and light must not be overlooked, whilst even more important may be the effect of traces of material dissolved out of the glass of which the vessel containing the colloid is composed. Traces of dust or organic matter in the vessel used may have a serious effect, and for this reason colloidal sols should not be stored in corked bottles. If proper care is taken to stabilise the sols, those used remedially can be stored indefinitely in ordinary glass-stoppered bottles as the stabilising agents which prevent the decomposition of the sols by silicates or alkalies dissolved from the glass do not affect the physiological activity of the colloids.

(*e*) *The effect of serum* or other physiological fluids on a sol intended for medical or surgical purposes should be fully investigated before employing the sol. Unless this is done, sols may be used which are quite useless owing to their premature decomposition. This applies particularly to " home-made " preparations ; those bought from reliable manufacturers have usually been investigated by independent authorities and their suitability can be ascertained by enquiry. Speaking broadly, pure suspensions of a colloid in water are quite useless physiologically and pathologically, as they are decomposed immediately they enter the blood stream. By preparing them in a suitable manner with the proper stabilising agent in each case, this objection may be completely overcome.

CHAPTER VIII

COLLOIDS AS GERMICIDES AND DISINFECTANTS

It has long been the desire of physicians and sanitarians to find a series of substances which will destroy disease-producing germs and yet prove harmless to human beings or even to domestic birds and animals. Many attempts have been made to obtain compounds analogous to carbolic acid, with a high germicidal and low toxic power, but only a meagre degree of success has been reached. This is only to be expected when it is realised that the human organism is composed of an indefinite number of cells and that any substance which kills bacteria or other disease-producing organisms is almost certain to have a similar action on these cells. The difference in action is merely one of degree, and is therefore subject to limitations and accompanied by risks which are far from satisfactory.

Moreover, some of the most virulent germs are able to flourish in solutions of carbolic acid (phenol) and other well-known disinfectants of a strength which would be poisonous to human beings, and also the evolution of germs of one kind into those of another renders almost chimerical the search for a general germ-poison which is non-toxic to human beings.

Fortunately, the recognition of bacteria and their products as essentially colloidal in character has greatly facilitated the study of disinfection. It is now realised that—disregarding the fact that bacteria are alive—they may—owing to their colloidal character and that of the toxins and some other substances they produce—be destroyed by substances which bear an electrical charge opposite to that of the bacteria or their colloidal products. The effect of an ordinary disinfectant on bacteria is the result of its adsorption by the latter, forming either a chemical compound, as appears to be the case with formalin, or a distribution of various phases in accordance with the well-known law of adsorption of colloids. In the latter case, colloids of opposite electric charge will precipitate each other so long as neither is in great excess, but if either colloid is in excess both will be rendered inactive though no precipitation may occur.

The great advantage of dealing with germs as colloids lies in the fact that the agents used for their coagulation and consequent destruction are not necessarily poisonous—an advantage which becomes of utmost importance when it is desired to destroy the bacteria *in corpore villi*. In other cases, where the use of phenol and other poisonous substances is less objectionable, their lower cost may rightly be taken into consideration. Some of the most fruitful results in this line of research are those which have followed the discovery by the late Henry Crookes in 1910 that certain metals when in a colloidal state have a highly germicidal action, but are quite harmless to human beings. It was previously known that certain finely divided metals had a feeble toxic action on the lower forms of plant life, and that the germicidal power of certain metallic salts depends to a very large extent on the degree of ionisation and on the specific properties of the individual ions, those of the metal having the chief germicidal power. In other words, the greater the extent to which the metal is set free in a very dilute solution of its salts, the greater is the germicidal power of the solution ! By converting the metal into the colloidal state it may be applied in a much more concentrated form and with correspondingly better results.

The importance of this twofold fact has been largely obscured, partly by the germicidal properties of some substances apart from their degree of ionic dissociation, partly by the manner in which some substances are adsorbed by the products accompanying the bacteria, and so are rendered inert before the latter are affected, and partly because of the ignorance of the means of preparing colloidal metals in a form sufficiently stable for administration as medicines.

Equally unfortunate was the death of Mr. Crookes before he had been able to extend the results of his discovery, though these difficulties and drawbacks have now been overcome and are chiefly of historical interest. It is now definitely known that the germicidal properties of certain colloidal metals are based partly on the chemical action of the metals themselves, different metals having greater specific action on some bacteria than on others, but chiefly on the fact that metals are in the colloidal (sol) state.

These colloidal metals—of which gold and silver are the best known—consist of such minute particles that the latter have ample space for an extremely active movement without touching one another.

Moreover, by virtue of a property well known in physics—the particles having a like electric charge tend to repel one another and thus increase the stability of the liquid. When such metallic particles are added to a fluid containing in solution, suspension, or in that intermediate state we recognise as colloidal, particles bearing the opposite electrical charge—or in some cases if the particles are neutral—coagulation or precipitation rapidly occurs.

The germicidal action of colloidal metals, such as silver and mercury, at a concentration of 1 : 20,000 is clearly shown by the following test made by the late Henry Crookes:—

Silver and mercury "Collosols" of the normal strength (1 in 2000) were diluted with 9 times their quantity of nutrient broth (1 in 20,000), and 10 cc. of this mixture were infected with two loopfuls of a vigorous culture of *B. coli communis*; after shaking, so as to mix thoroughly, streak cultures were made quickly on agar plates, the first within ten seconds, then at two, four, six, eight, and ten minute intervals. These plates were incubated at 37° C. for forty-eight hours, and gave the following results:—

Silver "Collosol" (1 in 20,000) with *B. coli communis*		Mercury "Collosol" (1 in 20,000) with *B. coli communis*	
After 10 seconds	Growth	After 10 seconds	Growth
,, 2 minutes	,,	,, 2 minutes	No growth
,, 4 ,,	,,	,, 4 ,,	,,
,, 6 ,,	No growth	,, 6 ,,	,,
,, 8 ,,	,,	,, 8 ,,	,,
,, 10 ,,	,,	,, 10 ,,	,,

In each case the blank or control streak gave a vigorous growth.

These experiments were repeated with silver and mercury "Collosols" at the normal strength of one part in two thousand. In every case, *B. coli communis* was killed within ten seconds, the only growths on the agar plates being those of the untreated control streaks. Several comparative tests were made with the *gonococcus* grown on agar plates smeared with fresh blood, with the usual precautions. A plate showing a vigorous growth and answering to the typical tests (viz. Gram-negative, no growth on gelatin or agar at 20° C. without fresh blood, but vigorous growth at 37° C. on agar with fresh blood, and displaying the well-known *diplococcus* in pus cells) was swabbed with "Collosol" silver for two minutes, after which time streak cultures were taken and transplanted to agar plates smeared with fresh blood as before, at intervals of two, four, six, eight, and ten minutes, and incubated in the usual way at 37° C. *Result.*—No growth whatever.

Many series of experiments similar to this gave similar results; for instance, a young vigorous growth of *B. tubercolosis* was killed by "Collosol" silver (1 in 2000) in four minutes. *Staphylococcus pyogenes*, various *Streptococci*, and other pathogenic organisms, are all killed in three or four minutes; in fact, no microbe is known that is not killed by this colloid in laboratory experiments in six minutes.

The following experiments were made by W. J. Simpson, C.M.G., M.D., etc., Professor of Hygiene, King's College, London, and R. Tanner Hewlett, M.D. (Lond.), F.R.C.P. (Lond.), Professor of Bacteriology in the University of London, were printed in the

Lancet of 12 December, 1914, and are of special interest.

