passes through a spireme-stage, breaks into very short rod-shaped chromosomes which split lengthwise and arrange themselves in the equator of the spindle, while the nuclear membrane fades away. *Noctiluca* (Fig. 42), as shown by Ishikawa and Calkins, agrees with this in the main points; but the nuclear membrane does not at any period wholly disappear, and a distinct centrosome is found at the centre of the sphere. The latter body, which is very large, gives
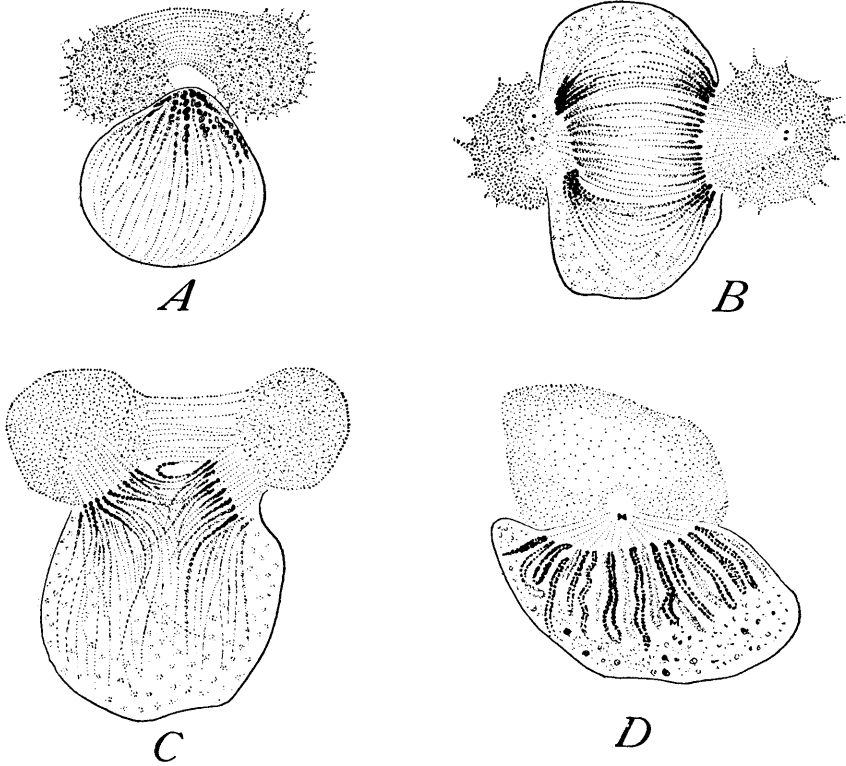


Fig. 42. — Mitosis in *Noctiluca*. [CALKINS.]

*A*. Prophase; division of the sphere to form the central spindle; chromosomes converging to the nuclear pole. *B*. Late anaphase, in horizontal section, showing centrosomes; the central spindle has sunk into the nucleus; nuclear membrane still intact except at the poles. *C*. Early anaphase; mantle-fibres connected with the diverging chromosomes. *D*. Final anaphase (which is also the initial prophase of the succeeding division of spore-forming mitosis); doubling of centrosome and splitting of chromosomes.

rise by a division to a fibrillated central spindle, about which the nucleus wraps itself while mantle-fibres are developed from the sphere-substance and become attached to the chromosomes, the nuclear membrane fading away along the surface of contact with the central spindle (Calkins). Broadly speaking, the facts are similar in

the diatoms (*Surirella, t.* Lauterborn), where the central spindle, arising by a peculiar process from an extranuclear centrosome, (sphere?) sinks into the nucleus in a manner strongly suggesting that observed in *Noctiluca*.

In the interesting form *Paramœba*, as described by Schaudinn ('96, 1), the sphere (" Nebenkörper "), which is nearly as large as the nucleus, divides to form a central spindle, about the equator of which the chromatin-elements become arranged in a ring (Fig. 43); but no centrosome has yet been demonstrated in the sphere. *Paramœba* appears to differ from *Euglena* mainly in the fact that at the close of division the sphere is in the former left outside the daughter-nucleus and in the latter enclosed within it.[1] The connecting link is perfectly given by *Tetramitus*, where no morphological nucleus is formed, and the sphere lies in the general cell-substance (p. 92); and we could have no clearer demonstration that the extra- or intranuclear position of sphere or centrosome is of quite secondary importance. As regards the formation of the spheres (pole-plates) *Actinosphærium* (Figs. 44, 45) seems to show a simpler condition than any of the above forms, since no permanent sphere exists, and Brauer ('94) and R. Hertwig ('98) agree that the pole-plates are formed by a gradual accumulation of the achromatic substance of the nucleus at opposite poles.

