Karyokinesis and its Relation to the Process of Fertilization.

By

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With Plate XIV.

The phenomenon which is indicated by the name "Karyokinesis" depends essentially on the appearance of distinctly visible and readily stained thread-like structures in the cell-nucleus, which change their form during its division. These structures were observed and figured before they were recognised as general and important occurrences. For example, Henle in his 'Splanchnologie' (1865, p. 355) gave the first drawings of karyokinetic figures for cells of the testis. Again, Heller and A. Kowalevsky (1869), and later on W. Krause (1870)—if we here leave out of consideration botanical writers—may be added as observers of facts in karyokinesis, without, however, giving a correct explanation of them. The honour of discovering karyokinetic (indirect, metamorphic or mitotic) nuclear division as a regular phenomenon, with its three chief constituents—chromatic nuclear figure, achromatic spindle and polar stars—belongs to A. Schneider, the zoologist of Breslau, at that time in Giessen. In his memoir, "Untersuchungen über Platyelminthen," in the 'Jahrb. der oberhessische Gesellschaft für Natur- und Heilkunde' (1873), he describes facts about the division of egg- and sperm-cells, as

1 Translated by W. B. Benham, D.Sc., from the 'Arch. für Mikr. Anat.,' vol. xxxii, 1888, pp. 1—12.
well as of tissue-cells, in a certain Flatworm (Mesostomum). Owing to its publication in an obscure journal, Schneider’s work was overlooked, and the discovery was independently made, shortly after, for a second time by Bütschli (41, 42) and H. Fol (65). Dr. Schleicher, one of van Bambeke’s pupils in Ghent, invented in 1878 (179) the name “Karyokinesis”—i.e. nuclear movement, for the series of phenomena in question; whilst Mayzel (133, 134), of Warsaw, and especially Strasburger (190—194), of Bonn, W. Flemming (57—63), of Kiel, E. van Beneden (18—24), of Liège, and recently Rabl (165), of Prague, have been the chief contributors to the advance of our knowledge of the process. Flemming must be particularly noted, as his version in the controversy of opinion has gained the most adherents. Place will be found in the course of the description for several further data in the development of our knowledge of karyokinesis. An accurate history of the literature will be found in the following monographs:—Strasburger’s ‘Zellbildung und Zelltheilung,’ 3 Aufl., 1880; ‘Neue Untersuchungen über der Befruchtungs Vorgang bei den Phanerogamen als Grundlage für eine Theorie der Zeugung,’ 1884; ‘Ueber Kern- und Zell-theilung im Pflanzenreiche nebst einem Anhange über Befruchtung,’ Jena, 1888; Flemming’s ‘Zells- substanz, Kern- und Zell-theilung,’ Leipzig, 1882; and van Beneden’s ‘Recherches sur la maturation de l’œuf, la fécondation et la division cellulaire,’ Ghent, Leipzig, Paris, 1883.


If we disregard the process of segmentation discovered in 1824 by Prévost and Dumas, H. v. Mohl (140) in Tübingen was the first to show in 1835 that cells and their nuclei increased by division in plants; Remak (171) in Berlin in 1841 in animals and in embryonic blood-cells. Through the numerous researches of the last, and of R. Virchow, on
KARYOKINESIS AND ITS RELATION TO FERTILIZATION.

normal and pathological conditions, it is now known that cell-division, in opposition to the doctrine of spontaneous generation of cells, holds the field, so that at the present day R. Virchow's phrase, "Omnis cellula a cellula," which concerns the chief facts in question, has universal acceptance. But, how does cell-division take place? The scheme of division sketched out by Remak assumes that the process commences with the nucleolus and extends thence to the nucleus and finally to the cell-substance. The nucleolus divides into two parts, then the nucleus, and finally the cell-body. The process was apparently a very simple one. At the same time it was obvious that we had no true knowledge of the nature of this important process, nor of the powers which are operating, nor of the causes which lead the cell to divide. It was perfectly certain that the study of the process in question was very primitive, and that further research was necessary.

It must be reckoned a distinct advance that the process of direct division of unicellular animals (Amoebae) and colourless blood-corpuscles (leucocytes) was followed under the microscope from beginning to end by Stricker (195), Klein (102), and especially by F. E. Schultze (184), and Ranvier (166). According to Schultze's description for Amoeba polypodia the nucleus first elongates, then becomes dumb-bell shaped, then the bridge between the knobs of the dumb-bell becomes thinner, then breaks across, and two nuclei are seen in the animal. At the same time a similar change is taking place in the clear area around the nucleolus. The whole process of division of the nucleus and nucleolus is to be regarded as a single act, which lasts about a minute and a half. Then the body of the cell commences to elongate in the same direction as the nucleus and nucleolus previously did, and then in the same way there follow constriction, band-like stretching of the connecting bridge, and finally its rupture. Nothing was observed of any peculiar appearances, except that emphasis is laid on the fact that no pseudopodia are present on the bridge between the cell-bodies; whereas they project in opposite
directions from the two ends, as if pulling these apart. The
division of the cell-body lasted eight and a half minutes, so
that the complete process occupied ten minutes.

I have studied the process in a similar way in an Infusorian
from the Frog's rectum; it took place somewhat more rapidly,
viz. in seven or eight minutes. Ranvier gives an hour and a
half, at the usual temperature of the room, as about the time
occupied by the process of division in leucocytes of Axolotl;
a remarkable change of form was observed in the nucleus,
which, however, was regarded by Ranvier as passive—condi-
tional only on the amœboid movement of the protoplasm.
J. Arnold (4) observed in amœboid cells of the lymph-
sac of Frogs an undoubtedly constricted nucleus, divide
completely within five minutes; the division of the cell
occupied in this case half an hour, in other cases longer.
Change of form in the nucleus and protoplasm was likewise
established.

Of the researches of Stricker and Klein, I will here merely
mention that they were the first to establish the process of the
division of the cell-substance, but they give no explanation of
the relation of the nucleus to the act of division.

But mention must here be made of a circumstance which
was noted by Stricker, and later also by Flemming (58),
Frommann (73), and J. Arnold (4). It is the disappearance
of the nucleus for a time during the simple, not karyokinetic,
division. No satisfactory explanation of this remarkable
occurrence is at present forthcoming.

I have here intentionally given the first place to the simple
process of nuclear and cell division, as it was inferred by
Remak, and as it was directly studied by the other authors
named, chiefly in order to be able to emphasise the
character of the karyokinetic division about to be described,
and because, as we shall see later, the old scheme of
nuclear division remains essentially true, even in the karyo-
kinetic form.

This scheme of Remak's, which we will, with Flemming, call
"direct nuclear division," or "amitotic division" of the
KARYOKINESIS AND ITS RELATION TO FERTILIZATION. 163

same author, is now contrasted with another mode of division, the "mitotic division" ("karyomitosis," "mitosis," or "indirect division" of Fleming; "karyokinesis" or "karyokinetic division" of Schleicher), the appearance of which differs in many respects from direct division. The striking and characteristic features of this mode of division lie in the fact that the nucleoli as well as the nuclear membrane disappear, or rather seem to disappear. Moreover, as already remarked, the place of the nucleus is taken by a very characteristic figure of threads, which changes in form and arrangement in a perfectly well-ascertained way, then withdraws towards the two sides, and forms the basis for two daughter nuclei. At the point where these are formed certain peculiar radiating appearances in the protoplasm are seen pretty early—stars, "asters," or "sunfigures." Cell-division then follows, in the usual way, after nuclear division.

On account of the change in position and arrangement of the nuclear threads, Schleicher has, as stated, given the name "karyokinesis" or "karyokinetic division" to the whole process, whilst Flemming's terms, "mitosis" and "karyomitosis," refer to the appearance of the above-mentioned thread figure.\(^1\)

The name "indirect division" is well chosen only in contrast to "direct division;" otherwise it seems, as Flemming admits, but little appropriate.

I will now represent in figures, copied chiefly from Rabl (165), some of the processes of karyomitosis, but I must briefly describe the essential structure of a nucleus not engaged in division, a so-called "resting nucleus."

In most of such nuclei (fig. 1) there can be distinguished the network ("Kerngerust"), the nucleoli ("Kernkörperchen"), the nuclear sap ("Kernsaft" of R. Hertwig or "Zwischen-substanz" of Flemming), and the nuclear membrane. Without going into the extensive literature, rich in controversy, on the subject, it is necessary to discuss further some of the details.

The nuclear network, in the ordinary condition of a nucleus

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\(1\) Κάρυον, nut, nucleus; κίνησις, motion; μυρός, thread,
(resting nucleus), consists of a network of distinct threads or strings, some finer, some coarser, the arrangement of which, according to the figures and descriptions of most authors, does not reveal a definite regularity or constancy. Some writers, on the other hand, such as Balbiani (9) and Flemming (58), Bütschli (44), Rabl (165), and others, have made out a special and regular arrangement of threads in nuclei of certain organs and in certain animals. Balbiani and Rabl go so far as to assume a regular arrangement as universal for all resting nuclei, but no generalisation can be formulated in regard to this. For example, Balbiani found in Chironomus-larva only a single greatly coiled thread in the resting nucleus. Flemming is inclined to regard this as a widely spread occurrence. Others dispute this (see below). Again, it is still doubtful if the threads, whether there be one or many, are non-anastomosing, or if there exist net-like anastomoses between the separate coils, in other words, a network (as in fig. 1). Were there a regular arrangement of threads in every existing nucleus, it would be of great importance in the interpretation of the phenomena of karyokinesis. Rabl has, indeed, expressly pointed to such an interpretation of the network of resting nuclei. He distinguishes "primary" from "secondary" nuclear threads; the former are longer and mostly arranged excentrically in the nucleus, and extend round the surface of it in such a way that at one point of it—the "polar-field" (Rabl)—they form loops, the apices of which are placed round the pole, whilst their free ends extend nearly to the opposite side, where a different arrangement is recognisable. This side of the nucleus, in which a polar area is not present, is called by Rabl the "Gegenpolseite" (antipole). Figs. 2, 3, and 4 serve to explain this. In fig. 2 the angles of the loops are directed towards the pole; in fig. 3 the "antipole" is represented. Neither figure, however, applies to the resting nucleus, but to the first stage of karyokinesis, the so-called "dense skein" ("dichter Knäuel"), where the secondary threads have disappeared and the primary threads are so prominent that the whole arrangement is distinct. Fig. 4 shows on the right side of
KARYOKINESIS AND ITS RELATION TO FERTILIZATION. 165

the drawing the plan of the arrangement of the threads in a resting nucleus according to Rabl's idea; on the left only the primary threads are drawn. The nucleus is represented in side view, the pole (p.) above, the antipole below. To the right, which represents the resting condition of a nucleus, two primary loops are to some extent recognisable, but passing from these are numerous secondary threads, uniting with one another and with the primary threads, and in some places the thread substance has collected to form knot-like masses (net-knots). A rounder nucleolus is also shown. One can easily see that the primary threads must be so much the more difficult to make out the more the substance of which they consists radiates into secondary threads and accumulates in knots. Thus it happens, according to Rabl, that in the resting nucleus the regular arrangement of thread-loops with pole and antipole seems to be obliterated, but it can be re-established in a moment if the fibrillar substance can in any way be made to return to the main course of the primary threads. Herein lies the importance of the regularity of the threadwork for karyokinesis. We shall return later to this point.

The structure of the network is peculiar in certain cilioflagellata, e.g. Ceratium tripos. Here Bütschli (44) finds a honeycomb structure with perfectly closed meshes, so that the nucleoplasm, although the nuclear membrane is absent, is not in direct communication with the protoplasm. In plant-cells no so-called secondary threads forming a network were found by Strasburger (191), nor was he able to make out with certainty whether during the resting stage only one thread was present or several threads; and if the latter, whether they have a definite arrangement.

We must now mention certain peculiarities in the behaviour of the nucleus and its constituents to chemical reagents and stains, as well as the constituents present in addition to the network; namely, the nucleoli, the nuclear membrane, and the nucleoplasm.

Weak acids (acetic, formic, &c.) render the network and the nucleoli distinct; water causes them to swell up; chromic
salts, on the other hand, render them indistinct. Nearly all
dyes—I mean those usually employed, such as acid-carmine,
hæmatoxylin, saffranin—stain the network and the nucleoli
very intensely, whilst the rest of the nucleus, the so-called
“nucleoplasm,” between the threads either remains unstained
or takes only a very feeble stain.

