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PRINCIPLES OF COLLOID THERA-
PEUTICS.*

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BEFORE considering the therapeutic application of colloids, it is advisable to make a few introductory and explanatory remarks.

It is true that the colloidal state of matter is still wrapped in considerable obscurity, and many fundamental questions await an answer. Yet it is certain that a broad and new field of scientific inquiry has been opened up and cultivated with an astonishing degree of success. Its achievement is great and its promise still greater.

If anyone were to ask—Is it possible to give a rigid scientific definition of a colloid, the answer must be in the negative.

It is now universally agreed that colloids do *not* represent a separate world of matter, as supposed by Graham when

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he first voiced his views, 60 years ago. The concept *colloid* was born of experiments on diffusion.

How, then, are we to regard them ?

The key to the answer lies in the limits of divisibility, or degree of dispersion, which can be effected in bodies, solid, liquid, or gaseous.

It is well recognised that there are innumerable and gradual transition stages, from coarse masses of material, *e.g.*, minerals and crystals, on the one hand, to powders of any degree of fineness ; to suspensions or emulsions of minute particles of solids or liquids, until we arrive at true molecular solutions, *e.g.*, salt in water, on the other hand : a true solution is nothing but a molecularly dispersed state of matter.

The diameter of a molecule is of the order, 0.1 to 1.0 $\mu\mu$.

The thickness of gold leaf is about 0.1 μ . The pores of the best porcelain filters are about 0.2 to 0.4 μ . in diameter.

Let us look at the subjoined table.

Dispersed Systems showing increase in degree of dispersion.

Dispersed Systems.		
Coarse Dispersions (Precipitates).	COLLOIDS	Molecular Dispersoids. (True Solutions).
V	V	V
Particles larger than 0.1 μ . do not pass through paper filters. Do not dialyse. Microscopically analy- sable.	0.1 μ . to 1.0 $\mu\mu$. Pass through paper filters. Cannot be analysed microscopi- cally. Do <i>not</i> readily diffuse or dialyse.	Smaller than 1.0 $\mu\mu$. pass through filter paper. Cannot be analysed microscopi- cally. Diffuse and dialyse.

The colloid state is a universally possible state of matter.

One and the same substance may appear in all possible degrees of dispersion, *e.g.*, sulphur.

From this table we gather that colloids are dispersed systems in which the diameter of the dispersed particles lies between $\frac{1}{1,000}$ m.m. and $\frac{1}{1,000,000}$ m.m. The term colloids connotes simply a degree of dispersion, or divisibility, within certain specified limits, conventionally accepted.

In other words, colloids represent a realm of matter differentiated for practical purposes from a continuous series of systems. We draw the line between colloid and molecular dispersion at $\frac{1}{1,000,000}$ of a m.m. In Ostwald's picturesque phrase, colloids are "the world of neglected dimensions."

By way of illustration let me adduce some familiar examples of dispersion in solids, liquids, and gases, *inter se*. Thus if gas (air) is diffused through liquid, we get *foam* (soap-suds); if, a liquid through gas, we have *fog*, *mist*, and *clouds*. A liquid dispersed through another liquid with which it is un-mixible yields an emulsion, *e.g.*, *milk*, the latex of plants, or *mayonnaise* sauce. A solid dispersed through gas is seen in tobacco smoke and in cosmic dust. A solid in liquid, *India ink*, and the various collosols now on the market. A solid—gold, dispersed through another continuous solid—glass, is illustrated in *ruby glass*. Faraday's marvellous and prophetic insight recognised this latter fact in 1857, four years previous to the classical researches on colloids by Graham in 1861. Alloys belong to the system solid + solid.

The terms colloid "emulsoids" (*e.g.* margarin) and "suspensoids" represent, respectively, the cases of finely dispersed liquid and solid particles. Liquid colloids are known as "sols;" their coagulation products, as "gels."

Protoplasm may be said to be a hydrated emulsoid. Living matter is constantly oscillating between the extremes of a solid "gel" and a liquid "sol," for our bodies are built up chiefly of colloids, and all life processes take place in a colloid system. Some important dyes are colloids, *e.g.*, congo red and night blue. Colloid dispersion is intimately related to our daily life in other respects. If there were no dispersoid particles in the atmosphere, *e.g.*, if the air were optically empty, human life would be impossible on our globe.