A distinct centrosome (centriole?) in the interior of the sphere has thus far only been observed in a few forms (*Noctiluca, Actinosphærium*), and neither its origin nor its relation to the sphere has yet been sufficiently cleared up. Both Ishikawa ('94) and Calkins ('98, 2) somewhat doubtfully concluded that in *Noctiluca* the centrosomes arise within the nucleus, migrating thence out into the extranuclear sphere. With this agree R. Hertwig's latest studies on *Actinosphærium* ('98), the spindle-poles being first formed from the pole-plates (themselves of nuclear origin), and the centrosomes then passing into them from the nucleus. Hertwig reaches the further remarkable conclusion that the centrosomes arise as portions of the *chromatin-network* extruded at the nuclear poles (Fig. 45), first forming a spongy irregular mass, but afterward condensing into a deeply staining pair of granules which pass to the respective poles of the spindle. It is a remarkable fact that these centrosomes are only found in the two maturation-divisions, and are absent from the ordinary vegetative mitoses where the spindle-poles are formed by two cytoplasmic masses derived, as Hertwig believes, from the intranuclear plates. Schaudinn ('96, 3) likewise describes and clearly figures an intranuclear origin of the centrosome in buds of *Acanthocystis* (Fig. 41), which are derived by direct division of the mother-

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[1] *Cf.* Calkins, '98, 1, p. 388.

nucleus with no trace of a centrosome. In this same form, as described above, the ordinary vegetative mitoses are quite of the metazoan type, with a persistent extranuclear centrosome.

The history of the chromatin in the mitosis of unicellular forms shows some interesting modifications. In a considerable number of forms a more or less clearly marked spireme-stage precedes the formation of chromosomes (diatoms, Infusoria, dinoflagellates, *Euglypha*); in others, long chromosomes are formed without a distinct spireme-stage (*Noctiluca*). It has been clearly demonstrated that in some cases these chromosomes split lengthwise, as in Metazoa (*Noctiluca*,
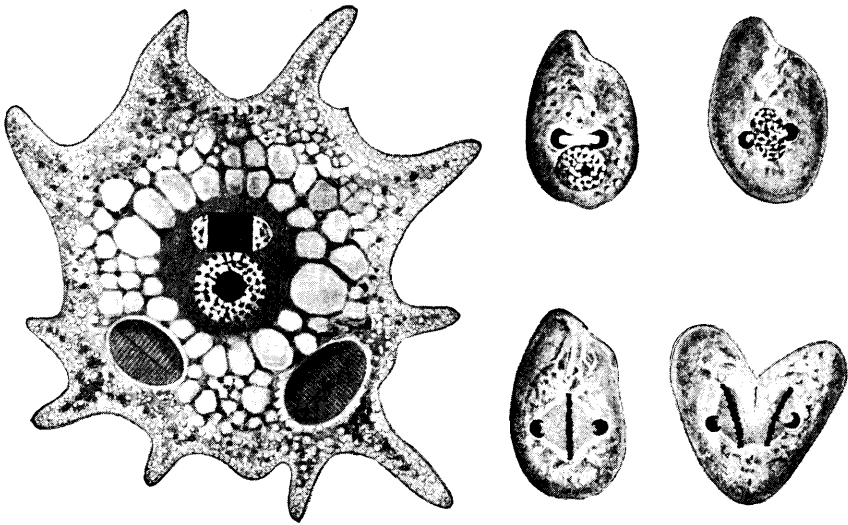


**Fig. 43.**— Mitosis in *Paramœba*. [SCHAUDINN.]
At the left, amœboid phase, showing nucleus and "Nebenkörper." At the right, four stages of division in the swarm-spores.