These differences in their behaviour to stains has led Flemming
to distinguish in the nucleus so-called “chromatic substances”
from “achromatic substances.” Amongst the former he places
the substance of the network and nucleoli which stains deeply
and intensely by alum-carmine and anilin dyes; with the
latter he places those parts which remain uncoloured, for
example, what is spoken of as the “spindle figure.” He calls
the colourable substance of the network “chromatin.” Re-
lying on Zacharias’ researches he regards chromatin as perhaps
identical with nuclein or with one of its derivatives.\(^1\)

The facts discovered by Balbiani (44) and Pfitzner (153)
appear to be of some importance, viz. that the chromatic threads
are composed of regularly arranged granules (spherules) of a tub-
like shape,—“discs” of Strasburger, “chromatin-spherules”
of Pfitzner, “microsome-discs” of Strasburger (194); this is
especially well seen during karyokinesis. It is now pretty
generally admitted that, besides these “chromatin bodies,”
an achromatic intermediate substance, the “nucleo-hyalol-
plasma” of Strasburger, is present in the threads. Carnoy
(47) believes that the single, greatly coiled chromatin thread
present in the nucleus in Arthropoda has a “plastin-envelope,”
consisting of nuclein substances; this view is confirmed by

\(^1\) Pfitzner goes still further in the use of the words chromatin and achro-
matin. With Flemming he calls the colourable substance of the nuclear
network “chromatin.” As the nucleoli behave somewhat differently to dyes
and present other points of difference, he named their substance “prochro-
matin;” by which would be implied that this was a first stage of chro-
matin. Later, he selected the word “pseudochromatin,” which does not
indicate any definite connection with chromatin. For “nucleoplasm” he
retains Flemming’s “achromatin;” giving, however, the name “parachro-
matin” to the substance of the spindle figure, which behaves differently from
nucleoplasm.
Ch. van Bambeke (12), without further examination of the chemical composition of the envelope.

In my opinion it is not finally proved what form is taken by the Balbiani-Pfitzner chromatin bodies. Pfitzner calls them "spherules;" Strasburger describes them, both in his earlier as well as in his latest papers (191), as tub-shaped discs; as also does Carnoy for Arthropoda.

The nucleoli present much difficulty in their interpretation. It is generally known that they are roundish structures, which stand out distinctly from the rest of the constituents of the nucleus, and are stained deeply. It is, however, doubtful what relation they bear to the network. Some authors, for example Flemming and Pfitzner, regard the nucleoli as distinct from the network; they are to be considered as independent structures inside this; not in connection with the threads, but separate from them, although they appear arranged along them. Others, for instance E. Klein (103), of London, regard the nucleoli as merely much-thickened knots of the network of threads, and as identical with these: I agree with him on account of their behaviour during karyokinesis. As a matter of fact such thick knots do occur in the chromatic network. These, according to Flemming (58), must be distinguished from true nucleoli. A glance at fig. 1 shows a well-defined and rounded nucleolus, in addition to the knots, or "net-knots" as they may be termed to distinguish them from the nucleoli.

According to Pfitzner, true nucleoli never have any connection with the chromatin coil, but lie freely in its meshes. Apart from this, Flemming further finds differences in the index of refraction and in behaviour to stains. In Ceratium tripos, Bütschli found the nucleoli lying in the nucleus to be formed of a fine network. E. Zacharias (209) says that in plant-cells the nucleoli are deficient in the characteristic nuclear-constituent nuclein; but, on the contrary, consist of a network of plastin-substance, in the meshes of which are other albuminous substances. This would point to the independence of nucleoli. Carnoy (47) would distinguish
four different types of nucleoli (in Arthropoda); if this be true, it seems to me questionable whether such different things should be called by one and the same name. Researches in Gaule's laboratory by Ogata (151) and Lukjanow (129), and again by Stolnikow (189), have shown that nucleolar-like bodies behave very differently towards stains (eosin, saffrauin, nigrosin, and ëæmatoxylin). They are therefore distinguished by these authors as (a) "karyosomes," bodies that are stained blue; (b) "plasmasomes," which stain red; (c) "hyalosomes," which are not stained (vide Lukjanow). As Ogata first pointed out, these bodies may wander out of the nucleus into the cell-body; the out-wandering plasmasomes form the so-called "paranuclei" (Nebenkerne), which take so important a share in the regeneration of cells.

The significance of all these things to the life of the cell is still very obscure. Strasburger and Pfitzner (l. c.) are inclined to look upon the nucleolus as a place of storage for the so-called "reserve substance," a view which is entirely supported by their behaviour during karyokinesis. They become lost, in fact, during the process, and reappear in the new nuclei after division. A. Brass (39) too brings the nucleolus into connection with the process of nutrition of the nucleus. In Spirogyra, according to Meunier (136), all the chromatin is contained in the nucleolus, and is from here exclusively converted into the mitotic figure.

The nucleoplasm is not by any means to be regarded as a simple watery liquid; everyone considers it rather as containing albumen. By means of different reagents fine granulations can be seen in the nucleoplasm; according to Flemming (58) these must be due to the result of coagulation—or rather precipitation—and are not to be regarded as structural. Carnoy (47) regards them thus, since he describes the nucleoplasm as a fine plastin-network, with more fluid contents ("enchylema"); whereas van Bambeke (l. c.) and Platner (161) are of a different opinion.

The nuclear membrane presents a good deal of difficulty; on all sides it is held—and I myself agree with this view—
that the network is denser near the periphery of the nucleus, and thus forms a perforated basket-like limiting layer. By others, an achromatic nuclear membrane is admitted for many nuclei, as, for instance, by Flemming (58); whilst many, like Strasburger and Pfitzner (154), believe in a membrane-like arrangement of the cell-protoplasm immediately around the nucleus—the "inner cell-membrane." In his later contribution (191, p. 30), Strasburger agrees with Guignard (84) that the whole nuclear membrane belongs genetically to the cell-protoplasm; it is a limiting layer of cell-protoplasm applied around the nuclear substance. At any rate it attains a more complete morphological individuality than the rest of the cell-protoplasm. It would certainly appear that the nuclear membrane belongs genetically to the cell-protoplasm, from the fact that in plant-cells it becomes associated with the protoplasm during karyokinesis, and becomes again arranged around the daughter nuclei.

With regard to the chemical composition of the substance of the nucleus—an important item for a correct conception of the process of mitosis—recent researches have proved much, especially on the botanical side. Besides the "nuclein," discovered by Miescher (137), which forms an essential part of the mass of the nucleus, Reinke and Rodewald (170) have found "plastin," and Kossel (111—113) "histon" and "adenin." According to all present opinions, nuclein is found chiefly in the chromatic substance; see E. Zacharias (208, 209). Franz Schwarz (185) gives the following names to the various constituents of the cell-body and nucleus:—(1) "Chromatin," which forms the substance of the Balbiani-Pfitzner chromatin bodies, of which a description has already been given. These are identical with Strasburger's "nucleo-microsomes," a name which its author in his latest publication (191) gives up, on the ground that the chromatin bodies are chemically and morphologically different from the "microsomes" ("cytomicrosomes"), which must be regarded as the chief constituents of the cell-protoplasm. (2) "Linin" (λινόν, thread). This substance is identical with Strasburger's "nucleo-hyal-
plasm,” and with Pfitzner’s “parachromatin;” it is the feebly-staining ground substance of the chromatic threads, in which the frequently mentioned deeply staining chromatin granules are embedded. We shall very easily become familiarised with the name “linin,” on account of its brevity, in place of the inconvenient terms “nucleo-hyaloplasm” and “parachromatin.” Strasburger, indeed, has already adopted the word in his latest work. (3) “Paralinin,” by which is meant the more fluid substance of the nucleus, which is present between the threads. Its synonyms are “Kernsaft” (O. Hertwig), “Zwischensubstanz,” and “Achromatin” (Flemming), and “Karyochylema” (Strasburger). (4) “Pyrenin” ($\pi\nu\rho\nu$ = nut, nucleus) refers to the substance of which the nucleoli are composed. It may reasonably be doubted, as is done, for example, by Strasburger (191), whether F. Schwarz is right in assuming a uniform substance for nucleoli. (5) “Amphipyrenin,” the substance forming the nuclear membrane. This is very similar to pyrenin. (Cf. what is said about the relation of the nucleoli to the nuclear membrane.) Nevertheless, pyrenin takes stains easily, whilst amphipyrenin does not; both exhibit reactions different from chromatin. According to Schwarz, linin agrees most nearly with nuclein in its reactions, and not with chromatin (in opposition to previous views, see above). Paralinin stands close to globulin. This paralinin is not a fluid in the usual sense, therefore the otherwise suitable word “Kernsaft” does not commend itself; moreover, it is achromatic. One can only admit a true “sap,” like karyochylema, in vacuoles. As this view agrees with that of Carnoy already mentioned, we must inquire further into it.

In opposition to most of the recent views, F. Schwarz (185) holds that in cell-protoplasm there is no preformed network, but that a part of it can form itself into threads and strings; that is, cytoplasm is a mixture in which, under certain circumstances, a separation of a denser, more tenacious, and of a more fluid substance can take place. For instance, vacuole formation is due to such a separation. As for the chemical
composition of cytoplasm, F. Schwarz recognises (1) "plastin" (Reinke) or "cytoplastin," a viscous, extensible mass, which resists pepsin and trypsin digestion; (2) "microsomes" insoluble in water and in cytoplasm. These are of different composition in different cases, and therefore cannot be compared with the chemically uniform chromatin bodies of the nucleus; (3) the substance dissolved in the vacuoles. The microsomes may be absent. Nos. 1 and 3 are always present. These are, of course, found chiefly in plant-cells.

We will now return to the process of karyokinesis, and follow the description of it which Rabl (165) has most recently given, and which, as already stated, agrees in all essential points with that given by Flemming (58).

We start with the resting nucleus, as represented in fig. 1, which also represents the first stage of karyokinesis in which all the secondary threads of the network, as also the nucleoli and net-knots have disappeared, their substance passing into that of the primary threads. Fig. 4 shows a nuclear scheme, in which, on the right side, net-knots and a nucleolus are distinct, whilst on the left they are absent. If we imagine the secondary threads, knots and nucleolus to become absorbed into the primary threads it will represent the first stage of karyokinesis, as is shown in fig. 2 as seen from the polar field. We call this stage, with Flemming, the "Knaüel-stadium" (skein stage), or "spirem,"

E. van Beneden (23) was the first to show, for the egg-cell, that the chromatic threads, with the distinct appearance of which karyokinesis commences, is only a portion of the network existing in the nucleus, and it is now distinct because of the denser aggregation of "chromatin." Rabl has recognised this in other cells, and generalised thereon.

Contemporaneously with this change an increase in size of the whole nucleus is perceptible.

Balbiani and Strasburger have, as already said, stated their opinions, with which the descriptions given by Flemming and Carnoy agree, that in the resting nucleus and at the com-

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ment of the "skein" only a single thread is present, which is greatly coiled and so has the appearance of a large number of separate loops. So difficult is it, as I know from experience, to be positive on this point, that I might agree with Rabl when he says that from the commencement numerous separate loops—as many as twenty in animal cells—are present.

Strasburger, too, in his later contribution (191) has given up his earlier views as to the presence of only a single thread. In the cells of Chironomus-larva, where Balbiani first recognised it, Strasburger has also admitted a single thread. Rabl, differing from his predecessors, describes the already mentioned typical arrangement of the thread-loops at right angles to the long axis of the nucleus, with a "polar field" at the pole (Polseite), and with an "antipole" (gegen-Polseite) at the opposite side, and believes that the threads in the greater number of cases lie at the surface of the nucleus (figs. 2 and 3).

Rabl does not find polar rays in the protoplasm of the cell (the "cytaster") at this stage (see fig. 7), whereas Flemming has observed them in an egg-cell clearly defined in this stage, and moreover regards a "dicentric arrangement" of the protoplasm as a very early phenomenon in tissue-cells about to divide, notwithstanding that a distinct radial arrangement of the protoplasm at two opposite poles is not yet recognisable (see later, under van Beneden's views).

The primary nuclear figure, which we have now described, is termed the "denser skein" (dichter Knäuel); it passes into the "loose skein" (fig. 5). This is brought about by the threads becoming thicker and shorter, and not being so tightly coiled. At the same time the single thread undergoes transverse division, so that the number of separate loops is increased. Rabl concludes, from Flemming's numbers and his own, that in one and the same species of animal and kind of cell the number of thread-loops at this stage is constant. For instance, in the epidermic cells of the Salamander there are twenty-four loops. Strasburger and Heuser (97) also give a definite number for certain
KARYOKINESIS AND ITS RELATION TO FERTILIZATION. 173

plant-cells; the former has recently stated that an absolute constancy does not exist, at least not in all kinds of cells. The generative cells exhibit in a remarkable manner the same number of loops (in one and the same species). (On this point cf. Boveri, p. 103.)