The red hot sun would scorch and glare upon us from the pitiless sky. It would stand in the heavens as a flaming disc upon a dark background. Wherever the sunlight did not strike directly there would be deep shadow; there would exist everywhere a garish contrast between the lighted and the un-lighted, and we would have no diffused and tempered daylight of the kind we now enjoy. (Wo. Ostwald).

In photographic processes the colloidal "sols" of silver

bromide are often wrongly termed "emulsions." This is a misnomer for, strictly speaking, they are "suspensoids," in which gelatin acts as a protective colloid. Similarly, what are commonly known as emulsions of bacteria are really suspensions, varying in dispersity, according to the kind of bacteria.

In connection with photography it is worth while to mention that a key seems now to have been found to an old-standing and fascinating puzzle, viz., the chemical nature of the substances comprising the *latent picture*. The chemical guess that this is due to certain hypothetical sub-salts of Ag has never been experimentally demonstrated and may be cast aside.

The truth about the latent image is this. It represents *adsorption* complexes of colloid silver in different degrees of dispersion, with normal non-reduced silver haloids. This view is beautifully demonstrated by the experiments of W. Reinders who has succeeded in producing these photo-haloids synthetically in the form of differently coloured crystals by allowing different silver haloids to crystallise in the presence of differently coloured colloid silvers. The truth is, that the photo-haloids of silver represent adsorption complexes of colloid silver in different degrees of dispersion with normal non-reduced silver haloids. (Wo. Ostwald).

Now minute sub-division of particles necessarily involves an immense increase in surface area, and this is a point of essential significance in the interpretation of many chemical and physiological phenomena. The enormity of the adsorbing surfaces in such dispersed systems is not generally appreciated.

Take, for example, the case of grains of shot. A sphere, with radius of 1 c.m. will have a surface of 12.6 sq. cm. If sub-divided into spheres of 1 m.m. radius, the surface will be 126 sq. cm. If into spheres of 1 m. radius, the surface will be 12.6 sq. m. In a true molecular solution, the same mass sub-divided into spheres of 0.1 $\mu\mu$. would have the enormous surface of 126,000 sq. m.

Or, take another example.

A cube, the side of which is 1 cm. has a surface area of 6 sq. cm. If distributed into cubes, sides = 0.01 mm. (the average size of a red disc) the surface would be 6,000 sq. m.

If the length of the side were reduced to 1 μ . (*i.e.* the size of a small coccus) the area would be 6 sq. m. Adsorption, *i.e.*, surface condensation, is chiefly dependent upon the size of the adsorbing surface is an important factor.

Let me illustrate to you experimentally the divisibility of matter, and also how colour depends upon the degree of subdivision. It is easy to show that gold and silver are pan-chromatic.

Gold. The two most convenient and simple reagents are those recommended by Wo. Ostwald, viz., Tannin, and Hydrazin. To a very dilute solution of *neutralised* auric chloride, add a few drops of a very dilute solution (about 0.1 per cent.) of tannin. Warm, shaking constantly.

According to the relative proportions, it is easy to get either red or violet gold. Ordinary tap water may be used. If a very dilute solution of a salt of hydrazin is added to a dilute *neutral* solution of gold chloride, a fine blue colour is obtained. *Purple of Cassius*, obtained by reduction of gold with stannous chloride is one of the oldest and most delicate tests for gold. So also is the colour imparted to a bead of borax, gently heated on a platinum loop with a very delicate solution of *au cez*.

Silver. Can be obtained as a bronze-like film by reduction with ferrous citrate (Carey Lea).

With other reducing agents it can be obtained as yellow or blue solutions. A few drops of dilute HCl added to any of these solutions will throw down the metal in a pure metallic state.

Therapeutics of the Colloidal State.

Colloid physico-chemistry is rapidly extending the sphere of its sway. For many years after its recognition it only languidly appealed to the curious scrutiny of physicists and chemists.