diatoms, *Actinophrys*, probably in *Euglypha*); but in some cases they are stated to divide transversely in the middle (Infusoria according to Hertwig, *Ceratium* according to Lauterborn). These chromosomes appear always to arise, as in Metazoa, through the linear arrangement of chromatin-granules (*Noctiluca*, *Actinosphærium*, *Euglena*), which themselves in many cases arise by the preliminary fragmentation of one or more large chromatin-masses (*e.g.* in *Noctiluca* or *Actinosphærium*). In other forms no such linear aggregates are formed, and -direct fission of the chromatin-granules appears to take place without the formation of bodies morphologically comparable with the chromosomes of such forms as *Noctiluca*. This is apparently the case in *Tetramitus*, and *Achromatium*, other forms having a distributed

nucleus,[1] and in such forms as *Chilomonas* and *Trachelomonas*, where the granules are permanently aggregated about a central body. Too little is known of the facts to justify a very positive statement; but on the whole they point toward the conclusion that in the simplest
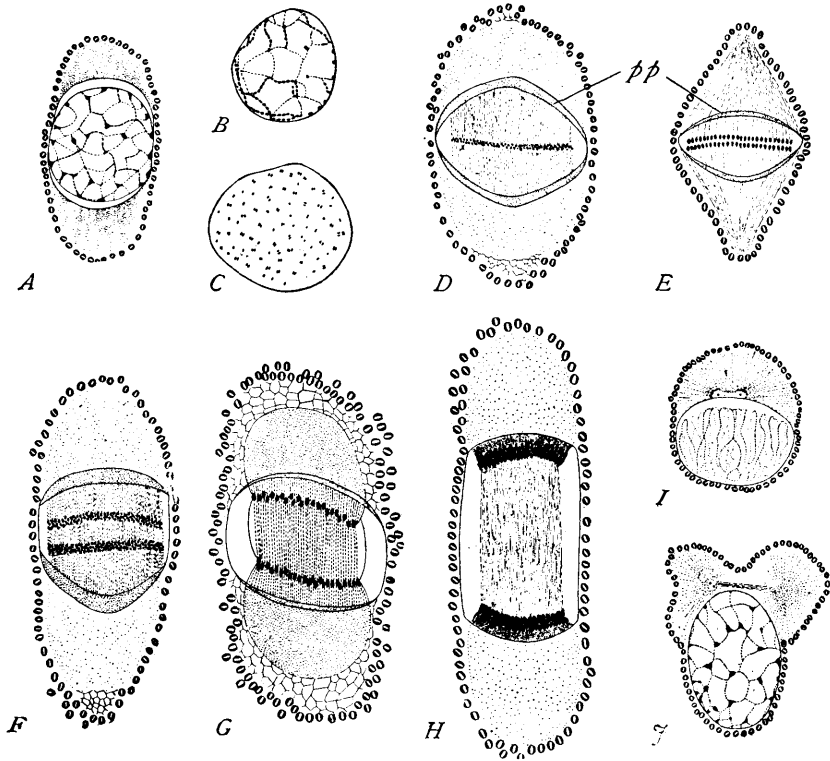


Fig. 44. — Mitosis in the rhizoped *Actinosphærium*. [BRAUER.]

A. Nucleus and surrounding structures in the early prophase; above and below the reticular nucleus lie the semilunar "pole-plates," and outside these the cytoplasmic masses in which the asters afterward develop. *B.* Later stage of the nucleus. *D.* Mitotic figure in the metaphase, showing equatorial plate, intra-nuclear spindle, and pole-plates (*p.p.*). *C.* Equatorial plate, viewed *en face*, consisting of double chromatin-granules. *E.* Early anaphase. *F. G.* Later anaphases. *H.* Final anaphase. *I.* Telophase; daughter-nucleus forming, chromatin in loop-shaped threads; outside the nuclear membrane the centrosome, already divided, and the aster. *J.* Later stage; the daughter-nucleus established; divergence of the centrosomes. Beyond this point the centrosomes have not been followed.

types of mitosis no true chromosome-formation occurs, thus sustaining Brauer's conclusion that the essential fact in the history of the chromatin in mitosis is the fission of the individual granules.[2]

[1] The fission of the individual granules is carefully described and figured by Schewiakoff in *Achromatium*.

[2] For speculations on the historical origin of the centrosome, etc., see p. 315.

