food material and has but little cytoplasm, most of which is usually modified to form a flagellum or other organ by which the spermatozoon may move actively and seek the egg. There is possibly another physiologi-
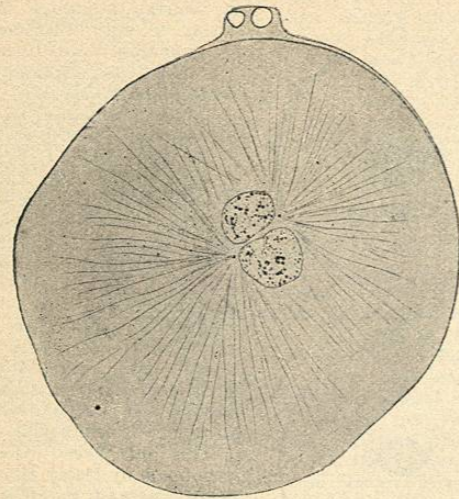


FIG. 2793.—Thalassema. Copulation of the germ nuclei. The sperm centrosomes are seen in the plane separating the two nuclei. (After Griffin.)

cal difference which will be noticed in connection with the function of the centrosome. The terms male and female cannot be applied properly to these cells, and should be used only as descriptive of the organisms that produce them or their equivalents.

There are two types of fertilization in animals, depending, as was first suggested by Hertwig, upon the time of entrance of the spermatozoon.

The eggs of echinoderms (Fig. 2790, *D, E, F*) pass through the whole process of maturation (see *Reduction Division*) before the entrance of the spermatozoon, the egg nucleus has resumed the form of a spherical vesicle, and the aster and centrosome of the last polar spindle have disappeared. The spermatozoon may enter the egg at any point. Soon after entrance the head of
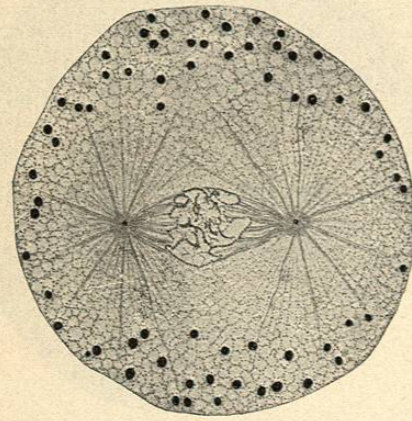


FIG. 2794.—Thalassema. The first cleavage amphiaster. Germ nuclei completely fused, with the chromatin in the spireme stage. (After Griffin.)

the spermatozoon revolves end for end and begins to enlarge, while a series of lines appear in the cytoplasm radiating from the position of the middle piece. These radiations form the *sperm aster*, and at their centre there is a small darkly staining spot, the *sperm centrosome*. The

head of the spermatozoon, now called the *sperm nucleus*, moves rapidly toward the *egg nucleus*, preceded by the aster. The latter touches the egg nucleus and divides into two, and shortly after this the sperm nucleus unites
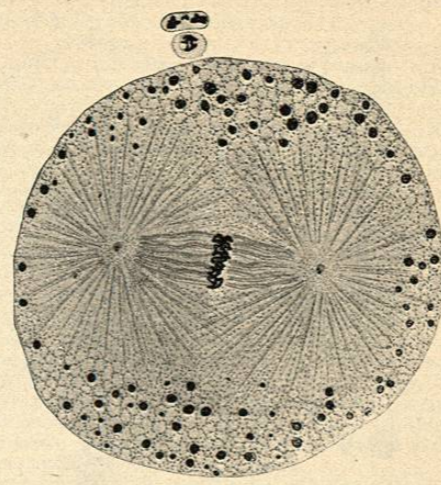


FIG. 2795.—The Same. First cleavage spindle in the late prophase. Chromosomes forming at the equator. The centrosomes have begun to divide preparatory to the second cleavage. This section passes through the plane of the two polar bodies, which are seen at the upper pole of the egg. (After Griffin.)

with the egg nucleus, the two becoming completely fused in a single segmentation, or *cleavage, nucleus*. In the mean time the two asters formed by division of the sperm aster have taken up positions at opposite poles of the nucleus. Soon the nuclear membrane disappears, chromosomes and spindle are formed, and the first cleavage begins. In this type of fertilization the two nuclei are of unequal size, the sperm nucleus being much the smaller.