Drs. Simpson and Hewlett mixed Silver Collosol solution with nutrient broth in various dilutions, taking 10 cc. of each in a tube. These were inoculated with one drop of 24-hour broth culture of the typhoid bacillus, incubated, and subcultures made after varying times. For the sake of comparison, similar experiments were carried out with corrosive sublimate under the same conditions. The results were as shown in the tables :

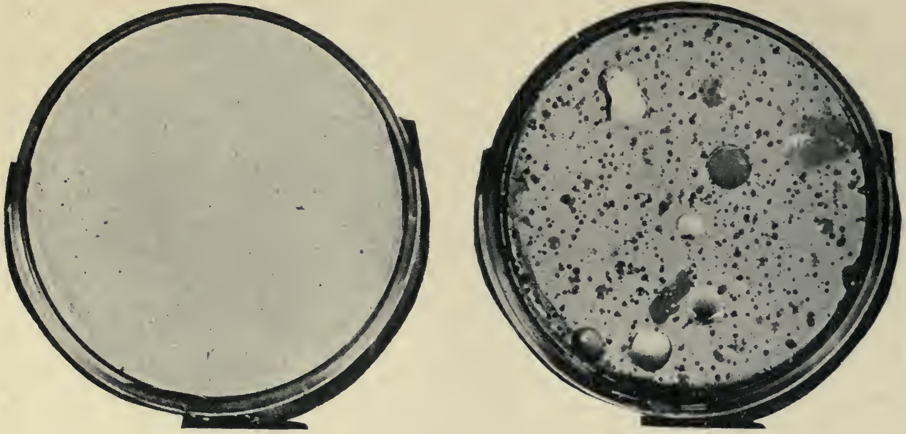
WITH COLLOSOL	Subcultures made after					Original tubes after
	15 min.	30 min.	1 hour	2 hours	24 hours	3 days
500 per million	+	0	0	0	0	0
100 ,, ,,	0	0	0	0	0	0
50 ,, ,,	+	+	0	0	0	0
25 ,, ,,	+	+	0	0	0	0
10 ,, ,,	+	+	+	0	0	0
5 ,, ,,	+	+	+	0	+	+

WITH CORROSIVE SUBLIMATE	Subcultures made after					Original tubes after
	15 min.	30 min.	1 hour	2 hrs.	24 hrs.	3 days
500 per million	+	0	0	0	0	0
100 ,, ,,	+	0	0	0	0	0
50 ,, ,,	+	+	0	0	0	0
25 ,, ,,	+	+	0	0	0	0
10 ,, ,,	+	+	+	+	+	0
5 ,, ,,	+	+	+	+	0	0

+ = growth ; 0 = no growth in the subcultures.

A comparison revealing such a small difference in germicidal power between the collosol and corrosive sublimate, considered in the light of the absolute non-toxicity of the collosol, is surely remarkable and cannot fail to evoke considerable interest.

Many other experiments of a similar nature have



A
Fig. 5

B
Fig. 6

Photographs Illustrating the Preservative Effect of "Collosol Argentum"

Two plates of nutrient gelatin exposed on a window-sill for half an hour. *A* had been covered previously with "Collosol Argentum" for five minutes; *B* was untreated. Both plates were incubated for forty-eight hours at 20° C. *B* contains about 350 colonies of microbes.

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been made by chemists and medical men, all testifying to the value of " Collosols " as bactericides.

On the 20th May, 1913, two plates of nutrient gelatin were exposed on the window-sill for half an hour. *A* had been covered previously with " Collosol Argentum " for five minutes ; *B* was untreated. Both plates were incubated for forty-eight hours at 20° C. ; after which, *A* remained sterile whilst *B* contained about 350 colonies of microbes. Figs. 5 and 6 illustrate this preservative effect of " Collosol Argentum."

It might be suggested that a liquid containing only one part of colloidal metal in 2,000 of fluid would be too weak to be of use, but this is not the case. There are at least 20,000 million active particles of metal in 1 cc. (=15 drops) of properly prepared colloidal silver of this concentration, and one great advantage of colloidal elements in such a low concentration is their complete harmlessness to the patient.

Not all elements in the colloidal state have a germicidal action. The following table, based on Henry Crookes' investigations, is interesting in this connection :

No germicidal action : Gold, platinum, palladium, rhodium, iridium, tantalum, cadium, magnesium, tin, graphite, selenium, sulphur (sulphur has a strong, stimulating action).

Slight germicidal action : Bismuth, lead, aluminium, zinc, copper.

Strong germicidal action : Thorium, cobalt, silver, mercury, antimony, mercuric cyanide, mercuric chloride, arsenious acid.

The germicidal action of metals and some other substances is clearly shown in Figs. 5 to 18, which are reproduced from photographs taken by Hy. Crookes of Petri dishes containing fish-agar, or other nutrient medium inoculated with various bacteria and kept under conditions favourable for their incubation and development. In the centre of each dish was placed a piece of the substance whose action was to be examined and its effect is clearly shown.

On examining the illustrations showing a dish containing a germicidal metal it will be seen that surrounding the latter is a vacant space in which no bacteria have grown, around it is a dense ring in which the germs have flourished to an abnormal degree, and between this ring and the circumference of the dish is practically the same as though no germicide were present. The cause of this arrangement—which is particularly marked in the case of silver (Fig. 10)—is the germicidal action of the minute amount of colloidal silver which has been formed immediately around the metal, whilst further away a still smaller proportion of the colloidal silver has a stimulating action on the bacteria. Still further away there is no colloidal silver, and the bacteria grow in the normal manner. The growth of the same bacteria in the presence of a germicidal and inert colloidal metal may be compared by observing the differences between Figs. 5, 6 and 10; the former, which shows the action of colloidal silver, exhibits the characteristic features very clearly; in the latter, which shows the result of using non-germicidal colloidal gold, these features are absent and the bacterial growth is fairly uniform.

The amount of colloidal metal produced under the

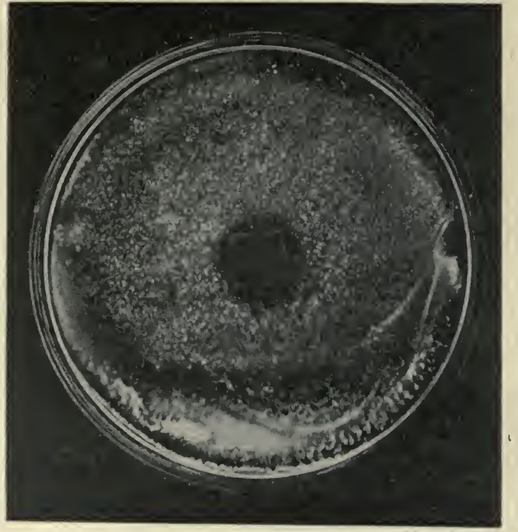

Fig. 7. Action of Zinc on *B. prodig.*
(H. Crookes)

Fig. 8. Action of Zinc on *B. phosphoresens*
(H. Crookes)

To face p. 74]

foregoing experiments is almost infinitesimal, so that its germicidal effect is very striking. Much more impressive results are obtained by the addition of a properly prepared colloidal solution to an inoculated medium—the bacteria then being destroyed quite rapidly—but the reproduced photographs show in an unmistakably clear manner the great potentialities of colloidal metals even under conditions which are not particularly favourable to their use. It has been estimated that in the death zone, where the concentration of the colloidal metal is greatest, the latter does not exceed twenty-five parts per million parts of nutrient medium.

The germicidal action of certain metals in the colloidal state having been demonstrated, it only remained to apply them to the human subject, and this has been done in a large number of cases with astonishingly successful results. It is not suggested that colloidal metal sols should replace the customary disinfectants for sterilising excreta, vessels of various kinds and for other general purposes, but for internal administration, either orally or hypodermically, they have the advantage of being rapidly fatal to the parasites—both bacterial and otherwise—without any toxic action on the host.

CHAPTER IX

TYPICAL COLLOIDAL REMEDIES AND THEIR USES

TURNING now to the use of colloidal liquids in the relief or cure of disease, it is important to realise the simple character of the active agents in many such liquids. In the majority of the most successful remedies definitely used on account of their colloidal properties, the active agent is a metal, such as silver, mercury, or palladium, or a non-metal element, such as iodine or sulphur. More complex substances, such as quinine and cocaine, have also been used successfully in the colloidal state, but not nearly to the same extent as the elements just mentioned. The reason is quite simple; with only a limited number of investigators it is impossible to proceed as rapidly as may be desirable, and the remarkable results which have followed the use of elements in the colloidal state has naturally resulted in attention being concentrated on these elements.

A great advantage which colloidal sols of elements possess over compounds is the facility with which their action may be studied. If a salt or other compound is administered there is always the chance of it undergoing hydrolysis or ionisation in the blood stream or alimentary canal, thereby setting up complex reactions in which elements other than the one under investigation are involved. For example, iron may be administered in the form of a carbonate which is converted in the stomach into chloride, and this, on dilution, is hydrolysed so that eventually there are formed both hydroxide and chloride of iron. If the iron were administered as an element, these complications would be avoided, and the investigator would be much more certain in drawing conclusions. Except in the colloidal form, it is impossible to administer elements in an active state apart from other elements necessary to bring them into solution, for no method of grinding has been discovered which will reduce the elements to so fine a state that they will remain in suspension in water for months without any tendency to deposition. The coarser product obtained by the most elaborate process of trituration is devoid of those properties which give colloidal sols their therapeutic value.