Anyone who like Flemming believes only in a single thread in the foregoing stage, must regard it as dividing in the stage of the "loose skein" into numerous pieces or loops.

As already observed, Rabl also believes in such a division into several loops, but from the commencement he recognizes numerous loops, so that for him the division is much more limited.

After the "loose skein" there follows, as a third arrangement of the first stage of karyokinesis, the so-called "segmented skein," a term given to one of the most important of Flemming's discoveries, and which is now known as a general phenomenon of karyokinesis, namely, the longitudinal splitting of all the thread-loops (see figs. 6 and 7). By means of the splitting of the several threads, as is proved by later events, a resolution of the whole chromatic mass of the nucleus into two equal parts takes place, and the succeeding phenomena result in the portions separating from one another, and grouping themselves as two new daughter nuclei.

Rabl says definitely that he has always found the longitudinal splitting of the chromatic threads to be completed at the end of the skein phase. E. van Beneden (for Ascaris megaloecephala) lays special stress on the fact that the two daughter-threads are exactly alike down to the smallest detail. The longitudinal splitting, according to him, is at first not complete, so that the sister threads for some time remain connected with each other at their two ends by means of a less deeply staining substance. This connection still continues when the sister-threads separate towards the two poles. There are then seen, as was first shown by van Beneden and later by Rabl, fine achromatic threads ("filaments réunissants" of van Beneden) stretching from the ends of the separating loops, which for some time connect the chromatic loops of the daughter-nuclei ("Dyaster"). These threads must be clearly
distinguished from those of the spindle figure (van Beneden, fig. 11). Besides the longitudinal splitting of the threads, however, the final stage of the "skein" exhibits during its course a series of other remarkable phenomena, chiefly the appearance of the so-called "achromatic nuclear spindle," and the commencement of the arrangement of the chromatic loops in a different position with respect to this spindle.

The well-developed nuclear spindle is shown in fig. 7; it consists of two poles and an equator. The delicate threads of which it consists are stained, as already mentioned, much more feebly than the thicker threads of the chromatic figure, at any rate with Flemming's so-called true nuclear stains (alum-carmine, anilin, Bismarck brown, gentian violet, methyl green, &c.), whereas on the other hand they become coloured by many carmine solutions, as well as by haematoxylin. The threads are much more delicate than those of the chromatic figure, especially in animal cells; but in plant-cells the spindle figure becomes evident almost directly. According to Carnoy these threads are continued into the cell-protoplasm at the two poles (cf. van Beneden below, and fig. 7, "Cytaster").

Further study of the achromatic threads shows that the spindle-threads disappear in solution of pepsin, and are rendered distinct in weak acids, especially hydrochloric. The figure has not always the shape of a spindle, but in plant-cells especially, it not infrequently presents a cylindrical shape ("cylindrical thread-bundle"), so that when seen from the pole it resembles not a star but a dotted barrel or tub.

As to its origin and meaning opinions differ. I shall return later on to this subject.

1 The most distinct spindle figure in animal cells, which I have had the opportunity of seeing, is in some very beautiful preparations by Mayzel; these are preparations of the epithelium of Descemet's membrane of the Frog (Rana esculenta). They were treated with weak chromic acid, and stained with carmine, and remain well preserved in glycerine after some years, without losing their distinctness. (Cf. Mayzel's work (184) in the 'Fest-schrift zu Ehren Hoyer's.') Recently I studied the spindle in the most perfect form in Kultschitzky's preparations of the eggs of Ascaris megalcephala made in this laboratory.
Rabl's researches further show that the spindle figure changes its position during division, and, what is especially remarkable, that the loops of the chromatic figure follow this change of position. It has been known since the discovery of karyokinetic cell-division that the threads of the daughter-nuclei group themselves round the poles of the spindle. Flemming and E. van Beneden have also taught that the daughter-loops move along the threads of the nuclear spindle in order to reach the poles. Rabl has shown that from the first appearance of the spindle figure it exerts an "arranging" influence, as it were, on the chromatic threads; and this takes place during the phase of the "segmented skein."

When the spindle figure first becomes visible it lies (in the Salamander), according to Rabl, in the neighbourhood of the polar area, and is so placed that its equator lies in the polar area, whilst its long axis is directed obliquely to the long axis of the nucleus. Later on it sinks deeper into the nuclear substance, and takes up a position such that its equator falls in that plane along which the division of the nucleus will occur (division-plane). The long axis of the spindle figure thus coincides with the "division-axis" of the nucleus. We may here add that this division-axis of the nucleus is not always the same as its long axis or as the long axis of the cell; e.g. a cylindrical cell may divide, not only transversely, but also longitudinally, as, amongst others, Arthur Kollmann in his beautiful work on the tactile apparatus of the hand (110) has shown to be the case with the deep-lying cells of the rete Malpighii, and as Rabl describes for the Salamander. Oblique division, too, may occur. In many cases things go on in such a way that, according to Rabl and Strasburger, the axis of division passes through the polar and antipolar areas of the mother-nucleus; in later stages therefore the polar area of one daughter-nucleus will coincide with the original polar area of the mother-nucleus, and that of the other daughter-nucleus with the original antipole (see fig. 12). This is not always the case, however, for Strasburger finds that in plants the division-axis more often lies parallel to the polar area.
With regard to the position of the chromatic loops relative to the nuclear spindle we have seen already that the angles of the loops at the commencement are in great part inclined to the polar area, i.e. to the equator of the now obliquely placed nuclear spindle. When the spindle sinks so that its equator comes to lie nearer the middle of the nucleus, then—and this is one of the chief figures of the last phase of the skein stage—the loops follow the equator of the spindle as if they were drawn down by it, and gradually group themselves in a ring round the equator with their angles inwards. It is evident, as Rabl points out, that with this the distinction of polar and antipolar areas ceases, and now two poles arise in the nucleus corresponding to the two poles of the spindle figure (see figs. 5, 6, 7).

Two processes belonging to the final phase of the skein stage remain to be mentioned—the polar ray-formation in the cell-protoplasm, and the disappearance of the outer nuclear contour.

The star figure ("Polar Strahlungen," polar rays, "aster") in the cell-protoplasm has already been touched upon. In many cells, e.g. egg-cells, it appears very early, as Flemming has shown (58). In most cells, however, it first becomes distinct at the final phase of the "skein"; the rays start from the pole of the spindle (figs. 7, 9, 10, 11). By all students of the subject it is agreed that the nuclear membrane becomes invisible towards the end of the "skein" stage. As to what happens to it the various opinions are not in agreement. Strasburger has been the most occupied with this part of the process, and according to his idea, which has already been given, the cell-protoplasm enters the cavity of the nucleus on the disappearance of the nuclear membrane and here mixes with the nucleoplasm so that the original outline of the nucleus is completely lost, and there only remain as a material expression of the nucleus the chromatic threads and spindle figure. If, with Strasburger, we believe that the spindle figure is formed by the inflowing cell-protoplasm, then the formal nucleus from this stage onwards is represented only by
KARYOKINESIS AND ITS RELATION TO FERTILIZATION. 177

the chromatic figure. Accordingly, the figures of Strasburger, as well as those of Flemming, Rabl, &c., of the final phase of the "skein" no longer show a boundary to the nucleus, but only a clear area round the thread figure which differs more or less in shape from the earlier outline of this nucleus.

How the mixture of the nucleoplasm with that part of the cell-protoplasm concerned takes place, most authors (with the exception of Strasburger) leave undecided. The above-mentioned clear area at which the nuclear- and cell-substance meet after the disappearance of the nuclear membrane has been especially described by Flemming and Rabl, and we shall refer to this point later on.

Finally, mention must be made of van Beneden's "pole-bodies" (Polkörperchen), which on the complete formation of the spindle figure appear at its poles (figs. 7 and 8). He discovered them in the egg of Dicyema (19). They are small shining bodies which must be regarded as independent structures, not as expressions of the junction of the spindle-threads. Their origin and meaning are still unknown. Carnoy (47) looks on them as stores of nuclear material which are partly formed from cytoplasm, and which are used up later on in the reconstruction of the daughter nuclei.

In plant-cells "pole-bodies" have not been hitherto observed (Strasburger). Polar rays exist here, though rarely (see below for polar rays and pole-bodies, as well as for the structures known as "attraction spheres" of van Beneden).

After the spirem stage, which we have up to this moment been describing and which terminates with the completion of the longitudinal splitting of the chromatic threads, there now follows the stage which is termed the "mother star," "aster," or "monaster" (fig. 7). The peculiarity of this is the arrangement of the chromatic loops around the equatorial plane of the spindle figure in such a way that the angles of the loops are directed towards the centre of the spindle and the limbs peripherally. Flemming was the first to describe the process. As he previously pointed out, the equatorial region of the spindle figure is a sort of area of attraction for the
chromatic loops, so that the process which was commenced in the previous stage will be completed at the beginning of this stage, and in a very remarkable and interesting way. The chromatic threads follow the equator of the spindle figure, and here group themselves close together in the way already described. If one looks at a nucleus from one of the poles of the spindle, the chromatic figure will appear as a star with a clear centre, in the middle of which is a second star, the pale spindle figure, from the pole of which one is looking (fig. 8). The longitudinal splitting is accompanied by a shortening and a thickening of the threads.

This stage lasts for only a short time, and quickly passes into the following, which is now termed by Flemming "metakinesis."

In this there is accomplished, essentially, the separation of the chromatic sister-threads resulting from the previous longitudinal splitting. E. van Beneden (23) was the first to show with certainty in animal-cells (segmentation of the egg of Ascaris megalocephala), and Heuser (97) at the same time in plant-cells, that of the two secondary threads (sister-threads) which arise from one original chromatic primary thread, one goes to one pole of the nuclear spindle, and the second to the opposite pole. Next to the recognition by Flemming of the longitudinal splitting of the threads, these discoveries by van Beneden and Heuser are certainly the most important which have been made on the subject of karyo-

1 The expressions "equatorial plate" (Flemming), "nuclear plate" (Strasburger), are, on account of the word "plate," best suited to the end of the monaster stage, when the chromatic elements are collected together in one plane at the equator. The word "metakinesis" is better used for the next stage, in which the halves of the loops begin to separate from one another; it does not quite correspond to the term "equatorial or nuclear plate." The word "plate" is moreover not particularly descriptive of a structure formed of loops; in some cases, namely, in plant-cells, it happens that the chromatic threads are very short and resemble granules; such thread-elements lie close together nearly in one plane, so that certainly the impression of a "plate" is conveyed. Mayzel, in his work already mentioned, represents such a condition in the spermatocytes of Liparis and Sphynx-larvæ, and in other animal cells. He described them previously (1881). Recently Platner has described similar structures in his work on karyokinesis in Lepidoptera (161).
KARYOKINESIS AND ITS RELATION TO FERTILIZATION.

kinesis during recent times; by means of them Flemming’s discovery first attained its full value, as van Beneden clearly appreciated (l. c., pp. 328, 379, and 380).

Flemming had already (58) given many minute details of the process, and Rabl (165) has recently added a very careful description of metakinesis in the connective-tissue cells of the Salamander. The figures 9 and 10 copied from Rabl (in which, as in fig. 11, the nuclear membrane is no longer evident) give a rough representation of the course of events.

Metakinesis now leads to the next—the fourth—stage, that of the “daughter-stars” (Dyaster), fig. 11. This commences when the open limbs of the loops of the chromatic threads, passing along the spindle figure towards the poles, no longer touch at the equatorial plane. The angles of the loops of each polar half approach one another, the open limbs lose the direction parallel to the spindle figure which they had during the separation, and resume that corresponding to the equatorial plane, so that in a polar view one sees at each pole the figure of a star, the daughter-stars. The angles of the loops do not here touch one another, so that each shows a light spot which is the “hilus” of Retzius (172). Flemming believes the loops of the daughter-stars to be all of equal length and symmetrical, in which he is opposed by Rabl (cf. the figures copied from the latter).

As a last phase there appears immediately after the daughter-star the daughter-skein or “dispirem” of Flemming. The threads become still shorter and thicker, and according to Rabl’s description the polar surface of the daughter-nucleus lies at the polar area where the above-mentioned “hilus” is situated; the limbs of the loops bend round towards the former equator, and meet at that surface of the nucleus directed towards the antipole. In plant-cells Heuser and Strasburger come to similar conclusions, although, according to Guignard (84) and Strasburger (191), the hilus may be absent. This stage is followed, when division of the cell ensues, as it does in most cases, by division of the cell-protoplasm, which is brought about, essentially, by a continually deepening con-
striction at the equatorial plane. For the process of division of the cell-body see below.