The second type is seen in the eggs of flat worms, annelids, and mollusks (Fig. 2790, *A, B, C*). In these groups the whole process of maturation of the egg takes place
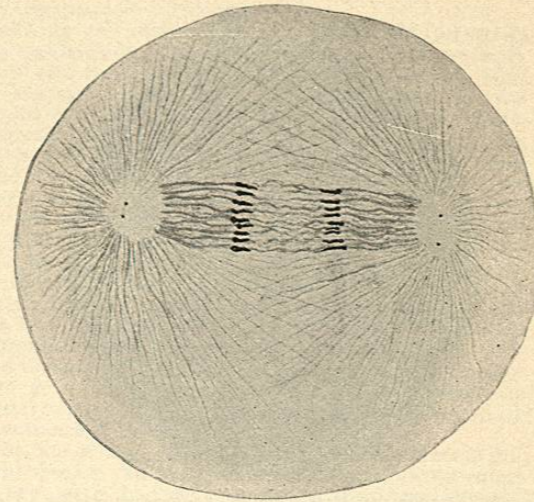


FIG. 2796.—The Same. Cleavage spindle in the anaphase. The chromosomes have divided and are separating to opposite poles. (After Griffin.)

after the entrance of the spermatozoon, that act being apparently the stimulus necessary to set the process in motion. While the two polar bodies are being formed, the sperm nucleus advances to the centre of the egg and becomes greatly enlarged, and at the same time the sperm

aster divides to form an amphiaster (Fig. 2791). At the completion of the second polar division the egg nucleus is reformed and moves toward the sperm nucleus (Fig. 2792). As a rule the egg aster and centrosome disappear. Finally the two nuclei, now of equal size, lie side by side, but without fusing, with the two asters derived from the sperm aster lying in the plane between them (Fig. 2793). Soon after this the chromosomes reappear in each nucleus, the nuclear membrane fades away, and the first cleavage spindle is formed as before (Figs. 2794, 2795, and 2796).

Between these two types there are various intermediate forms in which the entrance of the spermatozoon occurs either after the extrusion of the first polar body or during some other phase of the process of maturation.

The account given in the preceding paragraphs should be taken as merely a general statement of the main facts of fertilization. The details of the process vary to a greater or less degree in different species. In the slipper shell, Crepidula, for example, the protoplasm flows toward the upper pole of the egg, while the yolk becomes more concentrated in the lower part. This is true probably, more or less, in all eggs that divide unequally. In such cases the union of the germ nuclei takes place near the centre of the protoplasmic mass.

In the first type of fertilization it is impossible to trace the history of the chromosomes of the cleavage nucleus. But in many cases of the second type it is possible to do this very clearly. The eggs of Ascaris are known to be especially favorable objects as the result of the brilliant researches of Boveri, Van Beneden, and Herla. In such cases it has been shown beyond a doubt that of the chromosomes in the cleavage spindle, one-half are derived from the egg nucleus of maternal origin and the other half are in like manner derived from the sperm nucleus of paternal origin (Fig. 2797). Now during the mitosis preparatory to the first cleavage, each chromosome is divided into two and the halves separate to opposite poles of the spindle, so that each daughter nucleus receives an equal number of chromosomes of maternal and of paternal origin (Fig. 2796). The same thing occurs in all subsequent mitoses. Therefore if the chromosomes maintain their individuality during the resting stage, as there is reason to suppose they do (see *Chromosome*), each somatic cell is provided with chromatin derived in equal measure from the two parents. This is a fact of the greatest importance for our theory of heredity (see *Heredity*).

The origin and fate of the centrosomes of the cleavage spindle have been fruitful of much discussion, and the results of investigation are still somewhat contradictory. The majority of observers are agreed now that the centrosome accompanying the egg nucleus after the separation of the second polar body usually disintegrates and disappears before the union of the two nuclei (as seen in Fig. 2792). But Conklin maintains that in Crepidula this centrosome persists, unites with the sperm centrosome, and that the product of this union divides to form the centrosomes of the first cleavage amphiaster. If true, this is certainly exceptional. The sperm centrosome which appears near the sperm nucleus soon after the entrance of the spermatozoon appears to be derived from the middle piece, which in turn was formed from the centrosome of the spermatid (see *Spermatozoon*). At any rate, it appears in the position of the middle piece, or near it. But because of its minute size it cannot, as a rule, be supposed to represent more than a part of the middle piece. Some observers have asserted that it is a new structure that arises in the cytoplasm of the egg as a result of a stimulus from the spermatozoon, with which it has no morphological connection. But the view that it is derived from the middle piece seems to agree best with the observations in most cases. The fate of this centrosome is also a matter of doubt. At least in most cases it has been impossible to show conclusively that this centrosome gives rise to the centrosomes of the cleavage amphiaster. It may disintegrate, and a new centrosome may arise in the cytoplasm close by the united nuclei. But Griffin has asserted positively that in the