The effect of the administration of certain elements in a colloidal state to persons suffering from certain pathological conditions is extremely interesting, partly on account of the progress of the recovery, and partly on account of the absence of complications such as occur when the same element is administered in another form. For example, iodine and mercury, as ordinarily used, are both unsatisfactory on account of their great toxic action. This is almost wholly avoided when these elements are administered in the form of colloidal sols. The remarkable fact that colloidal silver and iodine do not stain the skin, whereas the pharmaceutical preparations of silver and iodine do so strongly, is a further indication of the striking difference between colloidal sols and ordinary solutions.

Widely as colloidal metal sols differ from the same metals as usually known and from their salts, such sols have a remarkably close resemblance to enzymes in their action on physiological products. The activity of both is greatly increased in alkaline solution up to a maximum which is followed by a reduction in activity with further increase in alkalinity.

There is also a striking parallelism between the poisoning action of various substances (prussic acid, hydrogen sulphide, and mercuric chloride) on a metal sol and on an enzyme (p. 42).

Recent researches on the action of various glands have also shown that the fluids they excrete are not only colloidal in character, but that in several instances they contain, as an essential constituent, some element which is not usually considered as an integral part of the organism. Thus, the dependence of the thyroid fluid on its iodine content has only been established within the past four years. In a similar manner the minute quantities of sulphur, phosphorus, and iron which are present in the animal organism are not adventitious. They play definite parts, and their absence or diminution results in a serious disturbance of function. Insufficient iodine in the thyroid gland induces cretinism and analogous diseases, an insufficiency of phosphorus accounts for certain nervous disorders, too little iron in the blood results in anæmia, and deprivation of sulphur is characteristic of rheumatic subjects.

The intense power of reaction possessed by elementary sols is very striking. They can induce chemical reactions to occur which would otherwise require conditions of temperature and pressure quite unattainable in the human subject. Thus, metal sols have a catalytic action as powerful as platinum black, and can effect such changes as the union of hydrogen and oxygen in the cold, the oxidation of hydriodic acid by oxygen in solution, and the decomposition of hydrogen dioxide.

The activity of some metal sols is so great as to be barely conceivable. Thus, platinum sol has marked catalytic properties when only 0·0000002 grain of the metal is present! This intense power of promoting reactions among other substances and of being themselves left free at the end of the reaction results in very small quantities of metal sols being capable of effecting changes which are wholly disproportionate to the amount of sol present. It also explains why changes which are of an extremely complex character when a catalyst is absent may be effected readily in the presence of an elemental sol, and, further, that the administration of such a sol will produce results in a short time which would require a long period if effected by means of a long series of successive reactions. Metal sols have the further therapeutic advantage of acting most rapidly in faintly alkaline solutions, so that when properly prepared they are not affected adversely by normal blood.

Before a drug can exert its full therapeutic action it must be converted into the ionised or into the colloidal state. Unfortunately, an element in the ionised state is always associated with the corresponding ions of the salt from which it was produced. Thus, mercuric chloride, when ionised, is separated into mercury ions and chlorine ions, and the net electric charge of the system is neutralised. When an element such as mercury is administered in the colloidal state, however, it, and it alone, is introduced as an active agent, the charge on the particles is quite definite and their activity is correspondingly great. Consequently, there is much truth in the statement that a drug to be fully efficient must be in a colloidal state, or convertible into it in the body of the subject.

The conversion of a colloid into the form required by the organism is most rapid when the sol is injected intramuscularly, but there is less pain and equally good (though slower) results by intravenous injections, and in many cases by oral administration.

The use of specific sols in medicine is no universal "cure all," but just as the administration of pure chemicals, such as quinine hydrochloride, marked a great advance over the use of a crude tincture of cinchona bark, so the employment of certain elements in the form of sols marks a still further line of progress in the conquest of disease.

Taking the chief colloidal sols which have been used medicinally, we may first mention several metal sols:

Colloidal gold was first prepared in a sufficiently pure state for effective examination by Faraday in 1857, but it was known in the Middle Ages, though its most important properties were not realised. As early as 1885, it was largely in use in the United States as the basis of a cure for dipsomania, but even then it was only one of a number of ingredients of a complex mixture whose manufacturer does not appear to have known much about the properties of the gold in his

Fig. 9. Action of Gold on *B. phosph.*
(H. Crookes)

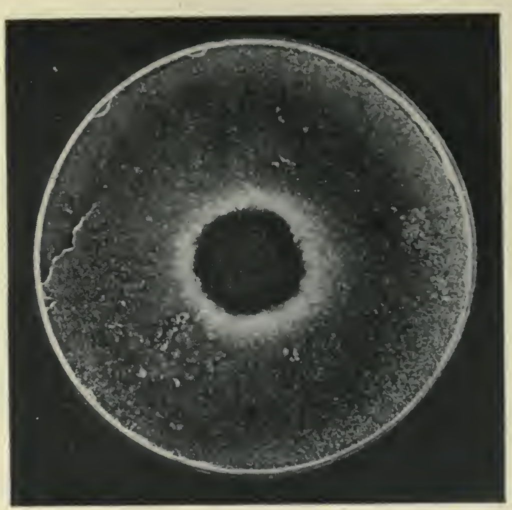

Fig. 10. Action of Silver on *B phosph.*
(H. Crookes)

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preparation, notwithstanding the statements in the advertisements of that day.

Colloidal gold is characterised by the great difference in its colour when it is prepared by different methods. As ordinarily prepared by reducing a slightly alkaline solution of gold chloride with formaldehyde or phosphorus, it is an intensely red liquid, the particles of which are negatively charged, but by the addition of suitable electrolytes (aluminium salts), it is also possible to produce a blue solution with positively charged particles. A colourless gold sol is produced if the electric field is too strongly negative or positive. Experiments by Garnet[1] on the refractive indices of colloidal sols of gold, silver, and copper show that the metal in each case is in suspension in the form of extremely minute spheres and that the different colours of gold sols are due to the particles of metal and not to any inherent differences in the nature of the dispersed particles.[2]

Colloidal gold sol is tasteless and non-poisonous, but the metal is readily precipitated by bases and salts, so that it is not easy to administer it satisfactorily. Moreover, the germicidal action of gold is very feeble (p. 73), so that its use in therapeutics is negligible. On the other hand, it is so easily prepared and is so highly sensitive that gold sol is chiefly used as a standard with which others may be compared.

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[1] *Phil. Trans.*, (A) 203, 1904, 385 ; and 205, 1906, 237.

[2] According to T. Sherrer (*Engineering*, 1919, 488), colloidal gold and silver hydrosols, when examined by X-rays, show interference bands characteristic of crystalline solutions ; the interference bands of the hydrosols of silica and stannic acid show that these substances are sometimes crystalline and sometimes amorphous. Colloidal albumen, casein, starch, and cellulose appear to be always amorphous.

Colloidal silver, containing 0·05 per cent of the metal in a colloidal form and not as a salt, is a clear cherry red liquid which possesses a marked oxidising action in addition to its power of coagulating colloids of opposite electric sign.

The colour of the pure silver sol is largely dependent on the manner of its preparation and the presence or absence of minute quantities of electrolytes. Even the glass of the vessel in which the sol is prepared may affect the colour by yielding traces of soda, silica, or other oxide to the sol. When prepared under suitable conditions and properly "protected," colloidal silver sol is quite stable even in the presence of salts and of the normal constituents of the blood. Its destructive action on toxins is very marked, so that it will protect rabbits from ten times the lethal dose of tetanic or diphtheric toxin. Colloidal silver is prepared in the following forms to meet clinical requirements:

(*a*) Aqueous solution, in bottles or ampoules.
(*b*) Pasta, in glyco-gelatin base.
(*c*) Ointment in lanoline base.
(*d*) Suppositories and pessaries.

Unlike certain organic compounds of silver, the colloidal metal is not organotropic and does not cause necrosis of the underlying tissues. Hence, it has been used for several months consecutively without staining the conjunctiva.[1]

Taken internally, the particles of colloidal silver are resistant to the action of dilute acids and alkalies of the stomach, and consequently continue their catalytic action and pass into the intestine unchanged. The

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[1] *Brit. Med. Journ.*, Jan. 15, 1915.

importance of this is obvious in such conditions as ulcerative urticaria and other forms of dermatitis suggestive of toxæmia,[1] bacillary dysentery, diarrhœa, and colitis.