Not until the cell has divided into two halves does the conversion of the daughter-skein into a resting daughter-nucleus commence. The first trace of a new nuclear membrane arises in the daughter-nucleus, distinctly before the commencement of cell-division, at the stage of the daughter-skein. Whence it arises is as little known as is the mode of disappearance of the mother nuclear membrane. According to Rabl, a daughter nuclear membrane is first seen at the antipolar side. The pole-bodies disappear with the commencement of the daughter-skein. Where the chromatic threads of the daughter skein touch they soon become branched and send out processes by means of which they unite with one another, so that later on a network of threads arises; they then lose their uniform thickness. Rabl is of opinion that certain thicker threads fuse by their limbs to form four longer threads, but denies, in agreement with his idea of the structure of the resting nucleus, that all thick threads unite with one another at their ends to form a single thread, so as to give rise to a single greatly wound daughter-thread, as Flemming, Retzius, and Heuser believe. Thus, a daughter "resting nucleus" succeeds the daughter-skein, which, together with its cell-protoplasm, has increased in size, and in all essentials resembles the resting mother-nucleus. As in the latter (cf. fig. 12) primary fibres, secondary fibres, pole-field, and antipole-field can be distinguished. The distinction between the two last regions is explicable, it is evident by the process of karyokinesis. As to when the nucleolus appears and how it arises, no concordant or satisfactory accounts have hitherto been given.

If we collect all that is known at the present day about the process of karyokinesis, we shall be able to express its essential character most simply in the following words of Boveri (36):—

"The collection of the chromatic nuclear material in a (definite) number of isolated parts, of characteristic form, varying with the kind of cell—the chromatic elements; the formation of an achromatic figure of threads, either from the nucleus
KARYOKINESIS AND ITS RELATION TO FERTILIZATION.

or from the cell-substance, with two poles; the arrangement of the chromatic elements, so far as their number, size, and form allow, in the equatorial plane of the achromatic figure; the division of the chromatic elements into two halves, of which one half goes to either pole; the transformation of the daughter elements into the network of two new nuclei."

We have now to speak in greater detail of certain points which have hitherto been only cursorily touched upon, and to add others which have not yet been mentioned. In the first place I must beg leave to propose a separate technical name "chromosome" for those things which have been called by Boveri "chromatic elements," in which there occurs one of the most important acts in karyokinesis, viz. the longitudinal splitting. The name "primary loops" does not do, since these things have not always the form of a loop. "Chromatic elements" is too long. On the other hand, they are so important that a special and shorter name appears useful. Platner (160) employed the term "karyosome," but since this suggests the nucleoli another name ought to be used. If the one I propose is practically applicable it will become familiar, otherwise it will soon sink into oblivion.

In the second place, with regard to the spindle figure and the radiating figure in the protoplasm, these are shown in figs. 5—11. The spindle figure was first figured and briefly described by Alexander Kowalevsky, then at Kiew, in his renowned work (114), 'Embryologische Studien um Wirrmern und Arthropoden.' The polar rays in the cell-protoplasm which emanate from each pole of the spindle figure were first shown to us by Herman Fol, of Geneva (64), and A. Schneider (181). Whereas Fol and Schneider give good figures and descriptions of the polar rays, that of Kowalevsky of the spindle figure is incomplete, and he interprets it as being due to a division of the nucleoli. Carnoy (47) has recently come to the conclusion that the nucleoli take a share in the formation of the spindle-threads. Bütschli (41, 42) was the first to give us minute details. In spite of the numerous researches which have been directed towards this point by Flemming,
Strasburger, and Mayzel, we are still in doubt as to the origin and meaning of the spindle figure and polar rays; nor do we know anything definite as to the ultimate fate of either of these structures. But unquestionably the "nuclear spindle" is one of the most important phenomena in karyokinesis, and I do not think I shall be mistaken if I anticipate further advance in our knowledge of the nature of mitotic division from the elucidation of the origin and fate of the spindle-threads.

If we exclude the isolated statement (already mentioned) that the nucleoli take a share in the formation of the spindle figure, there are at the present time three views as to its origin:—(1) The achromatic threads arise chiefly from the cell-protoplasm (Strasburger, Grignard, and others, chiefly botanists); (2) they arise from the achromatic thread substance of the nucleus (Bütschli, Flemming, Pfitzner, Carnoy, Rabl, O. Zacharias, and Schewiakoff); (3) they arise both from the achromatic nuclear constituents, and from the cell-protoplasm (E. van Beneden, Heuser, Platner, and others). With regard to Platner's view it should be remarked that in Arion (160) it is, according to him, formed only from the achromatic nuclear constituents. In a second contribution, however (161), he derives the polar part of the threads from the cell-protoplasm, and the equatorial part from the nuclear substance. He agrees in this with E. van Beneden, who holds the opinion (23, 24) that at first the two halves of the spindle figure are separated at the equator, so that instead of spindle-threads we have two cones. This agrees with Boveri's account of Ascaris megaloecephala (34), whereas Flemming (63) asserts that this condition has no claim to generality.

Boveri's view (34) sounds peculiar and contradictory, viz. that the spindle-threads in the formation of the so-called "directive bodies" (see below) arise from the achromatic nuclear constituents, but that during the segmentation of the egg-cell they arise from the cell-protoplasm (Ascaris megaloecephala).

Strasburger (191) recognises that in Spirogyra polytaeniata the greater part of the spindle figure is formed from the cell-protoplasm, and in agreement with van Beneden's
KARYOKINESIS AND ITS RELATION TO FERTILIZATION. 183

view states that at first the two halves of the spindle are separate, but later on unite at the level of the equatorial plate to form a single structure. The remainder of the spindle-threads attach themselves to the chromatic loops of the equatorial plate. Since the nuclear membrane remains present during the formation of the spindle figure, the spindle-threads have to perforate the membrane, which becomes sieve-like. Strasburger believes that there is here an explanation of Flemming's view that the spindle-threads can appear inside an apparently complete nuclear membrane; but within the nuclear membrane, besides the chromatic loops, there are some very delicate threads which unite the chromatic loops to the nuclear membrane. Whence these delicate threads arise, whether they originally belong to the nucleus or whether they penetrate from the surrounding protoplasm, what finally becomes of them, whether they unite with the chromatic loops or with the spindle-threads, Strasburger leaves undecided. He is disposed to derive them from the surroundings of the nucleus, i.e. from the cytoplasm, and to believe that they unite later on with the spindle-threads; in this respect the spindle-threads in *Ascaris megaloccephala* (Boveri and E. van Beneden) exhibit the same behaviour as in *Spirogyra*. The greater part of the threads later on stretch from both sides of the equatorial plate, but only a small number of them are directly connected with it, so that only some few threads extend from pole to pole. Boveri finds the same thing in the testis-cells of Crustacea.

On the other hand, Carnoy (47) believes that in all the Arthropods studied by him all the threads reach from pole to pole; the same thing obtains also in the testis-cells of Salamander, at least in all probability, according to Flemming. They have the same relation in the higher plants, according to Went (205) and Strasburger (191), whereas Berthold ('Protoplasma-mechanik') believes that only a portion of the threads extend from pole to pole (in plants).

Strasburger, however, does not regard his view as to the formation of the spindle figure as universal; in discussing the
work of Schewiakoff (178) he suggests the possibility that in Protozoa the spindle figure arises from the nuclear substance; he connects this with the permanent demarcation of the nucleus from the cytoplasm.

In Spirogyra those spindle-threads which have united with one another at the equatorial plane, remain for some time as "connecting threads" during the separation of the daughter-nuclei (Strasburger makes no mention of van Beneden's "filaments réunissants," which must be distinguished from the spindle-threads). Finally, Strasburger believes that all the spindle-threads are converted into cell-protoplasm, but that this part of the protoplasm will immediately be used up again for the nourishment, as well as for the completion of the daughter-nuclei.

Flemming (63) looks on a large part of what becomes the protoplasm of the daughter-cells as referable to the remains of the threads; but it does not necessarily follow that these threads also had their origin from the protoplasm. On the contrary, if the threads arise from the mother nucleus, and are converted into cell-substance, it is to be regarded as an important factor in the process of hereditary transmission. "It is possible to assign a certain predisposition to the cell-body." Flemming, however, especially points out that he has always regarded the chromatic alone as the essential nuclear substance. The relation, too, of the spindle figure to the formation of the cell-membrane is important. In plant-cells it consists essentially in the formation of small knob-like thickenings of the spindle-threads at the commencement of cell-division. The group of knobs ("dermatosomes" of Weisner (207, in another sense) and of Strasburger) forms Strasburger's "cell-plate." They indicate the plane of division of the nucleus and cell, and later on are in plant-cells converted into the cell wall, which consists essentially of a fusion of gradually increasing dermatosomes.

While the membrane is developing, numerous other thread unions arise, as Strasburger has shown very decisively in his latest contribution (191). Partition walls are not present in
the formation of animal cells, so that we do not expect knob-like thickenings of the spindle-thread such as are found in plant-cells. However, Mayzel describes a similar appearance in the division of endothelial cells of the anterior chamber of the eye, and E. van Beneden in the division of the Dicyemidae a low group of animals. Flemming, too (50), records on p. 246 that, in the commencing constriction of the cells, threads in many cases stretch distinctly to the equator; he was, however, unable to determine whether these threads were connected with the original spindle figure. On this point cf. Carnoy (47) in his discussion on the directive corpuscles, p. 46.

In Rabl’s memoir (165) we read on p. 282 that at the pole of the daughter-star a clear, strongly-refracting mass is apparent, which “undoubtedly” arises from the remains of the spindle-threads.

Well worthy of notice are the views of Platner (159) and La Valette St. George (121) that, in the formation of Spermatozoa, during the last of the mitotic divisions which are here present, the spindle-threads are converted into the so-called “paranucleus.” Compare the very careful and minute researches of Prenant (163).

Only a few authors have occupied themselves with the polar rays, and yet I think with Fol (68) that these must be regarded as of great importance. Auerbach (5), one of the first to study the ray-formation, regarded it as an expression of the disintegration of the nucleus, and as a distribution of the disintegrated nuclear substance to the cell-protoplasm; he called it therefore the “karyolytic figure.” Strasburger, as we know, speaks in favour of the intermixture of cell-sap and nuclear-sap during karyokinesis, yet we need not refer the radiating polar figure to it. The most detailed accounts of this important subject have been given by E. van Beneden and Platner. The former, from the commencement of his researches, has given the greatest attention to the processes in the cell-protoplasm during mitotic division. Thus, he shows that the protoplasm of cells whose nucleus is preparing for karyokinetic division
(as in cells of ovary of dogs) acquires a stronger refraction and a greater tendency to take stains. Van Beneden is unable to agree with Flemming that this depends on the formation of a more strongly refracting outer layer. The division over they lose this peculiarity.

Again, E. van Beneden (23) discovered the "Polkörperchen" and the "sphères attractives," about which we must now enter into some detail.

According to the recent work of van Beneden and Neyt (24) the "sphères attractives" appear very early in Ascaris megaloecephala, at the time, indeed, when the so-called pro-nuclei (see below, Part II) still retain a reticular structure and are far apart. They appear as two areas in the protoplasm, at first near one another, spherical in form, and deeply staining.

In the centre of this area lies the pole-body surrounded by a clear ring (van Beneden now prefers to call it the "central body"). Later on these move apart towards the poles, and from them there start the various streamings (radiating figures) which are observed in the egg-protoplasm, and at the position of the nucleus during the process of division. The dark part of the "sphère attractive" is called the "cortical zone," the light ring round the "central body" is the "medullary zone."

The streaming shows itself (1) as the spindle figure, the polar points of which are fixed at the two central bodies; (2) as the cone of rays known as the "cône-antipode" (fig. 13), which lies in an inverted position with the base towards the periphery; and (3) as the chief ray-figure in the protoplasm, the "star figure" or aster. All these three ray-figures unite at the central body; the "cône antipode" is part of the aster, contrasted with it by its more marked rays; where the antipodal cone touches the surface of the egg a circle is marked out—the "polar circle." Sometimes this is recognisable as a low ridge. A similar ridge circumscribes the star figures on each side of the equator, named by van Beneden the "tropical circle" ("circle subequatorial"). Between the two tropical circles there remains an equatorial zone free from streaming; this (bourelet équatorial) projects slightly. In this zone lie the
equatorial circle (circumference, boundary) of the spindle figure, as well as the chromatic loops during the stages of the equatorial plate and metakinesis. I have reproduced van Beneden's figure (fig. 13) which brings more clearly into view the points here described.