### 4. *Pathological Mitoses*

Under certain circumstances the delicate mechanism of cell-division may become deranged, and so give rise to various forms of pathological mitoses. Such a miscarriage may be artificially produced, as Hertwig, Galeotti, and others have shown, by treating the dividing cells with poisons and other chemical substances (quinine, chloral, nicotine, potassic iodide, etc.). Pathological mitoses may, however,
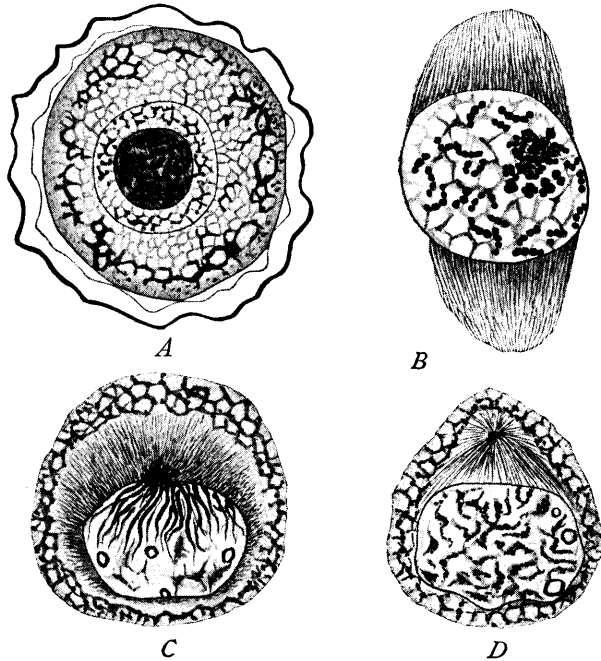


Fig. 45. — Mitosis in *Actinosphærium*. [R. HERTWIG.]

*A.* Encysted form, with resting nucleus; chromatin aggregated into large nucleolus-like body. *B.* prophase of division of the encysted form, showing chromosome-like bodies formed of granules, and spindle without centrosomes. *C.* Earlier prophase of the first maturation division, showing extrusion of chromatic substance to form the centrosome. *D.* Later stage, showing centrosome and aster.

occur without discoverable external cause; and it is a very interesting fact, as Klebs, Hansemann, and Galeotti have especially pointed out, that they are of frequent occurrence in abnormal growths such as cancers and tumours.

The abnormal forms of mitoses are arranged by Hansemann in two general groups, as follows: (1) *asymmetrical mitoses*, in which the chromosomes are unequally distributed to the daughter-cells, and (2) *multipolar mitoses*, in which the number of centrosomes is more than

H

two, and more than one spindle is formed. Under the first group are included not only the cases of unequal distribution of the daughter-chromosomes, but also those in which chromosomes fail to be drawn into the equatorial plate and hence are lost in the cytoplasm.

Klebs first pointed out the occurrence of asymmetrical mitoses in carcinoma-cells, where they have been carefully studied by Hanse-mann and Galeotti. The inequality is here often extremely marked, so that one of the daughter-cells may receive more than twice as much chromatin as the other (Fig. 46). Hansemann, whose conclu-
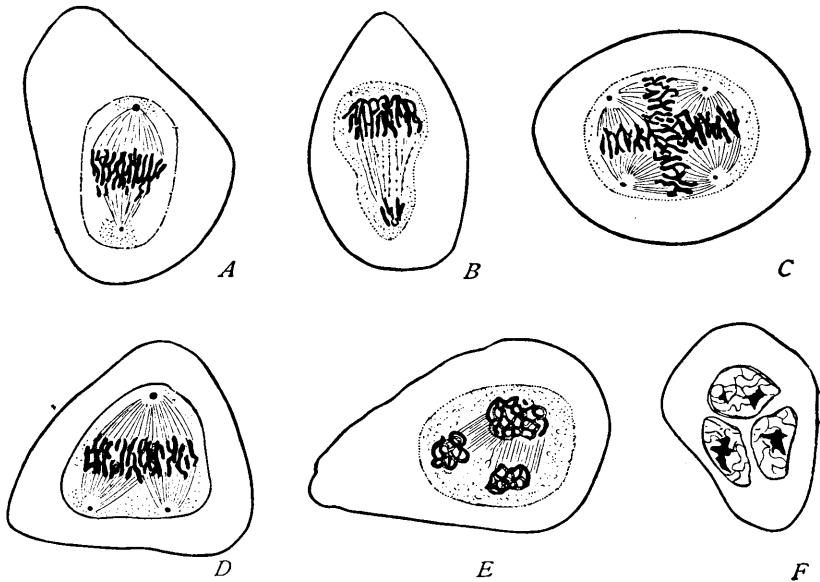


Fig. 46. — Pathological mitoses in human cancer-cells. [GALEOTTI.]