The use of collosol argentum in ophthalmic practice[2] and in the affections of the ear and in nasal catarrh[3] and its clinical effect by intravenous injection in septicæmia are reported in the medical journals.[4]

Colloidal silver has been used with marked success in the following cases, cited by C. E. A. MacLeod[5]:

Septic and follicular tonsilitis, Vincent's angina, phlyctenular conjunctivitis, gonorrhœal conjunctivitis, spring catarrh, impetigo (contagious acne of face and body), septic ulcers of legs, ringworm of body, tinea versicolor, soft sores, suppurative appendicitis after operation (the wounds cleaned rapidly), pustular eczema of scalp and pubes, chronic eczema of meatus of ear with recurrent boils, and also chronic eczema of anterior nares, offensive discharge in case of chronic suppuration in otitis media, bromidrosis of feet, axillæ and blind boils of neck. By injection: gonorrhœa and chronic cystitis (local), boils, epiditymitis.

Sir James Cantlie[6] has found it particularly effective in cases of sprue, dysentery, and intestinal troubles. Being non-toxic, the dose can be increased from 1 to 2 or more drachms twice or thrice daily.

A. Legge Roe regards stable colloidal silver as a most useful preparation[7] in ophthalmic practice, and particularly in cases of gonorrhœal ophthalmia, puru-

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[1] *Brit. Med. J.*, May 12, 1917.

[2] *Brit. Med. J.*, Jan. 15, 1917.

[3] *Brit. Med. J.*, Dec. 15, 1917.

[4] *Lancet*, Feb. 16, 1918.

[5] *Lancet*, Feb. 3, 1912.

[6] *Brit. Med. J.*, Nov. 15, 1913.

[7] *Brit. Med. J.*, Jan. 16, 1915.

lent ophthalmia of infants, infected ulcers of the cornea and hypopyon ulcer (tapping of the interior chamber and cautery, and other operative procedures being now rarely required, whilst if perforation does occur it is smaller and more manageable), interstitial keratitis, blepharitis, dacryocystitis, and burns and other wounds of the cornea. According to this authority, the great chemosis which usually accompanies the use of silver nitrate is avoided and, in his opinion, if colloidal silver were adopted in every case of purulent ophthalmia of infants " there would be no such thing as impaired sight or blindness from this cause." He has had many cases of interstitial keratitis in adults, in which the complete opacity of the cornea has become absolutely clear in from three to five months, and anyone who has had much experience of this disease in adults knows how often permanent impairment of sight results, and how long the treatment used to last, especially if irritants had been used prior to colloidal treatment The eye is kept under atropine or preferably scopolamine, and the colloidal sol is dropped in three times a day, the eye being kept closed afterwards for five minutes. When all active symptoms have disappeared, and not until then if any opacity remains, yellow oxide or mercury ointment may be used; but, if treated throughout as described above, this will rarely be necessary. In dacyocystitis, Dr. Roe recommends that "after probing, the sac should first be syringed out with saline solution and, after expressing any that remains, the sac should be filled with colloidal silver with the syringe. In cases of long standing this will not be sufficient; the sac should be incised and plugged with ribbon gauze, and for about a week the sac should be dressed daily by inserting it into ribbon gauze soaked in 10 per cent solution of potassium bichromate, or the lining membrane of the sac should be scraped. The wound is then allowed to close and the collosol injections continued."

T. H. Anderson Wells[1] used it intravenously in a case of puerperal septicæmia without any irritation of the kidneys and with no pigmentation of the skin. This physician has found that a series of intravenous injections, each of collosol argentum, every forty-eight hours produce no untoward effects and that recovery is rapid.

Sir Malcolm Morris[2] has found that colloidal silver is free from the drawbacks of other preparations of silver, viz. the pain caused and the discoloration of the skin ; indeed, instead of producing irritation it has a distinctly soothing effect. It rapidly subdues inflammation and promotes the healing of the lesions. He has had remarkable results in enlarged prostate with irritation of the bladder, in pruritis ani and perineal eczema, and in hæmorrhoids. It can be used in the form of suppositories whilst a solution is simultaneously applied to the irritated skin. In bromidrosis in the axillæ and feet it quickly gives relief. It causes a rapid disappearance of warts. Being non-toxic, it can be given internally in urticaria and other forms of dermatitis which are suggestive of toxæmia. In such cases, it is quickly beneficial.

In ophthalmology, colloidal silver has now largely replaced silver nitrate.

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[1] *Lancet*, Feb. 16, 1918.

[2] *Brit. Med. J.*, May 12, 1917.

J. Mark Hovell[1] has found colloidal silver beneficial for permanently restoring the potency of the Eustachian tubes and for reducing nasopharyngeal catarrh.

Colloidal silver has also been used successfully in septic conditions of the mouth (including pyorrhœa alveolaris—Rigg's disease), throat (including tonsilitis and quinsies), ear (including Menier's symptoms and closure to Valsava's inflation), and in generalised septicæmia, leucorrhœa, cystitis, whooping-cough, and shingles.

A preparation of colloidal silver which is opaque to X-rays has proved invaluable in certain diagnoses.

J. MacMunn [2] has successfully used silver sol in cases of gonorrhœal prostatic gleet by injecting through an endoscope into the substance of the prostate gland.

Collosol argentum has also proved useful in influenza, both as a prophylactic and for curative purposes when applied as a spray to the nostrils, for bathing the eyes, and as a gargle for the throat.

B. Seymour Jones has used an intranasal spray of colloidal silver in a case of cerebro-spinal meningitis. He has also used colloidal silver with marked advantage in several cases of rhinitis and œdematous enlargement of the posterior ends of the middle and inferior turbinates without true hyperplasia.

Colloidal mercury is quite free from the serious objections to the less soluble mercury salts—such as calomel—the delayed and irregular absorption with consequent undesirable results of other preparations and, unlike the soluble mercury salts, it is only feebly toxic.

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[1] *Brit. Med. Journ.*, Dec. 15, 1917.

[2] *Brit. Med. Journ.*, 1917, I, 685.

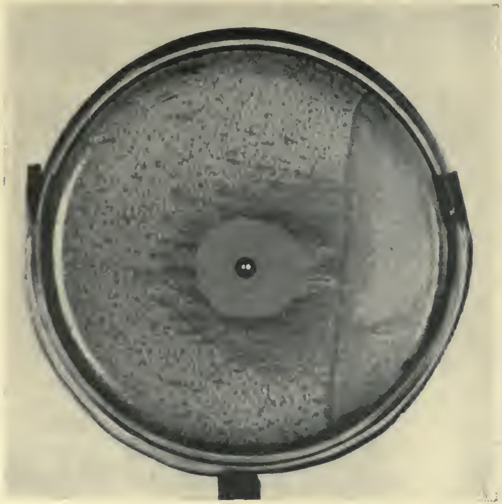

Fig. 11. Action of Mercury on *B. coli comm.*
(H. Crookes)

Fig. 12. Action of Cobalt on *B. phosph.*
(H. Crookes)

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With colloidal mercury, the diffusion is extremely rapid and chemical affinity low. Hence, the toxicity of colloidal mercury (1–2000) is so low that doses of two teaspoonfuls may be taken twice daily or intravenous injections of 30 cc. may be given with impunity.

Intravenous injections of colloidal mercury are painless, and this absence of pain is usual in the administration of colloidal preparations, and is due to their isomorphism with the colloidal lipoid and protein of the tissues and body fluids. Before the introduction of the arseno-benzene products, the routine treatment for syphilis was mercury and iodides, and undoubtedly many permanent and excellent results were obtained.

In late syphilis, iodine is more effective than mercury, and, conversely, mercury is more effective than iodine in early syphilis. According to J. E. R. McDonagh,[1] this is due to the fact that mercury acts as an oxidising agent and that the process of oxidation is more effective in the early stages of syphilis in producing the death of the causal organism, whilst as a reducing agent it is more effective in the later stages. In most cases, the alternate injection of colloidal iodine and mercury is more effective than if either be given continuously. According to J. E. R. McDonagh,[2] the first effect of injecting a suitable colloid is to break large protein particles into small ones and thus increase their activity by enlarging their surface area. In syphilis, there are many large particles to be broken up, hence the value of colloid sols. The injection of colloid sols also affects the state of oxidation or reduction of the system in which it is introduced, metallic sols increasing the oxidation and

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[1] *Prescriber*, June, 1919, 118–120. [2] *Brit. Med. J.*, 1917, I. 648,

non-metallic sols the reduction. Colloidal mercury has cured persistent relapsing malaria in a few days.[1]

Colloidal iron is the least irritating of all forms of iron, yet, according to Lyn Dimond,[2] it kills within six minutes such organisms as *B.typhosus*, *B. coli communis*, and various pyogenic cocci. The iron sol seems to have a definite elective bactericidal action upon such catarrh-causing organisms as the pneumococcus and various strains of the *Micrococcus catarrhalis*. Rapid relief follows the topical application of colloidal iron in cases of catarrh of the nose, larynx, or pharynx.