Very important is van Beneden's statement (24) that the "sphères attractives" are vestigial structures, which share in the successive divisions of the segmenting egg, and at first, indeed, precede the division of the nucleus. The division of the "sphère attractive" commences at the central body, both parts of which separate a little; then follows the division of the sphere, so that both daughter-spheres naturally lie close to one another. Imagine (see fig. 13) the first division of the egg-cell to be accomplished in its equator; there will then be, in the next division, in each of the two first blastomeres about to divide, the two corresponding daughter-spheres placed close to one another in the region of the polar circle. The cell-axis of each blastomere now passes from the middle of the polar circle between the two new central bodies to opposite ends of the cell; this axis then has evidently two dissimilar poles, since at the one pole lie one of the polar circles and two daughter-spheres with two central bodies, whilst at the other end of the axis nothing corresponding to this is found. Each blastomere is at this time of its existence uniaxial but bilaterally symmetrical, since it can be resolved into equal halves by a plane passing along the axis mentioned between the two spheres. Each blastomere must show this bilateral symmetry, and van Beneden concludes therefore that all cells have a bilaterally symmetrical structure, and he would see in this the foundation of the bilateral symmetry of the organism.

On account of the above-mentioned behaviour of the spheres during division, an important meaning must be ascribed to them ("nous sommes donc autorisés," says van Beneden (24), "à penser que la sphère attractive avec son corpuscule central constitue un organe permanent, non seulement pour les premières blastomères, mais pour toute cellule; qu'elle con-
stitue un organe de la cellule au même titre que le noyau lui-même: que tout corpuscule central dérive d'un corpuscule antérieur: que toute sphère procède d'une sphère antérieure, et que la division de la sphère précède celle du noyau cellulaire”). Van Beneden believes that the cause of division does not lie in the nucleus; but, on the contrary, in the central bodies and the spheres.

Platner (161) has described very minutely the radiating figures in the cell-protoplasm of other objects, viz. in Lepidoptera. He, too, figures the connection of the stars (cytasters) which correspond with van Beneden’s “cône antipode,” with the central body and with the spindle figure. He further describes arch-shaped rays from the two stars passing through the whole protoplasm, and joining one another at the equator. I cannot find that he mentions a zone free from rays.

I now pass on to a point which till lately has scarcely been studied; I mean the behaviour of the nucleoplasm during division. We have previously mentioned that, except in Protozoa, every trace of the nuclear membrane disappears at the time of the formation of the mother-star: we may look on this as we will. Nucleoplasm and cell-substance thus touch one another directly, and the idea presents itself that a mixture of the two takes place, and that in that is to be sought the reason for the disappearance of the nuclear membrane. In fact, Strasburger particularly emphasizes the penetration of the cell-constituents into the nucleus, and derives the spindle figure from these inflowing constituents. Carnoy (47) and Schewiakoff (178) regard the inflowing as from the cytoplasm towards the nucleus, and Carnoy inversely from the karyoplasm to the cell. From the figures and descriptions of all authors it is further evident that they regard the totality of the nucleus as ending with the disappearance of the membrane, and the idea has presented itself to most that the nucleus is then represented by the spindle figure and chromatic figure. At least, nothing of the nucleoplasm and previous boundary is to be seen in preparations made in the usual way, and, generally, little con-
sideration is given to the nucleoplasm, which yet forms so important a constituent of the nucleus.

When Sattler (177) and myself studied in 1882 the Frog's skin for nuclear division by employment of lunar caustic we always obtained only nuclear figures of Remak's earlier scheme, never karyokinetic figures, whereas we were easily able to demonstrate the latter in Frog's skin otherwise treated. We sought in vain to obtain chromatic figures in the division by means of silver. We obtained nothing. We expressed ourselves, indeed, in the following terms (p. 275):—

"If one tries to explain the differences of structure as shown by silver method and nuclear stains, the only admissible supposition appears to be that the other appearance of silver-nuclei must be due to the achromatic substance of Flemming, which I would now call 'nuclear sap.' This does not become evident by means of nuclear stains; at least it is masked in contrast to the striking pattern which is presented by the chromatic constituents of the nucleus during division. Silver always brings out the structure of the complete nucleus with its chromatic and achromatic substances, and one sees by the appearances obtained that the achromatic substance exhibits an amœboid movement during division, but in other respects during division behaves itself according to the simpler division-scheme. One must therefore deduce from the effect of stains and silver that the more fluid achromatic nuclear substance always remains around the nuclear fibres, and is not diffused in the cell-protoplasm, but shares in the nuclear network; whilst, therefore, the chromatin of the nucleus successively passes through the well-known striking changes in position and form, the achromatic substance divides in a simpler way, since it always forms a sort of envelope for the chromatic figure."

Recently Pfitzner (157), in his very remarkable work, has produced real proofs of this, so that it may be regarded as a fact. He succeeded in rendering visible during division simultaneously the chromatic thread figure and the rest of the constituents of the nucleus, which he now includes, with the
exception of the spindle, under the name "Kerngrundsubstanz," and he now sees pari passu a simple division of the "Grundsubstanz," in the form of a constriction, occurring together with the kinetic process in the thread figure. He therefore comes to the following conclusion:

1. The nucleus is at all times a perfectly independent structure inside the cell.

2. Karyokinesis is the expression of a process occurring in the cell-nucleus, in which no morphological constituent of the cell takes any active part.

Moreover, Pfitzner concludes that the configuration of the nucleoplasm (Kerngrundsubstanz) always closely agrees with the chromatic figure, so that he arrives at the supposition that the movement of chromatin is primary.

This statement is in agreement with the opinion of E. Zacharias (209) that the delimitation of the nucleus from the cell-protoplasrn is always distinct.

Strasburger, too (190, 194), has asserted that between the separating halves of the chromatic figure there always remains a substance which divides and that part goes to one and part to the other daughter-nucleus; but in opposition to Pfitzner, he believes in an incursion of the constituents of the cell-protoplasrn between the thread constituents of the nucleus. Again Tangl, in a work carried out in Flemming's laboratory (196a), has lately spoken in favour of such an intermixture of the "interfilarmasse" of the cell-substance with the nuclear sap during mitosis, and he endeavours to disprove the evidence of the preparations made by Pfitzner's method. In his latest memoir (191) Strasburger takes the same view, and confirms his earlier assertions, so that considerable doubt as to the correctness of the opinions put forward by Pfitzner, Sattler, and myself have been raised. I cannot allow this matter to drop, since, undoubtedly, the repeated discovery of true mitotic nuclear division in Protozoa is very important for the whole question. Here, according to the united opinion of all students (Bütschli (43), R. Hertwig (94), Pfitzner (156), Gruber (82), and especially Schewiakoff (178),

W. WALDEYER.
the nuclear membrane remains complete during the whole process and towards the end of it tightens, while all the rest of the process goes on essentially in the same way as in the objects usually studied. Strasburger (191) is, indeed, of opinion that this is possible only when no cell-division follows nuclear division, as is the case in the Protozoa. Yet this remark does not apply to the objects studied by Schewiakoff, in which this process takes place, and a regular cell-division follows upon it.

Schewiakoff comes to the conclusion that the invisibility of the nuclear membrane does not warrant the supposition that it disappears at a certain time during karyokinesis; he is even inclined, with Pfitzner, to hold the contrary view, although it cannot be put on a firm basis. I, for my part, lay no stress on the persistence of the nuclear membrane, but on the maintenance of the nuclear shape, by which I mean that the more fluid constituents of the nucleus retain their independence of the cell-body (cf. the above-quoted work of Sattler's).

In my first memoir on this subject (vide 'Deutsche med. Wochenschrift,' 1886, and 'Arch. für Anat. und Physiol.,' Physiologische Abtheilung, edited by E. du Bois-Reymond) I have spoken in the following way (in favour) of the view of the permanency of the nuclear contour during mitosis:—"I would now, after this discovery, put aside altogether the barrier between 'direct' and 'indirect' nuclear division. There is only one form of nuclear division, and that, if we exclude the nucleolus, is in accordance with Remak's scheme, whereby the nucleus, and later on the cell, becomes constricted in a definite plane—the plane of division—into two, usually, nearly equal halves. We have only now, thanks to improved technique, learnt to recognise that a certain constituent of the nucleus—the so-called nuclear network—undergoes certain special transformations, arranging itself in a peculiar way and resolving itself into two halves, but all this always within the frame of the complete figure, which divides in the old manner. When it is insisted that there are many cases in which during nuclear division the chromatic figure has not been observed—e. g. leucocytes—our reply is that
such cases become daily diminished in number. On this point we must refer especially to the beautiful researches of Flemming and his pupils (60), who have recently shown karyokinetic figures to be the rule in all lymphatic cells.

"The instances of nuclei with feebly-developed network, in which our methods have hitherto not sufficed to show the contortions of the threads during division, afford no ground for distinguishing a direct from an indirect nuclear division—the terms themselves are not happily chosen. These cases rather tend to show that the old simple form drawn up by Remak is the fundamental form in which modifications only occur in those cases in which the nucleus contains a distinct network with chromatic substance."

In the meantime, however, the number of doubtful cases of amitotic cell-division has increased, and I am no longer justified in repeating the statement which I made some pages later on in the paper just quoted, "We may say that we have to search for direct division, and that authenticated examples of it are very seldom recorded, and will continually be more seldom reported." For the rest, however, I must hold to the quotation on the grounds which I will give below. But first, I must describe some examples of amitotic and mitotic divisions, both of usual and abnormal form. Flemming (58) and Rabl (165) still cling to direct (i.e. amitotic) division for some leucocytes. Mayzel (Hoyer's 'Festschrift,' Taf. ii, fig. 49) failed to find mitosis in the formation of giant-cells in regenerating corneal epithelium of the Frog. Statements to the same effect have been made by Johow (101) and others for plants, especially the Characeae. Direct nuclear division was found by Frenzel (71) in the intestinal epithelium of Crustacea. In insects the same is seen, together with indirect division in special gland-cells of the intestinal crypts. Fraisse (70) very frequently missed karyokinesis in the regeneration of different tissues, and maintained in almost every case the occurrence of simple direct division. He is even of opinion that the typical nuclear-division figure makes its appearance only when the formation of a definite organ is concerned. Mitosis has been
declared absent, too, by Overlach (152) in the epithelium of the cervix uteri, in spite of active nuclear increase; and by Nissen (145) in the epithelial cells of mammary glands. Berggrün (25) found numerous amitotic nuclear divisions in the Tadpole's tail and in the Frog's cornea after mechanical irritation of the part concerned. Carnoy (47) finds direct as well as indirect division in various Arthropodan tissues. Division of an Infusorian (Euplotes harpa, Stn.), without the appearance of the mitotic figure in the nucleus, is described by K. Möbius (139), although we know true mitotic nuclear division in other Protozoa—see the examples given above. Especially remarkable are the numerous discoveries recently contributed on Spermatogenesis. A. Bolles Lee (32, 33) found amitotic division in the first generation of sperm-forming cells (Samenbildungszellen), the so-called "spermatogonia" of La Valette St. George, whereas in the following generations regular mitotic division was recognised. Dostojewski showed the same state of things in his observations of the sperm-formation in Amphibia, carried on in this Anatomical Institute. Similar observations have been made by La Valette St. George (121, 122), by Gilson (79), by Sabatier (175), and others. Only Piatner (161) established mitotic division exclusively in Pulmonata and Lepidoptera; of course deviations from the normal scheme would be expected.

At the present time nothing precise can be said as to how we should explain these differences, or in what way generally we should regard the relation of mitotic to amitotic division. There is no lack of statements on this point. Thus Piatner (155) and E. Zacharias are of opinion that amitotic division occurs only in those cells which must be regarded as gradually undergoing degeneration. The observations of Boveri (35), given in detail below, appear to be of the greatest interest in this respect. He finds that amongst the segmentation spheres of Ascaris megaloccephala there is always a limited number which during division exhibit chromatin loops distinctly, whilst in the majority of the segmentation spheres these loops are not easily visible, and the chromatin appears
only in the form of numerous granules during division. Boveri is of opinion that the cells with distinct mitosis are the ancestors ("Anlage") of the genital cells.

As a set off to these observations of direct division we have very numerous and constantly increasing observations on the mitotic process of division.