gepherian worm, Thalassema, he has been able to trace the history of the sperm centrosome continuously to the formation of the cleavage amphiaster. The centrosomes of this amphiaster pass one into each daughter cell during cleavage, and frequently each one divides into two before the first cleavage is complete, in anticipation of the second cleavage (Fig. 2796). This process is continued during subsequent cleavages; so it appears that the centrosomes of the first cleavage amphiaster give rise by division to the centrosomes of all the cells of the embryo, at least for a number of cell generations.

As to the function of the centrosome, Boveri maintains that it is a permanent cell organ and that it is the dynamical centre of the cell. The egg centrosome having been absorbed, he regards the sperm centrosome as the especial fertilizing agent introduced into the egg by the spermatozoon. That is, while the sperm nucleus introduces the physical basis for heredity of the maternal characteristics, it is the centrosome that furnishes the stimulus necessary to start the segmentation of the egg and development of the embryo. Boveri finds evidence for



FIG. 2797.—Fertilized Egg of *Ascaris megalocephala* var. *bivalens* just previous to the formation of the cleavage spindle. Two elongated chromosomes have appeared in each germ nucleus. The two large centrosomes are surrounded by extensive masses of granular archoplasm, and the second polar body is visible in the upper part of the section. Highly magnified. (After Boveri.)

this view in certain abnormal phenomena called partial fertilization. He observed that in sea urchin eggs it sometimes happens that the sperm centrosome gets so far ahead of the sperm nucleus that it conjugates with the egg nucleus and causes the egg to divide before the union of the two nuclei. The sperm nucleus, however, subsequently unites with one of the nuclei of maternal origin in the two-cell stage.