It is also used by subcutaneous, intramuscular and intravenous injection in cases of extreme chlorosis, anæmia, erysipelas, and cellulitis.

Iron is almost the only metal found in the animal organism which is also obtainable in a colloid state in the presence of water. The significance of the fact has not been sufficiently recognised. In the serum, the iron is probably present as a protein compound, the precise constitution of which has not been determined. Some authorities consider that the whole of the iron exists in the form of hæmoglobin. The total iron content of the normal body does not exceed thirty-seven grains, and although several organic compounds of iron have been recommended they are by no means satisfactory, being either too feeble in action or too readily decomposed *in corpore* and so rendered useless. Inorganic iron is held by many practitioners to be most efficient in the only true test of the value of an iron preparation, i.e. increase of hæmoglobin in the blood. Hæmoglobin

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[1] G. Cremonese, *Garr, D. Osp.*, 1918, 39, 427.

[2] *Lancet*, 1913, I, 1585.

was at one time thought to be a definite compound, but its adsorption properties seem to show that it is largely colloid in character and consequently is specially amenable to the action of another colloid such as iron. Hæmoglobin is electro-positive, and to increase its amount without disturbing the general characteristics of the serum any iron compound administered must be electro-positive when it enters the blood stream. For this reason, iron compounds (e.g. ferric chloride) which are electro-negative and act as coagulants should be avoided. The objection to iron carbonate and hydroxide lies in the fact that they are usually converted into ferric chloride or analogous compounds by the gastric juices.

Colloidal iron, on the contrary, not being affected by these juices, is able to enter the blood stream in a satisfactory and therapeutically active form. Hence the administration of iron in the form of a colloidal sol appears to be a simple means of increasing the amount of the protein compound in the serum, as this form of iron, when administered orally, is rapidly diffused in the stomach, and yet it is not absorbed in individual positions. It is found that the amino-acids formed during the process of digestion are readily able to absorb into their complex molecule a notable proportion of iron administered in the colloidal form, and from it to effect the synthesis of hæmoglobin.

Colloidal antimony has been used with remarkable and surprising results in the treatment of coccogenic skin disease, including deep abscesses, boils, and deep-seated impetigo. It has also been successfully used by intramuscular injection in bilharzia, leishmonnoris, granulama pupendi, ulcus molle serpiginosum, and in certain stubborn cases of gonococcal urethritis.

Colloidal antimony has been used in conjunction with manganese with extremely good results in gonococcic infections. In India, it has given very satisfactory results in Kala-azar, its administration in this disease being accompanied with less risk than that of arsenic.

Colloidal manganese has been used with remarkable and surprising results in the treatment of coccogenic skin disease, including deep abscesses, boils, and deep-seated impetigo. In superficial impetigo, chronic seborrhœic eczema, and acute folliculitis it is of little value when used alone, but it gives excellent results when employed in conjunction with intramine. The rapidity of its action,[1] combined with the saving of dressings, render the use of this form of manganese very attractive in deep-seated coccogenic lesions. It is usually injected intramuscularly in amounts of 3 cc. every few days. In most cases, one injection is sufficient. Indeed, colloidal manganese differs from all other remedies used in the treatment of boils, insomuch as it is only occasionally that fresh boils make their appearance during the treatment, and these quickly subside without further trouble.

E. W. Kirk[2] and Dr. W. Habgood[3] found colloidal manganese so good as to convince them that it should have a wider use in furunculosis and seborrhœic eczema following wound infection, and W. E. Levinson[4] has

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[1] J. E. R. McDonagh, *Medical Press and Circular*, Dec. 5, 1917; Sir Malcolm Morris, *Brit. Med. Journ.*, April 26, 1918.

[2] *Brit. Med. Journ.*, 1918, II, 377. [3] *Brit. Med. Journ.*, II, 76.

[4] *Brit. Med. Journ.*, 1918, II, 160.

Fig. 13. Action of Antimony on *B. coli comm.* and *B. prodig.*
(H. CROOKES)

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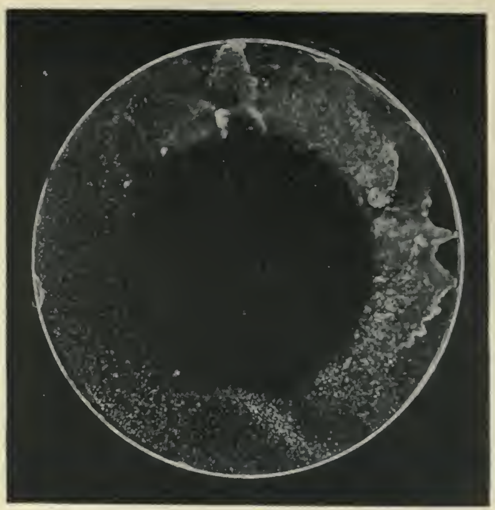

Fig. 14. Action of Antimony on *B. phosph.*
(H. CROOKES)

confirmed Sir Malcolm Morris's[1] recommendation of colloidal manganese for boils.

J. E. R. McDonagh[2] has also used intravenous injections of 33 cc. of colloidal manganese with excellent results in cases of poisoning by sulphur compounds, including mustard gas (dichlorethyl sulphide). Three typical cases reported by Sir Malcolm Morris are, in his opinion, so remarkable as to demand publication. At first the collosol manganese (Crookes) was used in the form of a single solution. Afterwards it was employed in the improved form of two solutions, which were mixed in the syringe; of this, much smaller doses (about one-half) suffice.

CASE I

"The patient, a medical man, came to me on November 24th, 1917, with large, deep-seated boils on the hairy part of the face, which he believed to be an infection from a carbuncle in a diabetic patient, from whom he had contracted a septic whitlow. Culture showed that the micro-organism was the *Staphylococcus pyogenes aureus*, and an autogenous vaccine was prepared, with which he was inoculated on November 30th. By this time a boil on the right cheek had enlarged to the size of a Tangerine orange; there was much œdema of the face and eyelids and great pain. On December 6th pus was discharged and the pain relieved; but during the next seven weeks boils continued to appear at intervals, usually in groups of four or five, on one or both sides of the face. By January 14th, eleven injections of vaccine had been given, antiseptic lotions

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[1] *Brit. Med. Journ.*, 1918, I, 446.

[2] J. E. R. McDonagh, *Medical World*, 1918, p. 137.

and ointments being also applied. On January 31st the patient consulted me again and I advised the injection of collosol manganese. The first injection was given the next day. ' Improvement,' to quote from the patient's own notes, ' began on the third day afterwards. Subsequent boils, which continued to appear for a further fourteen days, were not painful, and many of them aborted without pus formation.' In all, four injections were given—1·5 c.cm. on January 31st, 2·5 c.cm. on February 5th, 3 c.cm. on February 12th, and 1 c.cm. on February 28th ; the first and second in the gluteus, the third and fourth in the flank. In the first three the old preparation was used ; in the fourth the new. By March 5th I was able to report ' All clear.' From November 30th to January 31st, while the vaccine was being given, thirty-three carbuncular boils appeared ; after the collosol manganese was begun there were only seven, the last appearing on February 20th, three weeks after this treatment was begun. The patient's general health also greatly improved ; he began to feel better within a week of the first manganese injection."

CASE II

" The patient was an army captain who was subject to acne. When the first collosol manganese injection (0·5 c.cm. of the new preparation) was given on March 13th, he had been in hospital four months with facial boils and acute impetigo contagiosa of the same region. During that time he had had vaccine injections, and various antiseptics had been applied, without result.

Another manganese injection (0·5 c.cm.) was given on March 16th, and a third (1 c.cm.) on March 19th. By this time all the lesions had cleared up."

CASE III

"I saw the patient, a lady, for the first time on February 16th. She had extensive follicular impetigo of the scalp, which began in the preceding October, and had gradually become more severe. When she came to me, she complained of great pain from small multiple deep abscesses. There was a good deal of œdema, and the posterior cervical glands were enlarged. On February 18th 1·5 c.cm. of the old collosol manganese solution was injected. By February 22nd the lesions were beginning to clear up, the pain was nearly gone, and the general health distinctly better. A second injection (0·5 c.cm. of the new preparation) was given, and a third (1 c.cm.) three days later. By this time further improvement was manifest, and the patient was able to sleep. No further injection was required, and by March 19th recovery was complete, the only trace of the disease consisting in small bald areas on the site of the lesions."