For normal karyokinesis the well-known works of Strasburger (190, 191, 193) and Flemming (58—60) supply the greatest number of examples. In addition to the numerous cases there enumerated, I must mention amongst the recent literature the following:—Karyokinesis during the growth and regeneration of smooth-muscle fibre (Pützer and H. Stilling in 'Archiv f. mikr. Anat.,' Bd. xxviii, p. 396), Cattani ('Gazzetta degli ospitali,' 1885), Paladino ('Riforma medica,' 1886), Busachi ('Estratto giornale della R. Acad. di Medic. di Torino,' 1886, Nos. 3 and 4). Karoykinesis in striated muscular fibre (Nikolaides, 'Arch. für Anat. und Physiol.,' Physiol. Abtheil., herausgeg. von E. du Bois-Reymond, 1883, p. 441). In tooth-forming tissue (Canalis, 'Anatom. Anzeiger,' 1886, No. 7). In liver-cells (Podwyssotzki, in Zeigler and Manwerck, 'Beiträge zur path. Anat. und Physiol.,' Bd. i, and Canalis, 'International Monatsber. f. Anat. und Histol.,' Bd. iii, p. 205). As in the animal kingdom, so in the vegetable kingdom, every embryological and histological memoir brings forward new instances of mitosis.

In pathological cell-multiplication, also, the mitotic form comes into the foreground. Especially J. Arnold, in his work on the process of division in marrow-cells (Virchow's 'Archiv,' Bd. xxvii, 1884), gives an excellent list of the memoirs dealing with the process which have hitherto been published. We find this considerably increased in one of the later publications of the same author ("Üeber Theilungsvorgänge an dem Wanderzellen ihre progressiven und regressiven Metamorphosen," 'Arch. f. mikr. Anat.,' Bd. xxx, p. 205, 1887), and continued up till to-day in Schottländer's work (181[a]) from J. Arnold's laboratory. Again, Unna ("Neuere Arbeiten über Kern- und Zelltheilung," 'Monatsber. für prakt. Derma-
KARYOKINESIS AND ITS RELATION TO FERTILIZATION. 195
tologie,’ 1884, iii, No. 1) describes the occurrence of karyokinesis in pathological processes of cell-formation.

This is the place to speak of the peculiar, and in many respects abnormal, form of karyokinesis which is met with in wandering cells, and in the so-called giant-cells of the marrow. The wandering cells and all their kin, which we will include in the name “lymphoid cells,” appeared for a long time not to undergo karyokinesis. Thanks chiefly to the careful researches of Flemming (l. c.) and his pupils, we have to look upon this important and peculiar group of cells as behaving, in this respect, in the same way as other cells. Nevertheless in these cells direct nuclear division is always frequent, and the want of perfect agreement among writers on the subject leads to the supposition that there are a number of different forms or subforms of lymphoid cells, which may behave very differently in regard to the phenomena of division.

We know, as examples of lymphoid cells, the wandering cells in connective tissue, colourless blood-corpuscles, of which again various subforms must be distinguished (cf. the work of Ehrlich and his pupil Einhorn, especially the dissertations of the latter, ‘Ueber das Verhalten der Lymphocyten zu den weissen Blutkorperchen,’ Berlin, 1884), viz. the round-cells of lymphatic glands and the spleen, the thymus-cells as they develop post-embryonically in this at first epithelium-lined organ, and the marrow-cells. It is by no means quite clear how all these various forms of cells are related to one another. Löwit (127) and J. Arnold (4) especially point out that the nature of the lymphoid cells, in which mitosis has been studied, has not been established with that certainty which is desirable. It is possible, for instance, that in the colourless cells observed in the blood undergoing mitotic division, one is dealing, not with true wandering cells, but with the early stages of red blood-corpuscles, or with loosened endothelial cells engaged in mitosis. It is certain that mitosis has been observed in the colourless cells circulating in the blood, by J. Arnold (4), Peremeshcko, Flemming, Lavdowsky (123), Bizzozeri, Kultschitzky, by the latter in the new-born dog (‘Centralbt. f. d.
med. Wissenschaf, 1885, 5th Jan., and ‘Arch. Slaves de Biologie,’ t. iv, fasc. 2, p. 230); further, in similarly shaped cells in the marrow (Flemming, Werner, Löwit, Denys, Geelmuyden, Cornil, and J. Arnold, by the last of whom the list of authors, here quoted, is given. Without any doubt mitosis has been observed also in cells of lymphatic glands (Flemming, J. Arnold). Flemming (60), as was pointed out at the beginning of this section, is of opinion that the phenomenon was observed in true lymphoid cells, whereas Baumgarten (16) believes that the mitosis was seen only in the fixed, so-called stroma-cells of the lymph-glands.

J. Arnold, in his frequently quoted work (4), comes to the conclusion that the wandering cells, colourless blood-corpuscles, lymph-cells, and the corresponding form of cells in the marrow, the spleen, and the lymphatic glands, are able to multiply according to the type of mitosis, but that absolute proof of it has not been brought forward; at any rate, it may be doubted whether these cells divide only mitotically. Herein he agrees with Löwit. In such cells as connective-tissue cells, especially in the cells of new formations, and the so-called giant-cells of the marrow, all kinds of deviations from normal karyokinesis have been recorded. Thus, frequently tri- or multi-polar figures have been met with, e.g. in pathological new formations by J. Arnold and Martin (132). Rabl (165) also describes such a figure in a hematoblast in the spleen of Proteus. Mayzel (134) traced the mitotic division of a connective-tissue cell of a living Axolotl into four pieces. Denys (53) figures multifold mitosis in giant-cells, and Cornil (49) in sarcoma and carcinoma. Similar tri-polar nuclear spindles have been observed in plants. Unequal daughter-stars are mentioned by Rabl. J. Arnold has seen forms very different from the normal in marrow and spleen. Arnold, on the ground of his discovery, would adduce a new arrangement of the forms of nuclear division, and would distinguish:

1. Segmentation, with two subgroups, the direct and the indirect.
2. Fragmentation, also direct and indirect.
Division of the nucleus takes place in the way which we have so far been describing, or as it is carried out in the segmentation of the egg, i.e. the nucleus divides either in an equatorial plane or in the meridian (segmental plane), and the products of division which are usually exactly equal separate with an even surface; this is "segmentation." This is "indirect" if it is accompanied by karyokinetic appearances, otherwise it is "direct." In "fragmentation" (which word was originally applied by E. van Beneden to ordinary direct division, and by Strasburger was used for "nuclear disintegration"), the surface of separation of the daughter nuclei is quite uneven; portions are nipped off from the outside with irregular surface of separation, or may separate on the inside, and remain connected for a long time, by a bridge, with the mother-nucleus. In this case the portions into which the nucleus divides are not necessarily unequal in size, although they usually are. Here also karyokinetic appearances may be present ("indirect fragmentation"), or absent ("direct fragmentation"). When karyokinetic figures are found in fragmentation, they show themselves by an increase of chromatic substance, and by the appearance of chromatic loops and of granules in greater distinction and number; in all instances there is, however, in the case of "fragmentation" no indication of an equatorial arrangement, and in this consists the essential difference between fragmentation and segmentation. Further differences are shown in the more varying and irregular form of the chromosomes, which may appear as granules, threads, or bands. Arnold frequently found a band-like form of chromosome in the spleen. Again, the disposition of the chromosomes is irregular, not infrequently the polar arrangement is absent. Arnold leaves it undecided whether the typical longitudinal splitting always takes place. The nuclear membrane remains for a long time, and even in the earliest phases constrictions of the nucleus are observed.

As can be seen, fragmentation amounts essentially to a process of budding, as Arnold's drawings show. That this abnormal form of division, which results in a process of
budding, is especially frequent in pathological new formations, has already been repeatedly insisted upon by Virchow, e.g. 1857, in 'Arch. fur path. Anatom,' Bd. xi, p. 89, and especially in his article on stimulation and irritability ("Reizung und Reizbarkeit"), ibid., Bd. xiv, 1858, but this was undoubtedly without any knowledge of karyokinetic phenomena. Indirect and direct fragmentation are, according to J. Arnold, the forms of division most frequently met with in lymphoid cells, as well as in giant-cells. The giant-cells exhibit it both in the normal occurrence in marrow, as well as in their artificial culture after insertion of pieces of elder-pith into a lymphatic or into a serous body-cavity, as was done first (in connection with culture of giant-cells) by Bernhard Heidenhain (87) at my suggestion, and as has recently been carried out by Arnold in a very successful way. With regard to the giant-cells of marrow, Arnold's views have received contradiction from Denys, Cornil (49), and Fütteler (74). Denys (54) was unable to recognise the so-called "indirect fragmentation" of Arnold, i.e. fragmentation accompanied by mitotic phenomena. He finds either only a "direct division" (without either an increase or a change of chromatin) or a true mitosis (Arnold's "indirect segmentation") in which the nucleus, after the appearance of regular V-shaped chromatin loops, their longitudinal splitting, daughter-wreath, &c., divides into a large number of equal-sized daughter-nuclei, with corresponding segmentation of the cell. Denys was also unable to recognise the aberrant form described by Cornil. From the latter's figures of "direct division," we are reminded of a process of budding (Sprossungs-Vorgang), and I do not see why we should not retain this very descriptive and familiar name.

I have now to take up the question as to the relation of direct to indirect nuclear division. Are there, in fact, two different modes of division which have no intermediate stage, or is there only one fundamental form of nuclear division, which, like nearly all complicated organic processes, varies greatly under different circumstances, so that all the different changes represent only links in a chain, which can
all be derived from one fundamental form, or one from another? The regular, simple amitotic division would in the latter case be the first, and regular mitosis the final member of the series.

I must confess, as previously remarked, that even after Tangl's and Strasburger's objections, I cannot rid myself of the idea that nuclear division is a single process, with Remak's simple amitotic division as the fundamental form. The affirmative preparations of Pfitzner and Sattler are on my side, and even if an intermixture of nucleoplasm (Kernsaft) and cell-protoplasm takes place, the existence of the nucleus does not thereby become restricted to its chromatic constituents alone. On the other hand, we find, immediately after the reconstruction of the daughter-nuclei, the achromatic uniting with the chromatic constituents. Add to this the varied subforms, e.g. in Spirogyra, where the nuclear membrane disappears only after the formation of the spindle figure. Flemming, too, contributes similar observations, which he directs against the doctrine of the derivation of the spindle figure from the cell-protoplasm, as has been mentioned above. The recognised cases in various Protozoa of mitosis with retention of the nuclear membrane belong here. Arnold's observations, too, on mitotic segmentation and fragmentation must be here mentioned. Arnold himself (in a short publication) recognises subforms in mitotic fragmentation. I would interpret the facts in such a way that we have to regard as the fundamental form the simple amitotic division which is now proved for many cases; it always takes place where the nucleus either is poor in chromatin, or when it does not matter about strict bipartition of the chromatic material. Should the latter be required, then we shall find mitosis, since it is the most direct, most certain, and most simple manner in which an exact bipartition of chromatic substance is brought about. This may well be considered as the aim of karyokinesis.¹

As to this aim, see further below in the theoretical consideration of mitosis.

¹ See the repeatedly quoted memoirs of Carnoy, 'La cellule,' I, 'Arthropoda,' p. 395. 'Rapports entre les deux modes de division.'
Before I pass on to these considerations, some other abnormal forms of karyokinesis must be reviewed, and certain peculiarities brought together, which without a great digression could not well have been included within the compass of the previous descriptions. The process of cell-division must also have due consideration.

Sanfelice (176) describes a peculiar case of mitosis during spermatogenesis. An achromatic spindle is formed, at the two poles of which the chromatin is accumulated; then the latter separates from each pole in the form of a spherical body, and rests freely in the body of the cell; then division of the spindle takes place, and the reunion of each chromatic sphere with one half of the spindle follows; then the division of the cell occurs.

As to the important question about the cause of the movement of the chromatic loops from the equator to the poles (metakinesis), it should here be mentioned that E. van Beneden (23, 24) compares the thread structure of protoplasm with the fibrillar structure of muscular tissue. He considers the achromatic threads of the spindle figure as contractile, especially as he saw the small granules which compose them approach one another and then separate. He is of opinion that the threads of the spindle figure stand in connection with the pole bodies on the one hand, and with the chromatic threads on the other, so that the latter, by the contraction of the spindle-threads, will be drawn towards the poles. This opinion is also held by Boveri (34). E. van Beneden, especially, goes very closely into the structure of the protoplasm and nucleus in his often quoted memoir. Platner (161) holds similar views. I cite these views with especial reference to a question which is again giving rise to discussion, viz. what is the true element of the organism—is it the cell or the nucleus, or is it the most minute parts which were first named "microsomes" by Hanstein (86), (Mikrozymas, of Béchamp) and "granula" by Altmann (2)?