By degrees, and with increasing speed it has extended its tentacles in many directions and has gripped hold of innumerable problems in the arts and industries, in general biology, and in hygiene, to none of which can I now refer.

Among the more recent of its expansions is its application to therapeutics.

Colloids have long been used more or less unwittingly in medicine, *e.g.* resinous tinctures diluted with water.

Let us now inquire what foundation there is for the recent enthusiasm as to the reported therapeutic value of the new preparations.

In order to avoid prolixity a few examples must suffice.

Germicide Action.

Not all elements in the colloidal state have a germicidal action. Gold and platinum are inefficacious, whereas Ag, Hg, Sb, and As are active.

Observations recorded in Searle's book on "Colloids in Health and Disease" (1920. Constable and Co.) seem to establish the activity of collosols as germicides and disinfectants, and their great potentiality. It is not suggested that colloidal metal sols should replace the customary disinfectants for sterilising excreta, and so forth.

Local and Internal Use.

Bacteria possess a colloidal character, and, for local as internal administration, orally or hypodermically, collosols have the advantage of being rapidly fatal to the parasite without toxic action on the host.

The intense power of reaction displayed 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. This enhanced reactivity is largely due to the enormous increase of surface area conditioned by the extremely minute size of the colloid particles. This large increase of surface greatly favours *adsorption*, *i.e.*, surface condensation, which plays an important part in many chemical and biological phenomena.

In ophthalmic practice colloidal silver gives good promise. Dr. A. L. Roe (*British Medical Journal*, 16-1-15), is so optimistic that, 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." Can any of my hearers confirm this? Colloidal silver is not organotropic and has been used for several months con-

secutively without staining the conjunctiva. (*Culture plates exhibited*). Colloidal silver has been successfully used in pyelography with *x*-rays by Dr. Frank Kidd (*Brit. Med. Journ.*, 13th May, 1922).

In another class of cases, colloidal manganese has been used with remarkable and surprising results in coccogenic skin diseases, *e.g.*, boils, deep-seated impetigo and acne. The three cases of such kind reported by Sir Malcolm Morris (*British Medical Journal*, 1918. I. 446) are so remarkable that they demand close attention. It was extraordinary how quickly the lesions cleared up and the general health improved.

My own limited experience of the utility of colloidal manganese inclines me to support this contention.

I may here refer to a striking case under my care. A lady aged 26, was referred to me by Dr. Rainsford. She was afflicted with severe acne of the face for 15 years, and was hopeless of ever being cured. The face, forehead, cheeks, and especially the chin, was thickly studded with hideous pustules, deep-seated red nodules, and large indolent lumps. The skin of the chin, even where fairly level, was thoroughly unhealthy, in a boggy condition, and easily broke down on pressure. There were very few comedones.

So distressed was she by the disfigurement that she dreaded to meet people, and it so preyed on her mind that, for a time, she was placed in an asylum on account of melancholia. When she left the asylum, restored in mind, she passed under my care in January of this year.

The local treatment was very painful, but I am convinced from long experience, that it is the best method of dealing with such obdurate cases. There is little or no use in mere surface treatment with lotions or ointments, for the disease is too deeply situated.

It is absolutely essential to get to the bottom of the nodules and pimples. This is effected by a tiny curette, or, better, by a blunt pointed bit of hard wood, which must be forcibly pushed into the base of each pimple.

The point is dipped into a mixture of tinct. iodi. and glyc. ac. carbol, say, two or three parts to one, and the drilling out of each pimple is done two or three times if necessary. The free bleeding is easily staunched, and then each little hole or

cavity is stuffed with "Bipp" ointment. I can vouch for the success of this energetic line of treatment.

Taking into account the long duration and intractable recurrences of the disease in this case I thought it a suitable one to supplement the local treatment by the internal use of colloidal manganese. The drug was given by intra-muscular injection into the upper arm; an ampoule each time. Each ampoule contains 1 c.c. of colloidal manganese (2.5-1,000). In all she got some 10-12 injections. This plan succeeds in cases which had been previously treated by others unsuccessfully with vaccines. Doubtless, much of our practical therapeutics is based more upon our personal impressions than upon strict proof. Still, I cannot avoid believing that the cure in this case was materially aided by the manganese, and the tendency to recurrence checked. The girl is now practically quite well, and has regained her natural good looks and spirits.