Sir Malcolm Morris attaches much importance to the great improvement in the patient's general health observable in each case a few days after the first injection, and the fact that although the injections were all intramuscular they were followed by no reaction.

D. McFarland Livingstone has used colloidal manganese with great advantage in three cases of gonorrhœal ophthalmia. The first was not of great severity, but the drug was satisfactory. In the second case, corneal ulceration had set in, but the eye healed rapidly. The third case was of the most virulent type, and the effect of colloidal manganese was most striking. Prior to treatment, both eyelids were greatly swollen and almost solid; there was great tenderness and pain and the surrounding cheek was also red and swollen. On opening the lids, the cornea was found to be completely hidden by overlapping folds of œdematous bulbar conjunctiva. There was an abundant discharge of pus. The eye was bathed with warm boric lotion and argyrol was used every six hours. An injection of colloidal manganese was given intra-muscularly into the buttock. On the second day there was a slight improvement. On the third day there was slight pain; on the fourth day a second injection of 1 cc. of colloidal manganese was given, and by the following morning all pain had ceased, all the swelling of the bulbar conjunctiva had completely vanished, the œdema had lessened, and the discharge was considerably reduced. The cornea was perfectly clear, and the eye was apparently out of danger. After one week from the first injection, a third and last injection of manganese was given, and after a further week the eyes had become normal, except for gumming of the eyelids after sleep. Dr. Livingstone reports of this case that "in a fairly wide and long experience in the treatment of gonorrhœal blenorrhœa it had never been my good fortune to witness such a dramatic change. No local measures of which I am acquainted would have brought about such a satisfactory termination."

It is not suggested that undue importance should be attached to a single case, however striking, yet it is

Fig. 15. Action of Copper on *B. coli communis*
(H. Crookes)

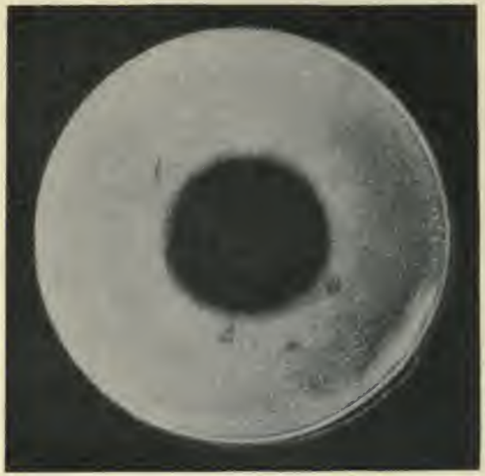

Fig. 16. Action of Thallium on *B. phosph.*
(H. Crookes)

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clear that such a good indication of what may be expected under similar conditions should not pass unnoticed.

Colloidal manganese has also been used successfully in the case of toothache due to abscess.[1]

Colloidal copper sols are blue, red, orange, or green, according to the conditions under which they are prepared, and the agent used to stabilise them. Thus, if protalbinic acid followed by hydrazine is used for reducing copper sulphate, the sol is red or orange, whilst with protalbinic acid and sodium chloride Paal obtained green copper sols. Copper has a special action on the liver and is well known as a fungicide and as restraining the growth of the lower organisms and embryonic cells. In the form which has given the best therapeutic results, colloidal copper sol is a dichroic liquid, blood red by transmitted light and muddy red by reflected light, which contains 0·1 per cent of copper as cuprous subhydroxide, protected by a combination of amino-acids, which *per se* have a very low physiological action. The solution is very stable, but should not be exposed unduly to the action of air or light, and for this reason the product is issued in hermetically sealed ampoules, each containing sufficient for one injection.

It appears to be of use in some cases of cancer, and the dissipation of a nodule in a patient who had previously been operated on for scirrhus of the right breast (cancer) is reported. Results are in many cases satisfactory, particularly in the initial stages of the growth and in preventing recurrence after operation.

[1] D. A. Wood, *Brit. Med. Journ.*, 1919, 330.

Where pain is present, great relief is obtained by the intravenous injection of colloidal iodine. If any streptococcus is present, injections of colloidal manganese should be given alternately with those of copper. In some cases where an improvement is manifested, but not maintained, injections of a reducing agent, such as pallamine (colloidal palladium) or intramine may be given alternately with copper or manganese. Injections of colloidal copper should always be given intramuscularly, preferably in gluteus medius. The dose is 3 cc. and the injection is preferably given on the first, fourth, seventh, and twelfth days and then once a week. Treatment should be continued until all symptoms have completely disappeared, after which one injection per month should be continued for about a year.

The use of colloidal copper injected intravenously can aggravate boils if administered in large doses; in smaller quantities and injected intramuscularly it has the opposite effect, but is far inferior to colloidal manganese for this purpose.

In malignant disease the intramuscular injection of copper has proved beneficial, the metal having been shown to be present in the growth within twenty-four hours of the injection. Merchel de Gers and others[1] have stated that colloidal copper exerts an inhibitive action on all cell-metabolism and it has been used extensively on the Continent in the treatment of cancer. In this connection, it is important to note that cases of cancer in which copper can be shown to be present in the growth are certainly the ones which are most amenable to treatment. The

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[1] *Med. Press*, 1912, II, 26; 1913, I, 87.

difficulty lies in causing the copper to penetrate to the periphery of the cancer.

Pessaries of colloidal copper in glyco-gelatin have proved serviceable for uterine fibroids.

Luton [1] refers to the value of the salts of copper in tuberculosis; its various forms yield more or less rapidly to the treatment when begun regularly. The existence of high fever is regarded as an obstacle to the treatment.

Colloidal platinum sol has been extensively used in promoting various chemical reactions. It appears to be too powerful for use in medicine, but has been employed to a limited extent for the same diseases as colloidal silver.

Dr. A. G. Auld has obtained encouraging results with colloidal platinum in case of pyrexia, e.g. subacute pleuritis and pneumonic conditions and protracted paratyphoid fever. He found that colloidal silver acted even more intensely than the year-old platinum colloid previously used, and as it is less drastic it is, in every way, preferable.

Colloid palladium oxide has been applied successfully in the treatment of obesity by injecting it hypodermically into the fatty areas.[2]

Colloidal palladium is a reddish liquid of a peculiarly active character

A. C. King-Turner [3] has used colloidal palladium (pallamine) with good results in epilepsy, the results of injecting each patient intramuscularly with 0·5 cc.

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[1] *Prov. Med.*, Dec., 1912.

[2] *Brit. Med. Journn.*, 1918, I, 195.

[3] M. Kauffmann, *Münch. Mediz. Wochenschr*, 525, 1913.

of " pallamine " at intervals of three days being most marked and encouraging. To cite three cases:[1]

" H. G., male, aged forty-five, suffering from epilepsy and of doubtful traumatic history, had an average of at least four fits weekly. These fits were of a very violent nature, the convulsion stage lasting on occasions for an hour, followed by stupor, confusion, and excitement. Since the three injections, only one fit has occurred in a fortnight, and that of a mild nature, lasting only thirty seconds. The patient feels greatly improved in general health, is less morose, more conversant, expressing himself more lucidly, and is very grateful for the treatment.

M. A. L., female, aged fifty-three, an epileptic of thirty years' standing, with an average of six fits per week of a very violent nature. Since injection, three weeks ago, no fit has occurred, but she has had a few sensations. She is now very placid, well behaved, and much better in every way.

M. A., female, aged sixteen, congenital epilepsy. She had seldom less than three or four fits per day. Since injection, three weeks ago, only four fits have occurred. She is much brighter, greatly improved in general health, and has now great hopes of being discharged from the institution, recovered. In two cases where manganese sol was injected after pallamine, a fit resulted, showing that careful selection of the appropriate metal is necessary."

Like colloidal platinum, pallamine is a very powerful catalyst, and such strongly combined organic substances as nitro-benzol, and numerous acids, aldehydes,

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[1] *Brit. Med. Journ.*, 1918, II, 255.

ketones, diketones, and nitriles are readily reduced by passing hydrogen through them, if a little colloidal palladium is present and the products are kept neutral by the addition of sodium carbonate.

Sols which are not normal constituents of the body, e.g. mercury, arsenic, are liable to be toxic, but mercury is less toxic than arsenic, as it has less affinity for nerve tissue, and the colloidal preparations are quite unlikely to be dangerous in the hands of medical men. It is, of course, important that they should be prescribed with due care as, otherwise, oxidation may occur where reduction is desired, or vice versa, but the risk of serious results to the patients is far less than when certain crystalloid remedies or tinctures, etc., are used.