    A. Asymmetrical mitosis with unequal centrosomes. B. Later stage, showing unequal distri-
bution of the chromosomes. C. Quadripolar mitosis. D. Tripolar mitosis. E. Later stage.
F. Trinucleate cell resulting.

sions are accepted by Galeotti, believes that this asymmetry of mito-sis gives an explanation of the familiar fact that in cancer-cells many of the nuclei are especially rich in chromatin (hyperchromatic cells), while others are abnormally poor (hypochromatic cells). Lustig and Galeotti ('93) showed that the unequal distribution of chromatin is correlated with and probably caused by a corresponding inequality in the centrosomes which causes an asymmetrical development of the amphiaster. A very interesting discovery made by Galeotti ('93) is that asymmetrical mitoses, exactly like those seen in carcinoma, may be artificially produced in the epithelial cells of salamanders (Fig. 47) by treatment with dilute solutions of various drugs (antipyrin, cocaine, quinine).

Normal multipolar mitoses, though rare, sometimes occur, as in the division of the pollen-mother-cells and the endosperm-cells of flowering plants (Strasburger); but such mitotic figures arise through the union of two or more bipolar amphiasters in a syncytium and are due to a rapid succession of the nuclear divisions unaccompanied by fission of the cell-substance. These are not to be confounded with pathological mitoses arising by premature or abnormal division of the centrosome. If one centrosome divide, while the other does not, triasters are produced, from which may arise three cells or a trinucleated cell. If both centrosomes divide, tetrasters or polyasters are formed. Here again the same result has been artificially attained by chemical stimulus (*cf.* Schottländer, '88). Multipolar mitoses are
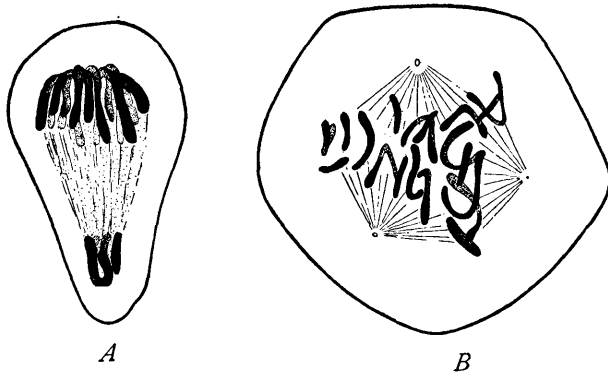


*A*          *B*

Fig. 47. — Pathological mitoses in epidermal cells of salamander caused by poisons. [GALEOTTI.]

*A.* Asymmetrical mitosis after treatment with 0.05 % antipyrin solution. *B.* Tripolar mitosis after treatment with 0.5 % potassic iodide solution.

also common in regenerating tissues after irritative stimulus (Ströbe); but it is uncertain whether such mitoses lead to the formation of normal tissue.[1]

The frequency of abnormal mitoses in pathological growths is a most suggestive fact, but it is still wholly undetermined whether the abnormal mode of cell-division is the cause of the disease or the reverse. The latter seems the more probable alternative, since normal mitosis is certainly the rule in abnormal growths; and Galeotti's experiments suggest that the pathological mitoses in such growths may be caused by the presence of deleterious chemical products in the diseased tissue, and perhaps point the way to their medical treatment.

[1] The remarkable polyasters formed in polyspermic fertilization of the egg are described at page 198.

## D.   The Mechanism of Mitosis

We now pass to a consideration of the forces at work in mitotic division, which leads us into one of the most debatable fields of cytological inquiry.
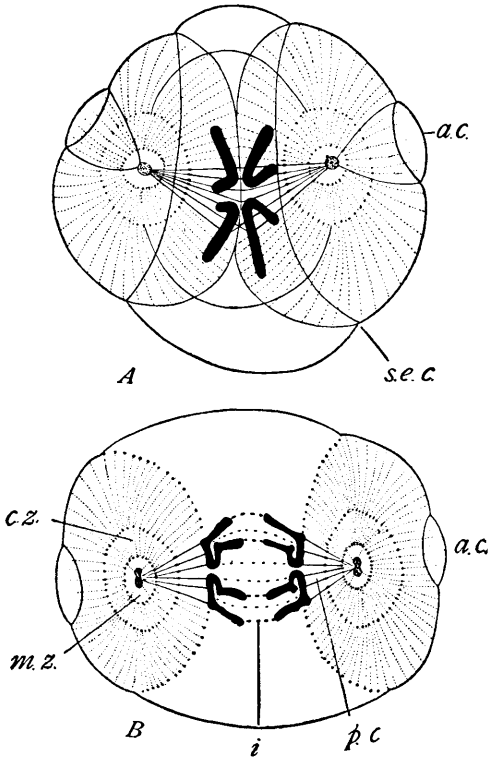