We find in Carnoy's works (46—48) no small divergencies from the hitherto described mode of karyokinesis. He was certainly the first to maintain that the longitudinal splitting
KARYOKINESIS AND ITS RELATION TO FERTILIZATION. 201

of the threads occurs not infrequently in daughter-nuclei. E. van Beneden had suggested it as very probable, since in fact he found the number of threads greater in them than it would be after a single longitudinal splitting. Flemming now corroborates this statement, but as to its significance Carnoy and Flemming differ considerably from one another, as I shall shortly show. It is further important that Carnoy has observed a true "cell-plate," in Strasburger's sense, in the formation of the so-called directive corpuscles. It follows, therefore, that the formation of the directive corpuscles is to be regarded as a true cell-division. Boveri comes to the same conclusion.

The chief results of Carnoy's observations, which would certainly find a larger circle of readers if they were published more briefly, and in a more widely-read journal, lie herein, that he enters a protest against the regularity of the so-called karyokinetic law laid down by Flemming (58). The karyokinetic process presents so many abnormalities that it is as yet impossible to lay down any sound general rule. At all events, none of the various phases present in karyokinesis appear essential; any may be omitted or may be changed. Carnoy repeats, in his last publication, 'La Cellule,' t. iii, p. 311, the saying, "Tous les phénomènes caryocytiques sont variables: aucun d'eux ne paraît essentiel."

It is difficult to admit this in regard to that most important phenomenon of karyokinesis, the longitudinal splitting, and the equal distribution of the sister-threads to the two poles, wherein the whole reason of karyokinesis appears to lie, for only in this way can the equal distribution of the chromatic substance to the two daughter-nuclei be considered as perfectly assured. This might also be possible by a symmetrical transverse division of the stronger threads at the equator, if it resulted in equal-sized portions; but this is difficult to establish by observation. Carnoy, in fact, admits this as a form of karyokinesis, e.g. in Astacus, Forficula, and Scolopendra ('La Cellule,' 1885, t. i, fasc. ii, p. 334). In many cases, according to him, the chromatic segments arrange themselves without a previous longitudinal splitting in the axis of the spindle.
figure, as long rods (Tonnenform, couronne à bâtonets of Carnoy), then follows the transverse division of these rods at the equator, and the separation of the two halves towards the daughter-poles. This is quite at variance with all previous conclusions. According to this statement the chromatic figure behaves just like the spindle figure.

According to Carnoy, too, a karyokinetic arrangement of chromatic threads at the two poles can occur without any longitudinal or equatorial transverse splitting, e.g. loc. cit., pl. v, fig. 178, in Clubionna (an Arachnid). A. Bolles Lee (32) has lately made the same statement for karyokinesis in the spermatogenesis of the Chætognatha. No longitudinal splitting of the equatorial chromatic elements (chromosomes) was seen in Forficula by La Valette St. George; on the contrary, his figures show a transverse division (see Festschrift für A. v. Kölliker, Taf. iii, figs. 35, 36, &c.). Prenant likewise makes similar statements. In all such processes equal distribution of the chromatic substance would be uncertain.

As we have already mentioned, Carnoy found that the longitudinal splitting, which he in nowise denies, may even occur during the stage of the formation of the daughter-nuclei. If this is true (Ascaris megalcephala, according to Carnoy), longitudinal splitting is of only a very subordinate value. Flemming (63) has recently taken up a determined position against this reduction of longitudinal splitting to a phenomenon of subordinate significance. He found in the spermatogenesis of Salamander an abnormal form, which appears at first sight to confirm Carnoy's assertion. But here longitudinal splitting of the threads occurs, at the commencement of karyokinesis, in the so-called spirem stage (see my previous figure). The two sister-threads remain connected so as to form an elongated ellipsoid, stretch themselves, and all the ellipsoids, greatly elongated, now arrange themselves in a "barrel figure" (couronne à bâtonets of Carnoy) around the equator of the spindle figure. The chromatic elements (Fäden, chromosomes) are, however, not simple primary rods, but ellipsoid rings, greatly drawn out, each of which consists of two sister-
KARYOKINESIS AND ITS RELATION TO FERTILIZATION.

threads, arising by longitudinal division, but remaining connected at their ends, and already clearly formed at an earlier stage. Compare with this van Beneden's statement (ante). When now transverse division takes place at the equator there is no difference from Flemming's principle of karyokinesis; and the longitudinal splitting described by Carnoy may take place in the Dyaster stage without prejudice to this principle, as van Beneden and Flemming show. This, therefore, is not the primary process, so significant for karyokinesis, but another and a secondary one, which perhaps has no general significance, since it has hitherto been observed only in a few cells (sexual cells). (Compare Weismann, 'Directive Corpuscles,' p. 39, et seq.)

In another deviation, which Flemming describes as the "homöotypic Form" (that is to say, "a form more like the usual one than the one just described, which he names 'heterotypic'"), it would appear as if Carnoy were correct in his assertion, that longitudinal splitting may be entirely absent. Even here, however, longitudinal splitting occurs in the spirem stage; the sister-threads quickly separate completely from one another, become short and thick, so that they resemble the primary threads (chromosomes), and might easily be mistaken for them. In this case no regular monaster is formed at the equator, but simultaneously with their formation some of the threads move towards the poles. The commencement of metakinesis coincides with the monaster form. Now, here in the formation of the daughter-nuclei, if one had not noticed the longitudinal splitting in the spirem stage, one might well suppose that a karyokinesis occurred without longitudinal splitting. Flemming is certainly right when he suggests, with that calmness and objectivity usual with him—which distinguishes all his works so favorably—that Carnoy has overlooked in his abnormal discovery the first longitudinal splitting. On the other hand, one cannot blame Carnoy if he does not admit this without more ado, but protests with vehemence, and claims that anyone who wishes to confute him must investigate the same objects which he did. Till this happens the dispute will not be ended. Indeed, I ought to add that suitable
objects should be chosen. It would be a good thing were scientific meetings, especially those of the recently founded German Anatomical Society, more utilised than hitherto for bringing to an end such differences, by an exhibition of the preparations concerned. I note, in opposition to Carnoy's idea, that Strasburger, in his latest memoir (191), agrees with Flemming in regarding longitudinal splitting of the mother-segments (chromosomes) and the separation of the threads arising from such splitting into two daughter-nuclei, as a general process, at least in the higher animals and plants, and as the highest point of mitotic nuclear division (loc. cit., p. 135).

Platner (161) indeed, like Carnoy, sometimes found in Lepidoptera a quite irregular separation of chromatin bodies without a previous formation of an equatorial plate, and without longitudinal division. Yet he will not decide whether this process must be regarded as normal or as an indication of degeneration of the cells concerned.

At all events we see that, in the present state of the case, most authors look upon Flemming's longitudinal splitting as the essential phenomenon of karyokinesis, and, as I believe I can say from my own researches, rightly.

Abnormal conditions are also briefly described by Oskar Schultze (183) in confirmation of the earlier work of Bellonci (16 b) in the segmentation of Axolotl. Here the thread-skein is not brought about by a direct transformation of the threads of the network, but by the appearance of small chromatin bodies (Pfizner's "Kornchen," O. Schultze) in the nuclear membrane, within which in this object the skein wholly lies; these later on unite and arrange themselves in a series of loops.

We have already mentioned that the nucleus, as well as the spindle figure arising from it, undergoes a change of position during the course of karyokinesis. This is especially distinct in the formation of the directive corpuscles (see Part II). The consideration of these things becomes very important in the study of egg segmentation. In reference to the influences coming into question here, Pflüger has alluded to the action of gravity, whilst O. Hertwig, in his memoir—"Welchen Einfluss übt die Schwer-
KARYOKINESIS AND ITS RELATION TO FERTILIZATION.

Kraft auf die Theilung der Zellen? Jena, 1884—rejects this, and suggests that the nucleus always endeavours to take up that position in the cell which corresponds to the centre of its sphere of action. In a perfectly spherical protoplasmic egg-cell this will be the centre; in a meroblastic egg, where the protoplasm, representing the sphere of action of the nucleus, rests like a cap on the yolk, it will lie in the geometric centre of this cap, and must extend itself in the spindle figure in the longitudinal direction of the protoplasm. Now since the division of the nucleus always takes place at right angles to the axis of the nuclear spindle, the position of the nucleus will determine, according to Hertwig's law, the direction of the division-plane in segmentation. Oskar Schultze (182, 183) has endeavoured to explain the peculiar position of the spindle figure during the formation of the directive corpuscles. I here refer the reader to his interesting description.

Finally, the re-establishment of the nucleoli in the daughter-nuclei, as well as the actual division of the cell, must be mentioned. As regards the former point, Strasburger (191) saw in the chromatic threads of the daughter-nuclei, and lying close to them, a number of small bodies make their appearance, which later on fuse together to form one or two larger nucleoli (Spirogyra). Meunier (136), in agreement with his previously published discovery, states that all the chromatin (nuclein) of the daughter-nucleus unites to form a nucleolus, which has a special membrane. I omit other accounts, only very scattered and poor, which exist in the literature as to nucleoli and their formation in karyokinesis, since they are not sufficient for us to form even an approximately definite opinion on the subject.

I mentioned above that cell-division usually occurs in the phase of the formation of the daughter-skein. As for the details about the phenomenon of cell-division, it may here be briefly stated that in animal cells, according to Flemming's description (58), a constriction of the cell-protoplasm occurs at the level of the equator of the spindle figure. At this time, as Rabl (165) has especially pointed out, the protoplasm distinctly exhibits two zones, an outer darker and an inner lighter one (see fig. 12).
The inner zone surrounds the nucleus, i.e. the daughter-nucleus, without a sharp outline. The constriction begins usually on one side, and, corresponding to it, a more highly refractive substance is perceptible, which persists during the subsequent separation, and stains more deeply with haematoxylin (see fig. 12). The process of division of the cell-substance must, as Rabl remarks, go on comparatively rapidly, since it commences with the daughter-skein stage, and is already finished before the resting stage of the daughter-nucleus is reached.

I have already pointed out, in describing the spindle figure, that in plant-cells separate knot-like thickenings occur on the threads at the equator. Moreover, the number of spindle-threads increases, and as the thickenings become crowded together, and extend outwards to the surface of the cell, there arises what Strasburger calls a "cell-plate," which later represents the "partition wall" between the two daughter-cells. Since, as already stated, such a wall is absent in animal cells, we do not find any formation of a cell-plate, or, at the most, only a trace of it, of which an account has already been given. Herein, therefore, is a difference between the issue of the process of cell-division in animals and plants. I repeat here, as said on p. 201, that, according to Carnoy's observation, during the formation of the directive corpuscles of Ascaris megalcephala a distinct cell-plate makes its appearance in the position of the above-described thickenings. In preparations which van Gehuchten showed me I was able to satisfy myself on this point.

Attempts to approach the striking phenomenon of karyokinesis from the theoretical side are, of course, not wanting. Excluding the writings of Bütschli (43), Fol (67), and Mark (131), who deal, on a broad basis, with the problem of cell-division and the physical forces to be taken into account the works of Roux (174), Pfitzner (153, 154), Carnoy (47), and Platner (161) must be mentioned. It can hardly be maintained that the theories suggested are good ones. It is always dangerous to theorise when the facts themselves are insufficient. Recent publications have shown that much is
still to be done in the investigation of matters of fact, and as
we know next to nothing as to the origin of the nuclear spindle
and polar rays (polar streaming), about their fate, about the
nuclear membrane, about the behaviour of nucleoplasm, about
the chemical and physical constitution of the chromatic and
achromatic substances, and as it is still an unsettled controversy
between the foremost authorities on the subject, Flemming
and Strasburger, as to how far the cell-body shares in karyo-
kinesis—since even the equatorial longitudinal splitting as a
typical phenomenon is disputed, we are not yet in a position to
formulate any well-founded theory about karyokinesis. Yet I
must oppose those who, like Brass (38, 39), Fraisse (69), and
Fol (68), would deny to the chromatic nuclear figure any
essential significance. Brass maintains that the chromatic
substance is simply nutritive material for the rest of the
nucleus and cell, which is stored up in the nuclear network in
order to be utilised for the life and maturation of the cell and
nucleus. To the clear plasma of the nucleus (Kernsaft) he
ascribes the most important active rôle in all the phenomena
of life of the cell and nucleus, especially during division. The
chromatic substances he regards as passive masses; they are
attracted by the two nuclear poles, and follow the movements
of the nucleoplasm. Certainly it would be an exaggera-
tion to regard the chromatic figure as the chief thing in
nuclear division, and to place the motive power in the substance
composing it. At the same time we must guard against the
error of denying to them their proper significance in nuclear
division. The facts brought forward, on which Brass depends,
do not in the least warrant his assumption. His statement
that in starved cells the chromatic nuclear figure is absent, or
if present is imperfect, does not appear to be universally true,
inasmuch as Rabl (165) found in a salamander, which had re-
mained for five months without nourishment, abundant chro-
matic substance in the division figure. If it is true, as Rabl says,
that a ground-plan of the chromatin-containing thread, with
polar and antipolar areas, persists even in a perfectly resting
nucleus, it is difficult to regard it as quite meaningless, and to
ascribe to the nucleoplasm alone the active rôle. The remarkable behaviour of the chromatic elements during fertilization must especially be referred to: but about these we shall speak in greater detail below.