Colloidal nickel has been used in meningitis.

Of the non-metal elements, the most widely used are iodine and sulphur.

Colloidal iodine may be obtained in four forms: (i) aqueous, and (ii) oil, (iii) ointment, and (iv) suppositories with glyco-gelatin base. The aqueous colloid (1 in 500) contains the element in its most active form, and is suitable for administration in all cases in which iodine or an iodide is indicated. Its action is more gradual, but more certain, than that of iodides, and there is complete avoidance of "iodism" and nausea.

The whole of the colloidal iodine is absorbed, whereas 85 per cent or more of the ordinary iodides administered are excreted within twenty-four hours.

When injected intravenously, the action of colloidal iodine is more rapid, and as much as 300 c.cs. has been injected with impunity in cases of pyæmia, and also to produce softening of fibrous tissue, thus showing its absolute non-toxicity. In itself, colloidal iodine is only slightly parasitotropic and bacteriotropic, but micro-organisms are very greatly influenced by its action, and it greatly increases the effect of a subsequently administered remedy.

Colloidal iodine is also indicated in syphilis by prior injection, and also by internal administration, and in cancer by intravenous injection.

In rheumatism, a piece of flannel soaked in colloidal iodine attached to the positive pole of a battery and applied as near as possible to the affected area has been successful. It has also been used beneficially as a spray in bronchial and nasal catarrh and internally in recovery from alcoholism.

Colloidal iodine oil (3 per cent) is very useful for eczema and other forms of affections and abnormal conditions of the skin. On application, the iodine particles penetrate the pores of the skin without staining the epidermis, the latter being kept supple and soft by the hydrocarbon oil in which the colloidal iodine is exhibited and stabilised. Thus, the staining and hardening effects of alcoholic solutions of iodine, such as tincture of iodine, are avoided.

In some cases of bad chilblains[1] colloidal iodine oil rubbed in four or five times a day caused every trace of the condition to disappear in four days. Equally valuable is this colloid in severe cases of trench feet with ulceration, and in many cases of Charcot's bedsores which are so troublesome a complication of spinal injuries in military hospitals. In the earlier inflammatory stages of lupus erythematosus,

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[1] *Brit. Med. J.*, May 12, 1917.

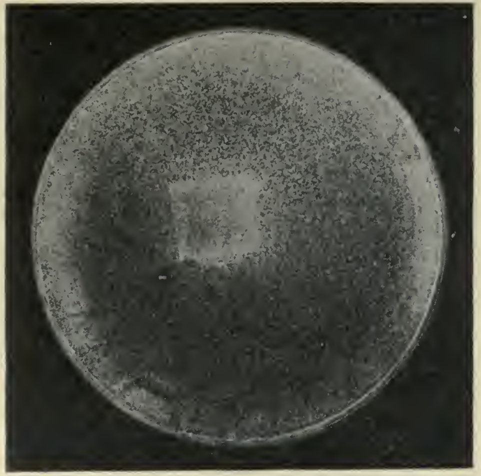

Fig. 17. Action of Palladium on *B. phosph.*
(H. Crookes)

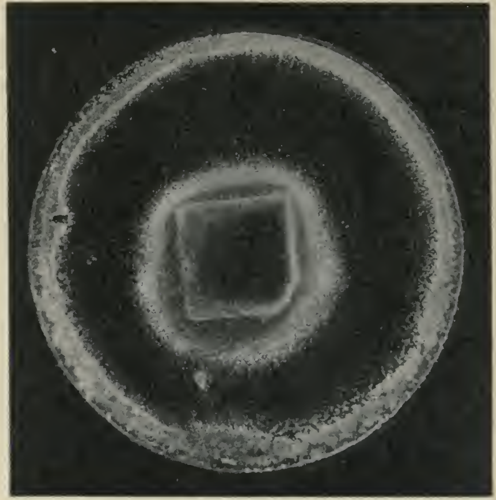

Fig. 18. Action of Sulphur on *B. phosph.*
(H. Crookes)

To face p. 100]

before atrophy has supervened, it is far more suitable than the ordinary form of the drug because of the absence of irritation. Similarly, it is preferred for internal administration in the later stages of syphilis, because there need be no fear of iodism. Parasitic affections show a striking amenability to this remedy. In a case of dhobie's itch, in which the disease had spread from the groin and invaded the trunk, legs, and arms, under the quite painless application of colloidal iodine oil the extensive lesions all cleared up in three weeks ; with ordinary remedies, the case would undoubtedly have been more protracted, and the treatment would inevitably have put the patient to a good deal of pain.

Colloidal sulphur (1 per cent) has proved invaluable in cases where there is a deficiency of this element in the system. The value of sulphur has long been known, but the forms in which it is usually administered are crude. It has been necessary to employ excessively large doses of an insoluble form of sulphur or to administer "Harrogate water," or some equivalent and unpleasant preparation of hydrogen sulphide. There is little doubt that an insufficient amount of available sulphur in the system impairs the action of the liver, with consequent production of intestinal poisoning (constipation, headaches, arthritis, etc). Externally, in the form of ordinary sulphur ointment, the element is in far too coarse a state to penetrate the epidermis efficiently, whereas in the colloidal form it does so readily. Colloidal sulphur ointment (5 per cent) is a brown paste ; when this is rubbed on the skin its colour rapidly disappears owing to the penetration of the sulphur into the skin, the colourless disperse medium remaining behind. This marked distinction between the behaviour of colloidal and ordinary sulphur is obvious to every one who has compared them.

Colloidal sulphur is extremely active, readily combines with protein, and is entirely absorbed in the stomach. The products of this combination are rapidly taken into circulation, and those parts of the organism for which sulphur is necessary are thus supplied. Ordinary sulphur is not absorbed in the stomach at all, and passes practically unchanged into the intestines.

A very interesting property of colloidal sulphur sol is its power—when taken internally—of completely deodorising the fæces, and thus acting in precisely the reverse manner to ordinary sulphur. The importance of this in phthisis, malignant disease, etc., is obvious.

In many cases of rheumatism and neuritis, and even in " arthritis deformans," relief has been rapidly obtained by its internal administration. In acute rheumatism, the intravenous injection of colloidal sulphur has proved beneficial.

Colloidal sulphur baths have been of service in rheumatic conditions and skin affections. The colloidal sulphur content in the bath is far greater than that of natural sulphur water, and as the bath contains no impurities or free sulphuretted hydrogen, it is free from the many objections associated with the use of natural sulphur waters.

Sir Malcolm Morris[1] has found that among the

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[1] *Ibid.*

affections in which colloidal sulphur is beneficial are various forms of acne (including acne rosacea and seborrhœa), generalised dermatitis, acute psoriasis, and painful fibrositis, whether of connective tissue, of muscle, or of joints. Baths medicated with this colloid are, in his experience, at once soothing and quickly curative.

Colloidal sulphur increases tolerance to mercury in syphilis and enhances its efficacy. It has also been recommended for use by subcutaneous injection in cancer.

Sulphur can be administered as a simple sulphur sol or as a complex colloid, di-ortho-amino-thio-benzene (intramine) as prepared by J. E. R. McDonagh. These differ somewhat in their action, but for the cases previously mentioned either form may be used.

Colloidal arsenic (0·2 per cent) in doses of 2 cc. has an extraordinary effect in pernicious anæmia and herpes deformans.

In influenza, Capitan[1] obtained cures in 50 per cent of otherwise hopeless cases with doses 6–9 cc. of colloidal arsenic and the same volume of colloidal silver. The colloidal arsenic contains about 4 mgm. per cc. of arsenic, and the colloidal silver 2 mgm. per cc. of silver, the solutions being given intramuscularly or intravenously. The number of injections varied according to the effects produced, from 3 or 4 to 6 or 7 in prolonged cases. In very severe cases, 6 cc. of colloidal arsenic and 3 cc. of silver were injected intravenously at once, and twelve hours later the same dose was given intramuscularly. The dose was repeated next day if

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[1] *Bull. Acad. de méd.*, Par., 1918, 3e Ser., **80**, 388–93.

the patient's state remained grave. If there was obvious improvement, a single intramuscular injection of 9 cc. of arsenic and 6 cc. of silver was given. Patients who recovered after one or two injections showed a complete change in their general condition; the prostration, coma, and delirium disappeared, the temperature fell rapidly to normal, and the pneumonia resolved without delay. Apart from a little headache and nausea, no bad effects were produced. Intramuscular injection of stannic oxide in colloidal suspension is advocated by Netter,[1] who has used them in 139 cases, 92 of whom were children and 47 adults. The injections were given for several days in succession and appeared to shorten the duration of the disease, diminish its gravity, and reduce the mortality. The mechanism of the action of stannic oxide is not clear, as the bactericidal power of tin is much less than that of silver, although Netter has found colloidal silver much less effective than stannic oxide in such cases. Witte [2] recommends the rectal injection of a 2 per cent solution of collargol[3] from two to four times daily as long as the fever lasts, the patient being given 10 cc. in each injection. The treatment should be begun as early as possible, especially in the age-period in which the mortality is highest, namely, from twenty to forty.