Of great interest in this connection are the observations of Hertwig, Morgan, Loeb, and Wilson upon the production of artificial parthenogenesis in unfertilized eggs. Hertwig, using solutions of strychnine, and Morgan, using chiefly solutions of sodium and magnesium chlorides, found that unfertilized echinoderm eggs when treated with these substances might undergo cleavage; and Morgan discovered, moreover, that as a result of this treatment there might appear in the cytoplasm of the egg a large number of asters, each having at its centre an accumulation of material like a centrosome. This last observation would seem to raise a serious objection to the idea that the centrosome is a peculiar and permanent cell organ. Loeb subsequently made the remarkable discovery that by careful treatment with various inorganic salts, and even with sugar and urea, unfertilized eggs of two species of echinoderms and of one annelid could be induced, not only to segment, but to give rise to swimming larvæ. These results have been fully confirmed by Wilson, who has shown that in the case of the sea urchin, Toxopneustes, the eggs, which begin development under the influence of a twelve-per-cent. solution of $MgCl_2$ without fertilization, do not develop a vitelline membrane and contain only the number of chromosomes normally present in the egg nucleus. So there can be no question of accidental fertilization. Wilson has worked out the cytological changes occurring in such eggs. He finds much variation and many abnormalities, which result in the death of the embryo. Where nearly normal development takes place, he finds that always a *new* centrosome with its surrounding aster forms close to one side of the nucleus. It then divides, the two halves passing to opposite poles of the nucleus to form an amphiaster, and then cleavage proceeds very much as usual. If the primary centrosome fails to divide, it may go
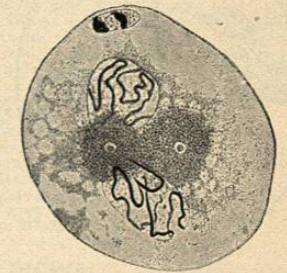
through certain periodic changes, increasing and decreasing in size, and these changes are accompanied by division of chromosomes in the nucleus, but no cell division takes place. The cleavage of the egg then appears to the process is essentially the same. In the sexual reproduction of all plants that have been examined, it has been found that fertilization is effected by the union of a single germ nucleus of paternal origin with the egg nucleus.
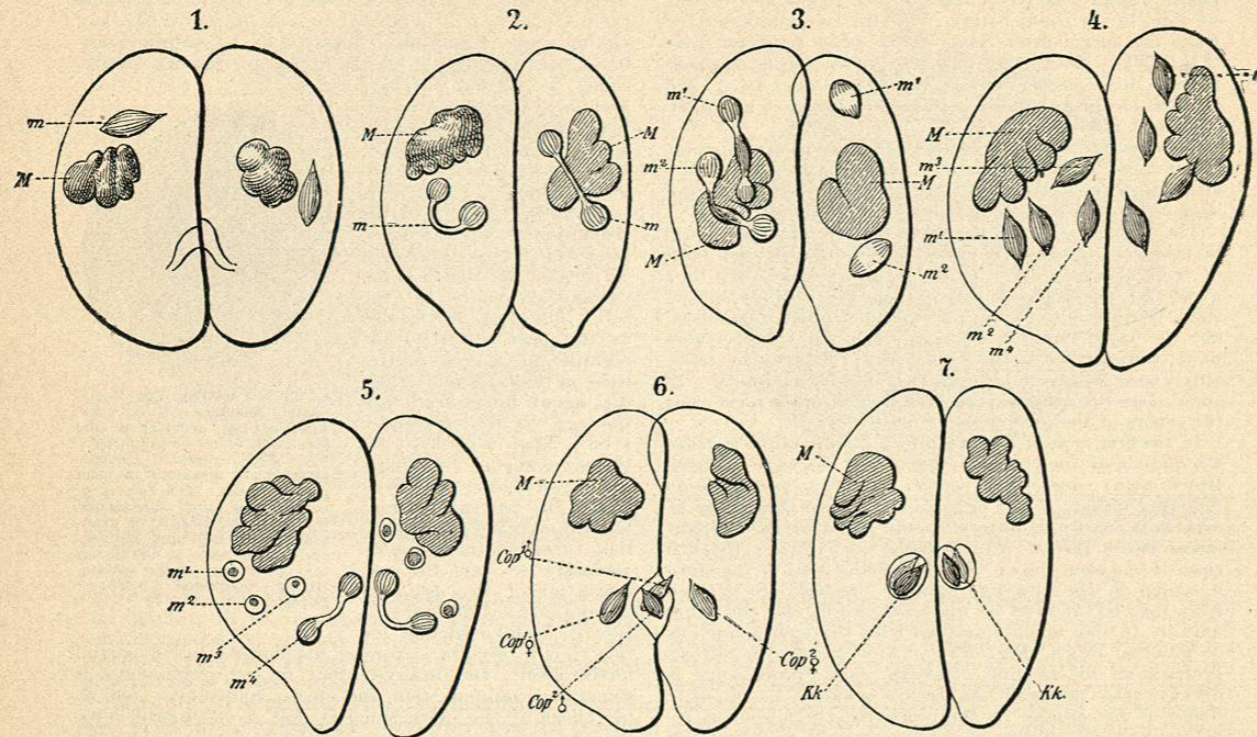


FIG. 2798.—The Conjugation of Infusoria. (From Weismann, after Maupas.) 1, Two infusoria copulating; M, meganucleus; m, micronucleus; 2–5, successive divisions of micronuclei; 6, fertilization by the migration of one of the persisting micronuclei from each infusorian into the other; 7, union of the interchanged micronuclei.

depend upon the normal behavior of a centrosome closely associated with the nucleus, but this centrosome may be caused to arise *de novo* by appropriate chemical stimuli. It, however, acts much more slowly than the centrosome introduced with the spermatozoon. But the centrosome is not capable of producing cleavage of the egg nucleus unless accompanied by a nucleus. For example, Wilson has found that asters containing centrosomes may be produced by chemical stimulus in enucleated fragments of eggs obtained by shaking unfertilized eggs to pieces. Such asters may multiply by division, but the cytoplasm does not divide. And Boveri has observed that sometimes during cleavage of fertilized eggs all of the chromatin will go to one daughter cell, the other receiving only an aster. In such a case the aster in the enucleated cell will continue to divide, but the cell will not.

Hertwig, Boveri, and others have found that if enucleated fragments of unfertilized eggs be mixed with spermatozoa of the same or closely related species, the spermatozoa will enter the fragments, the nucleus will undergo regular mitotic division, the cytoplasm will divide, and larvæ will be produced that are indistinguishable from normally produced larvæ, except for their smaller size. The sperm nucleus is, then, perfectly equivalent to the egg nucleus and only needs to be supplied with the necessary envelope of cytoplasm in order to undergo the same series of changes; and under certain conditions the normal cycle of life may be inaugurated by either the sperm or the egg nucleus without union with the other, even in species in which normal parthenogenesis is unknown.