Many things distinctly point to our regarding the poles of the spindle figure, as well as the attraction spheres of van Beneden (Richtungsonnen of Kultschitzky) as very significant points, we would prefer to say "centres," for karyokinetic phenomena: nearly all who have dealt with the subject have acknowledged this. But I would give a caution against lulling ourselves into the delusion that all the essentials are known, and that we can now, from this point of view, include the whole of the phenomena in a theory, and account for them uniformly. The very different views held by authors who all acknowledge the pole as full of significance, show that at present this is still impossible. With Flemming and Rabl I think that the time has not yet come when we can formulate a satisfactory theoretical conception of karyokinesis.

There is one point referred to by Rabl (165) which I must not leave unmentioned, and I connect with it a circumstance already emphasised. If it is true, as Rabl states, that even in the resting nucleus the main threads are present in typical form (see figs. 2, 3, 4, 12), then we must acknowledge that the total change of form of the karyokinetic figure may be simply a question of dividing the thread-substance between the two new cells with rapidity and strict equality. One can scarcely imagine a simpler solution of this problem than the method used by nature in karyokinesis, viz. the appearance of polar and antipolar areas in the resting nucleus, the typically-arranged chief threads drawing in their constituents emitted in the form of processes, and nucleoli; then their arrangement in a very regular figure, gathering themselves in the middle (division-plane) of the nucleus (mother-nucleus): each (mother) thread or chromosome dividing along itself into two daughter-threads; the two daughter-threads arising from one mother-thread simply separating from one another towards opposite
pores of the nucleus, in order to return to rest again with the
typical fundamental figure.¹

At present we cannot give an explanation of the variety of
form of karyokinetic figures: at least it is purely hypothetical,
when Carnoy (loc. cit., p. 402) suggests as the aim of karyo-
kinesis, that it leads to the restoration of the dicentricity of
the cell, that it renders possible a complete regeneration of
nuclear constituents, and imports into the cell-protoplasm new
plastin elements. It is still difficult to understand polar star-
formation and the spindle figure: the attention of future
workers will have to be concentrated particularly on these.

That the nuclear membrane disappears seems quite intel-
ligible, when we consider that such an envelope would be a
decided hindrance to a division of the totality of the nucleus.
This, too, is a point which requires further explanation, espe-
cially as we do not yet even know correctly what happens to
the nuclear membrane.

It is clear from what has just been said that the theoretical
appreciation of karyokinetic phenomena is still in an unsatis-
factory position, and that no particular significance can be
assigned to its details. On the other hand, they seem to have
significance in relation to some other facts, as has been already
pointed out.—I mean in all questions dealing with the
phenomena of proliferating new formations (Neubild-
dungen) and regeneration in plants and animals.

Formerly, if we wished to ascertain what cellular element was
concerned in such a process, from what particular point and
what special cells, for example, the normal growth or rege-

¹ For plant-cells, Strasburger in his latest memoir (191) lays it down as a
general occurrence that the chromatic loops consist of thick tub-shaped
"chromatin-scheiben," regularly alternating with thin "linin-scheiben."  
During the process of karyokinesis, as in a passage from a resting to a
kinetic form, the chromatin granules are seen to gradually approach and fuse
to form the "scheiben," thereby the mass of chromatin is increased, whilst
that of the connecting linin decreases. The reverse takes place in the forma-
tion of daughter-nuclei. Strasburger is of opinion that this regular storage of
chromatin, preceding the longitudinal splitting of the threads, is a contrivance
for the closest possible halving of it in division.
eration of a tissue proceeded, one could only address oneself to the discovery of constricted cells and nuclei, or of bi- and multi-nucleated cells. The conclusions from such a discovery were, however, in many cases of a doubtful nature, especially as the question would be raised, whether generally bi- or multi-nucleate cells can give proof of cell-division taking place. By means of karyokinesis we have obtained a good basis for conclusive judgment about these important matters: and since the karyokinetic phenomena take place so obviously and definitely, the research is considerably facilitated. The above-mentioned works of Flemming (60), and A. Kollmann (110), the works of Kolliker (107), Altmann (1), Merk (135), Podwyssotzki (162), Bizzozero and Vassale (29), Rauber (168), and others, the researches carried on in my laboratory by Koganei (109), Uskow (198), Simanowsky (187), Beltzow (17), and Biondi (26), show how karyokinesis may be fruitfully utilised in this direction. I must here especially refer to the researches on the origin and growth of neoplasms, and the cellular products of inflammation, upon which we have already memoirs from Homén, Klemensiewicz, Eberth, Mayzel, J. Arnold, Ostry, Unna, Beltzow, Simanowsky and others (see the Bibliography given by J. Arnold (4) and Schottländers (181a).

Notwithstanding the short time during which we have known something of karyokinesis, we are already, according to the old German custom, which other scientific nations are beginning to imitate, familiar with a goodly store of different nomenclatures. Of these I must here briefly explain the most common so far as they have not already been mentioned. If one is speaking of the whole body of a cell (without the nucleus) one uses the term "cell-substance" (Zellleib, Zellkörper, Zellsubstanz). In this two chief constituents are to be distinguished, which were called by Kupffer by the name of "protoplasma" and "para-plasma." By the first he meant the more solid mass of the cell-substance, the arrangement of which in threads, whether with or without a network, has recently been recognised, thanks to the researches of Heitzmann, Fromman (73), Kupffer, Flemming,
Karyokinesis and Its Relation to Fertilization. 211

Leydig (126), and others. Flemming has proposed for it the terms “Filarmasse” or “Mitom,” Hanstein and Strasburger would speak of it as “Cytohyaloplasma,” and Leydig as “Substantia opaca.”

Kupffer’s “paraplasma” comprises the more fluid substance of the cell-body, which fills up the spaces between the network of the protoplasm (Mitom); its synonyms are “Interfilarmasse,” or “Paramitom” (Flemming), “Substantia hyalina” (Leydig), “Cytochylema” (Strasburger). The last, however, distinguishes in cytochylema two different constituents, “plasmo-chym” and “cytochym,” since he understands by “plasmo-chym” the thick fluid albuminous substance of the cell-body, and by “cytochym” the more watery sap, which is present in the so-called vacuoles of plant-cells.

We have already mentioned the usual names for the constituents of the nucleus. In reference to Strasburger’s nomenclature it must be added that he calls the nuclear network (Gerüst) by the name of “Kernprotoplasma,” or “Nucleoplasma.” It consists of a hyaline ground substance, “nucleohyaloplasma,” with the Balbiani-Pfitzner chromatin spherules embedded in it, which, as mentioned above, are called by Strasburger “Nucleo-mikrosomes.” To the nuclear sap (Kernsaft) which fills the spaces in the Nucleohyaloplasma he gives the name “Nucleochylema.” When, as is often the case, mikrosomes are present in the thread-network of cytohyaloplasma, these would be named “cyto-mikrosomes.”

With reference to the name “Mitom,” Flemming has proposed the name “Karyomitosis” for Schleicher’s term “Karyokinesis,” as we mentioned at the beginning. By the name “Kernspindel” Flemming and Pfitzner mean the achromatic spindle figure, which Strasburger in his recent work (191) adopts. The “Kernplatte” is Strasburger’s name for the mother-star arrangement of chromatic threads (v. fig. 7). Strasburger prefers to use the name “Kernplatte” instead of Flemming’s “Monaster” or “Mutterstern” (mother-star), for the condition seen in plants, since there is frequently no distinct star arrangement, but in the middle of the so-called star
(aster), closely-packed loops appear, so that when seen from the pole it does not present the form of a star, with an empty centre, but resembles a plate made up of threads closely collected together in one plane. We have already explained what is meant by “Aequatorialplatte” and “Metakinesis” (see especially the remarks on pp. 177, 178). Finally, it should be mentioned that Strasburger has recently used the name “prophase” for all the karyokinetic phenomena, up to the longitudinal splitting of the threads; “metaphase” for the stage of division itself up to the complete separation of the daughter-threads; and “anaphase” for the remainder of the phenomena, up to the establishment of the resting daughter-nuclei. For the star figures of the cell-body, the so-called “Polstrahlungen,” (polar rays), we may with Flemming use the term “Cytaster” (helioma, aureola) ; for that of the nucleus, i.e. the spindle figure (Kernspindel, in Flemming’s sense), the name “Karyaster.”

Carnoy used the name “Cytodiérèse” (after Henneguy (92)), for cell division.

Strasburger (192) now arranges the course of phenomena during mitosis for the higher plants—essentially in agreement with Flemming—in the following way:

I. Prophase.
1. Network of the resting nucleus.
2. Dense skein or coil.
3. Loose skein or coil.
4. Displacement towards the nuclear plate.
5. Nuclear plate (equatorial plate—mother-star).

II. Metaphase.

III. Anaphase.
7. Star (daughter-star, dyaster).
8. Loose (daughter-) coil.
9. Denser (daughter-) coil.
KARYOKINESIS AND ITS RELATION TO FERTILIZATION. 213

Carnoy uses the terms:
Aster = 2. Couronne équatoriale.
Metakinesis = 3. Ascension polaire.
Dyaster = 4. Couronnes polaires.
Dispirem = 5. Reconstitution du noyau.

It is, however, desirable that in the classification of the mitotic processes in different stages the most important of them—the longitudinal splitting of the segments, and the appearance of the nuclear spindle,—should have separate places. They may perhaps be grouped as follows, so as to obtain a classification suitable to all cases:

A.  I. Resting mother-nucleus.
    II. Mother-coil (spirem).
    III. Splitting of the loops and spindle-stage.
    IV. Mother-star (monaster).
B.  V. Metakinesis.
C.  VI. Daughter-stars (dyaster).
    VII. Daughter-coils (dispirem).
    VIII. Resting daughter-nuclei.

A couple of words must be added in explanation of this suggested grouping.

All workers agree that the resting stage is followed by another, which shows the chromatin arranged in the form of distinct threads. Like the words “Knäuelstadium” or “Mutterknäuel” (skein-stage, mother-skein), “Spirem” does not prejude anything as to whether there is one thread only or numerous threads, which at first appear inextricably intertwined. It does not appear to me to be necessary to speak of a denser or a looser coil or skein. On the other hand, it is incontestably very important that in the further course of mitosis distinctly separate segments (chromosomes) in the form of rods or loops arise; that these undergo a longitudinal splitting, and that the nuclear spindle figure makes its appearance at this stage.
We certainly know that the longitudinal splitting may occur either sooner or later, that it may not occur till the mother-star is formed, but it always takes place between the first appearance of a distinct skein and the complete mother-star. We know further, especially from Strasburger's last memoir, that probably in most cases numerous threads are present even in the resting nucleus and the skein stage, perhaps always the same in number as the distinct segments which are seen later on. Nevertheless, one cannot, in the skein stage, distinctly separate the different segments from one another. It is undisputed that, in all cases, between the skein- and the mother-star-stage phases the separate segments (chromosomes) stand out very distinctly, usually in the form of loops, and that at the same time that important phenomenon, the nuclear spindle makes its appearance. These are the grounds which induce me to choose the most important processes instead of the "loose-skein stage," and the stage of "displacement towards the nuclear plate," for signalizing corresponding phases of mitosis, and to speak of "the splitting of the loops and spindle-formation stage."

The words "Kernplatte," "Aequatorialplatte," do no good in many cases; in my opinion Flemming's "Mutterstern" (monaster, mother-star), or even "Aequatorialstern" ("couronne équatoriale" of Carnoy), recommend themselves more. Instead of "Metakinese," which is not clear in its meaning without something in addition, probably "Trennungs-stadium" (separation-stage) would be better. This would hold for every case, even if, as in Spirogyra, for example, no special change of position or form occurs. In regard to nomenclature compare Flemming's paper, "Zur Orientirung über die Bezeichnung der verschiedenen Formen von Zell- und Kerntheilung," 'Zool. Anziger,' 1886, No. 216.

(To be continued.)