Colloidal Copper.

Messrs. Oppenheimer put this on the market in the form of a dark red, dichroic liquid, which contains 0.1 per cent. of copper in the cuprous state, protected by a combination of amino-acids, which, *per se*, have a very low physiological action. Its trade name is "Oscol" cuprum.

It has been recommended and used in some cases of cancer, but the evidence on this point is not yet convincing. Dr. Bewley lately reported a remarkable case of an abdominal tumour in a lady, involving the wall of the abdomen. The diagnosis lay between malignant disease and some kind of inflammatory effect, and, clinically, the balance of opinion inclined to malignancy. She was terribly emaciated, and her life was in dire danger. Colloidal copper was given, and, after the first dose, improvement was manifest. Ultimately, the tumour disappeared, and she was restored to perfect health. Radium was also employed in this case.

One case does not count for much, yet the result which was as satisfactory as unexpected, is also suggestive.

Everyone will admit that most of the heavy elements have powerful pharmacological effects, and can be safely given only in small doses, which are usually soon excreted, or, otherwise disposed of and put out of action.

Further, the action of each metal is, more or less specific in itself, and is addressed to particular organs or tissues of the body.

In the case of mercury it is realised that minute quantities administered frequently have an effect which is entirely different from that of the same substance administered in a single large dose. (Searle).

Colloid Sulphur.

This preparation, the last to which I shall refer, has, I think, a future before it, and is worthy of attention.

It is put up in different forms: as a milky, acid, watery fluid; as a dark green oil, and, as a brown ointment. If the dark oil is rubbed on the skin its colour disappears when spread in a sufficiently thin layer.

Colloidal sulphur is extremely active, readily combines with protein, and is entirely absorbed in the stomach. Ordinary sulphur is not absorbed in the stomach at all and passes practically unchanged into the intestine (Searle)

A curious property of colloidal sulphur is its alleged power—when taken internally—of completely deodorising the fæces, and thus acting in precisely the reverse manner to ordinary sulphur. (Searle).

When we recall the extensive use of ordinary sulphur in the treatment of ringworm and other parasitic diseases of the skin, it is odd that H. Crookes found that colloid sulphur exhibited no germicidal action on exposed plates of nutrient gelatin, and even stimulated growth. Accordingly, I asked my friend, Dr. E. C. Smith to test this statement, and I show you his culture plates. It is evident that the colloid sulphur checks microbic growth, as might naturally have been expected.

Colloidal fluids retain their characteristic properties only so long as their active ingredient is in a properly dispersed and suitable colloid state.

Some of the reported observations on colloid therapeutics are inconclusive, and probably exaggerated, and some of the preparations put upon the market at first were carelessly prepared and were unstable.

Still, after making due allowance, there remains a substratum of evidence which is worthy of careful attention.

Any singularity in the operation of colloidal remedies may be ascribed to three chief factors :—

- (a). Extremely minute subdivision of particles.
- (b). Consequent enormous increase in surface area. The reaction-velocity of solids with liquids is proportional to the area of contact. (Weuzel).
- (c). Activity of surface energy. Adsorption, *i.e.*, surface condensation.

The gist of the matter appears to lie in the fact that, in elementary collosols, when internally, or hypodermically administered, the active ingredient is gradually and slowly liberated, and passes into true solution.

We may thus conclude with Bayliss (*Lancet*, Jan. 7th, 1922) that, up to the present, no good evidence has been produced that the chemical or pharmacological action of substances in the colloidal state differs fundamentally from that in true solution otherwise than in the matter of gradual slow effect due to the minute size of the particles, and the enormous increase of surface area.

Exhibits of Experiments.

1. Diffusion through gelatin gel—Congo Red (—); Methylene blue (+).
2. "Protective" influence of a gel on chemical reaction.
3. Germicide action of "Argentum collosol."
4. Colloidol Gold (red and blue).
5. Colloidol Silver (gold-like).
6. Liesegang's Rings.