The simultaneous presence of a lipoid or colloidal protein appears to be essential to the proper reaction of arsenic. Thus, salvarsan *per se* has little action on *Spirochæta pallida*, which can move readily for some

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[1] Netter, A., *Bull. Acad. de méd.*, Par., 1918, 3e Ser, **80**, 427–36.

[2] Witte, F., *Deutsche med. Wochenschr.*, Berl. u. Leipz., 1918, **44**, 1250–1.

[3] Collargol is a silver sol.

hours in a solution of salvarsan. Yet the introduction of a little serum or digested protein will cause their immediate death. Organic arsenic compounds cause rapid sterilisation of the blood stream and disappearance of spirochætes, but, owing to rapid elimination, the arsenic is unable to reach every spirochæte or its spore, and it is for this reason that the intramuscular or subcutaneous route is sometimes chosen as giving slower absorption and consequently slower elimination and more prolonged action (Harrison). The disadvantage of this method is the pain usually caused. Colloidal arsenic is not so easily eliminated and may therefore be administered by the longer route. Its low toxicity, combined with the small dosage required, reduces the risk of its retention to a minimum.

Colloidal oxides do not prove to be so satisfactory as the corresponding metals, though *Colloidal alumina* (gel) (Eng. Pat. 104, 609) has shown excellent astringent effects in various kinds of diarrhœa and is less toxic than the bismuth compounds usually administered in such cases.

Various *alkaloids* have been prepared in the colloidal state and have been used in medicine. The colloidal state is the ideal condition for the administration of alkaloids ; in it they are isotonic with the colloidal protein of the body fluids, and until this condition has been reached the full physiological action of the drug is not complete. The two most important of these alkaloids are quinine and cocaine. In the usual quinine solutions, time is wasted converting the alkaloid to this state and there is frequently considerable upset of the conditions regulating the blood and tissue cells. Thus, when an acid quinine solution is injected intravenously, precipitation at first occurs, and the quinine is rapidly taken up again by the serum as a colloidal sol, but, in this process, the normal condition of the serum is destroyed. When colloidal quinine, which is faintly alkaline, is injected, no precipitation can occur, and consequently there is no upset of the normal condition of the blood.

Colloidal quinine sol appears to be free from the chief drawbacks of quinine salts. As the latter, as well as the colloid, are readily decomposed *in corpore*, much more research is required before much can be said as to the real action of quinine. Curiously, colloidal quinine has no action on the parasite of malaria.[1]

Colloidal cocaine is peculiarly difficult to prepare and little is therefore known of its value as a local anæsthetic.

Colloidal combinations. The colloidal elements have usually been employed singly. This is important as the improper combination of colloidal sols may result either in an inert substance or in the production of conditions precisely the opposite of what is intended. For instance, A. C. King-Turner[2] has found that whilst the administration of colloidal palladium is helpful in epilepsy, yet subsequent administration of colloidal manganese induced further fits. On the other hand, suitable mixtures of colloidal elements have great possibilities, which are, as yet, only dimly realised. For instance, a mixture of colloidal manganese and iron can be prepared in an entirely stable form, and

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[1] Stroud, *Lancet*, 1917, II, 911.

[2] *See* pp. 97, 98.

whilst the therapeutic properties of such a mixture have not been thoroughly ascertained, it appears that it not only possesses the remarkable properties of colloidal manganese and iron, when administered separately, but also has an additional effect, the nature of which requires further investigation.

Complex colloids, such as gelatin, gum-acacia or the protein colloids, are injected intravenously in cases where it is desired to prevent undue loss of the saline constituents of the serum. Such colloids adsorb these crystalloids, retaining them in the blood-vessels, raising the osmotic pressure, expelling the toxins and generally reducing the effects of shock. After severe hæmorrhage, both the colloidal and the crystalloidal constituents are deficient, and an injection of a complex colloid mixed with a hypertonic saline solution is the most efficacious restorative. If the saline is administered alone, much of it is rapidly excreted and lost. The simultaneous introduction of a suitable colloid ensures the adsorption of the saline matter and ensures its efficacy. Under normal conditions, there appears to be a considerable proportion of a crystal-colloidal complex in the body-fluids and for the retention of health a sensitive or labile equilibrium between the crystalloid and colloidal contents must, therefore, be maintained.

CHAPTER X

CONCLUSION

The form in which colloidal sols are employed has, naturally, a considerable influence on their effect. Several German preparations, placed on the market by British merchants, have given disappointing results because those physicians who employed them were insufficiently well acquainted with the nature of colloidal sols. Thus, for the purposes of ordinary chemical experiments, sols which have been evaporated to dryness and redissolved in water immediately before use are often convenient, but for the much more severe conditions of medical use such dried sols have proved unsatisfactory.

Again, it is comparatively easy to prepare sols which will meet the ordinary requirements of the chemical lecturer, but such crude preparations are usually too unstable for medical purposes, or their stabilising agent or other constituents bring about undesirable complications in the patient. It is, therefore, of the greatest importance that the colloids used by physicians should be prepared with special skill and care. Many samples which have been examined show great variations according to the sources from which they have been obtained, but it is satisfactory to be able to state that the preparations to which special reference has been made in this volume have invariably proved satisfactory when tested.

There is, in some quarters, an idea that colloidal sols are too unstable to be of real value in pharmacy. This is undoubtedly true of the crude preparations made by those who have not the necessary knowledge and skill, but it is emphatically false when applied to the preparations to which reference has already been made.

There is also a disposition on the part of a small number of recent writers to confuse ideas of the difference between colloidal elements and complex organic compounds which may be used either in a colloidal state or in the form of a true solution. This is an unfortunate attitude, as there is no necessary incompatibility between the two classes of remedies. The excellent work of Ehrlich and his associates has had most remarkable results. It has clearly shown a line of attack which is likely to prove of still further value in the conquest of syphilis and allied diseases. On the other hand, it cannot be denied that the use of arsenic in a highly poisonous form in association with an organic complex which is intended to neutralise its toxic action is fraught with risks which, at present, appear to be much greater than the use of colloidal elements of very low toxicity.

One unfortunate result of the use of improperly made colloidal sols has been the publication of a few statements in which the use of colloidal sols as remedies is condemned in general terms. If the origin of these statements is traced, it will be found that they have been made by those who have insufficient knowledge of colloids and have not made the necessary tests before jumping to conclusions, or they relate to colloidal sols of low activity, or to those which are not isotonic with serum and other body-fluids.

Obviously, any conclusions based on such imperfect data should be regarded with grave suspicion ; they are certainly inapplicable to the colloids, mentioned in the foregoing pages, which have been used with such highly satisfactory results.

No one with sufficient knowledge of colloidal substances would claim that all drugs should be administered solely in this form. There are, in fact, many crystalline compounds which are invaluable for special purposes. Thus, there is, in health, a definite equilibrium between the saline (or crystalloid) and the colloidal content of the body-fluids which must be restored when it has been disturbed as the result of wounds or some bacterial or other disease-producing agency. Under normal conditions, the cells and serum are colloidal sols which retain 0·7 to 0·9 per cent of crystalloid or saline matter.[1] When the saline content is reduced below the lower of the limits just mentioned, the administration of a hypertonic crystalloid solution is usually indicated. If, on the contrary, an excessive amount of colloidal sol is present, the appropriate remedy may consist either (i) in raising the concentration of the crystalloids by the administration of a saline, or (ii) in precipitating the foreign colloid by means of another colloidal sol of the opposite electric sign. The use of salines is well known, but the discovery of artificially prepared colloids which are stable

[1] B. Moore, *Nature*, 1919, 131.

when in the human organism is, however, so recent and the results obtained from their administration are so remarkable that it seems desirable in the interests of all that their general characteristics should be set out briefly and clearly in order that still further progress may be made in the utilisation of colloids both in health and disease.

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