The process of fertilization in plants has not been studied so extensively as in animals. But enough has been learned to show that, so far as the nucleus is concerned, This was described for the first time by Strasburger in 1884, and his results have been confirmed by Guignard and a number of other investigators in a variety of plants of various orders. In some plants the paternal gamete is an actively motile spermatozoid, in others it is an immobile cell that reaches the egg cell by a process of growth, as is the case with the pollen tube of the higher plants. But in all essential features the process is the same in both cases.

Although Guignard, in 1891, described with much detail a conjugation of centrosomes in connection with fertilization in the lily, his results have not been confirmed; and most observers have failed to find any evidence of a centrosome in any way connected with either of the conjugating nuclei of plants. This would seem to indicate that the presence of a centrosome is not essential to fertilization. But Strasburger has found that a centrosome appears in Fucus on the side of the cleavage nucleus that is derived from the sperm nucleus, and Wilson approves of his suggestion that in plants "the sperm nucleus may import into the egg either a formed centrosome (probably thus in Fucus) or a certain quantity of 'kinoplasm' which excites the mitotic phenomena in the absence of individualized centrosomes."

The pollen tube of angiosperms contains two sperm nuclei, of which only one unites with the egg nucleus. In 1898 Nawaschin published the interesting discovery that in *Lilium martagon* and *Fritillaria tenella* the other sperm nucleus conjugates with the two "polar nuclei" to form the embryo sac nucleus, the division of which gives rise to the endosperm of the seed. The same phenomenon was described in more detail by Guignard in 1899, and confirmed by Miss Sargent. It immediately occurred to De Vries, and independently to Webber, that

this might explain a phenomenon called *xenia* by Focke (1881). For a long time it has been known that if the pollen of one variety of maize be allowed to fall upon the silk of a different variety, the kernels in the ear may show the characters of the male parent. Until this process of double fertilization was discovered, the embryo was the only part known to have a double origin, and the appearance of the paternal characters in a part of the seed supposed to be purely of maternal origin seemed very mysterious.

From a careful study of the phenomena of xenia in maize, in which the only undoubted cases occur, Webber has reached the conclusion that they are perfectly consistent with the theory of double fertilization, no xenia appearing in characters not connected with the endosperm. But the actual double fertilization has not yet been observed in this plant.

Xenia has been supposed to be a similar phenomenon to *telegony* in animals. But it seems impossible for any such process of double fertilization to occur in animals, and Ewart has found that in the mare "the spermatozoa lodged in the upper dilated part of the oviduct are dead, and in process of disintegrating, eight days after insemination." Moreover, the supposed existence of telegony has been entirely discredited by Ewart on experimental evidence, and by Pearson on evidence from statistics.

In the conjugation of the unicellular animals and plants, we find a process clearly analogous to the fertilization of the higher groups. The two conjugating cells may be similar or diverse in form. In many motile Infusoria (Fig. 2798) two similar individuals come together, exchange nuclei, each one giving off a "male pronucleus," which enters the body of the other and unites with its "female pronucleus," and then the two separate. In other cases there is a motile "microgamete" that forms a permanent union with a sessile "macrogamete," comparable to spermatozoon and egg respectively. In each case the essential feature of the process is a union of two equivalent nuclei, preceded and followed by a complicated series of divisions that we need not discuss here.

Summing up the subject of fertilization, Wilson says ("The Cell," ed. 2, p. 230): "We thus find the essential fact of fertilization and sexual reproduction to be a union of equivalent nuclei; and to this all other processes are tributary." The almost universal occurrence of this process in animals and plants of all grades, from the protozoa to man, indicates that it has some profound significance, but what this is is unknown. According to Weismann, fertilization has for its object the mingling of ancestral germ plasms and the consequent production of variability in the offspring. But Pearson, as the result of statistical investigations, holds that variability is not produced by fertilization. According to Maupas, fertilization has for its object a rejuvenescence of protoplasm, which thus wards off the senescence and "natural death" that must inevitably overtake it if fertilization does not take place; and Minot finds evidence for this view in the results of his investigations of the law of growth (see *Growth*). But when we consider the innumerable generations of domestic plants that have been produced with unimpaired vigor by cuttings, grafts, and other purely asexual methods of reproduction, the existence of any such "natural death" appears to be extremely doubtful. So while our knowledge of the details of fertilization has advanced enormously during the past quarter century, the origin and object of the process remain as mysterious as ever.

*Robert Payne Bigelow.*

BIBLIOGRAPHICAL REFERENCES.

Wilson, E. B.: Atlas of Fertilization and Karyokinesis, New York, 1895.—The Cell in Development and Inheritance, second edition, New York, 1900. (This gives, in addition to an extensive discussion of the subject, a complete bibliography to the time of going to press. The titles of some of the more important papers that have appeared since then are given below.) Experimental Studies in Cytology. I. Archiv f. Entwickel. d. Organismem, xii., 1901, pp. 519–596; II. and III., l. c., xiii., 1901, pp. 353–395.
Webber, H. J.: Xenia, or the Immediate Effects of Pollen, in Maize. Bulletin 22, Div. Vig. Physiol. and Path., United States Dept. Agric., 1900.—Spermatogenesis and Fecundation of Zamia. Bulletin 2, Div. of Plant Industry, United States Dept. Agric., 1901.
Ewart, J. C.: The Penycuik Experiments, London, 1899. Experimental Contributions to the Theory of Heredity, A. telegony, Proc. Roy. Soc., London, vol. lxv., pp. 243–251.

**INCOMPATIBILITY, MEDICINAL.**—The word *incompatible*, used in connection with the mutual relations of medicines, is one of very loose application. Thus, in a sweeping way, a medicine is said to be *chemically* "incompatible" with anything that will produce a chemical or physical change in its condition, and *physiologically* "incompatible" with anything that produces the reverse of its so-called physiological effects. Under these definitions, however, it is evident that in many cases so-called "incompatibility" may yet not interfere at all with full medicinal power or purpose. Practically, the subject of medicinal incompatibility deals with those chemical, physical, and physiological mutual relations of medicines that require consideration in the prescription of different medicinal substances in conjunction, and such topic it is that will here be considered.

As regards *chemical* and *physical* reactions there are many which are special, between special medicines. Such must be learned in connection with the individual medicines concerned. But, also, there are certain reactions that affect broad categories of medicines, and which, therefore, admit of general consideration. Such reactions and the practical bearings thereof in prescribing are as follows:

1. *Acids and bases tend directly to combine, to form salts.* This reaction may be utilized, if it be the object of the prescriber to obtain the salt that will result from the bringing together of an acid and base; but if the purpose of the prescription be to retain free acidity or alkalinity, acids and bases must not be conjoined in prescription.

2. *Stronger acids or bases tend to displace, in the case of salts in solution, weaker bodies of their own respective kinds.* Thus, if sodium carbonate in solution be treated with nitric acid, the nitric acid will displace the carbonic to the formation of sodium nitrate in solution and the evolution of carbon-dioxide gas. Strictly speaking, the statement of this reaction is a *circulus in definiendo*, since one acid is known to be "stronger" than another only by

TABLE OF NOTABLE MUTUALLY PRECIPITANT SOLUTIONS.

| | Solutions of alkalies. | Carbonic acid and solutions of carbonates. | Sulphuric acid and solutions of sulphates. | Phosphoric acid and solutions of phosphates. | Boric acid and solutions of borates. | Hydrochloric acid and solutions of chlorides. | Hydrobromic acid and solutions of bromides. | Hydriodic acid and solutions of iodides. | Solutions of sulphides. | Tannic acid. | Arsenical solutions. | Albumin. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Alkaloidal solutions (generally) | Prec. | Prec. | ..... | Prec. | ..... | ..... | ..... | Prec. | Prec. | Prec. | Prec. | Prec. |
| Metallic solutions (generally) | Prec. | Prec. | ..... | Prec. | Prec. | ..... | ..... | ..... | Prec. | Prec. | Prec. | Prec. |
| Lead solutions | Prec. | Prec. | Prec. | Prec. | Prec. | Prec. | Prec. | Prec. | Prec. | Prec. | Prec. | Prec. |
| Silver solutions | Prec. | Prec. | Prec. | Prec. | Prec. | Prec. | Prec. | Prec. | Prec. | Prec. | Prec. | Prec. |
| Calcic solutions | Prec. | Prec. | Prec. | Prec. | Prec. | ..... | ..... | ..... | ..... | Prec. | ..... | ..... |
| Magnesic solutions | Prec. | Prec. | ..... | Prec. | ..... | ..... | ..... | ..... | ..... | ..... | ..... | ..... |
| Albuminous solutions | ..... | ..... | ..... | ..... | ..... | ..... | ..... | ..... | ..... | Prec. | Prec. | ..... |
| Gelatinous solutions | ..... | ..... | ..... | ..... | ..... | ..... | ..... | ..... | ..... | Prec. | ..... | ..... |