**Fig. 48.** — Slightly schematic figures of dividing eggs of *Ascaris*, illustrating Van Beneden's theory of mitosis. [VAN BENEDEN and JULIN.]

*A.* Early anaphase; each chromosome has divided into two.  *B.* Later anaphase during divergence of the daughter-chromosomes.  *a.c.* Antipodal cone of astral rays; *c.z.* cortical zone of the attraction-sphere; *i.* interzonal fibres stretching between the daughter-chromosomes; *m.z.* medullary zone of the attraction-sphere; *p.c.* principal cone, forming one-half of the contractile spindle (the action of these fibres is reënforced by that of the antipodal cone) ; *s.e.c.* subequatorial circle, to which the astral rays are attached.

1. *Function of the Amphiaster*

All observers agree that the amphiaster is in some manner an expression of the forces by which cell-division is caused, and many accept, in one form or another, the first view clearly stated by Fol,[1] that the asters represent in some manner centres of attractive forces focussed in the centrosome or dynamic centre of the cell. Regarding the nature of these forces, there is, however, so wide a divergence of opinion as to compel the admission that we have thus far accomplished little more than to clear the ground for a precise investigation of the subject; and the mechanism of mitosis still lies before us as one of the most fascinating problems of cytology.

(*a*) *The Theory of Fibrillar Contractility.* — The view that has taken the strongest hold on recent research is the hypothesis of *fibrillar contractility.* First suggested by Klein in 1878, this hypothesis was independently put forward by Van Beneden in 1883, and fully outlined

[1] '73, p. 473.

by him four years later in the following words : " In our opinion all the internal movements that accompany cell-division have their immediate cause in the contractility of the protoplasmic fibrillæ and their arrangement in a kind of radial muscular system, composed of antagonizing groups " (*i.e.* the asters with their rays). " In this system the central corpuscle (centrosome) plays the part of an organ of insertion. It is the first of all the various organs of the cells to divide, and its division leads to the grouping of the contractile elements in two systems, each having its own centre. The presence of these two systems brings about cell-division, and actively determines the paths of the secondary chromatic asters " (*i.e.* the daughter-groups of chromosomes) " in opposite directions. An important part of the phenomena of (karyo-) kinesis has its efficient cause, not in the nucleus, but in the protoplasmic body of the cell." [1] This beautiful hypothesis was based on very convincing evidence derived from the study of the *Ascaris* egg, and it was here that Van Beneden first demonstrated the fact, already suspected by Flemming, that the daughter-chromosomes move apart to the poles of the spindle and give rise to the two respective daughter-nuclei.[2]

Van Beneden's general hypothesis was accepted in the following year by Boveri ('88, 2), who contributed many important additional facts in its support, though neither his observations nor those of later investigators have sustained Van Beneden's account of the grouping of the astral rays. Boveri showed in the clearest manner that, during the fertilization of *Ascaris*, the astral rays become attached to the chromosomes of the germ-nuclei ; that each comes into connection with rays from both the asters ; that the chromosomes, at first irregularly scattered in the egg, are drawn into a position of equilibrium in the equator of the spindle by the shortening of these rays (Figs. 90, 147); and that *the rays thicken as they shorten.* He showed that as the chromosome splits, each half is connected only with rays (spindle-fibres) from the aster on its own side ; and he followed, step by step, the shortening and thickening of these rays as the daughter-chromosomes diverge. In all these operations the behaviour of the rays is

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[1] '87, p. 280.

[2] '83, p. 544. Van Beneden describes the astral rays, both in *Ascaris* and in tunicates, as differentiated into several groups. One set, forming the " principal cone," are attached to the chromosomes and form one-half of the spindle, and, by the contractions of these fibres, the chromosomes are passively dragged apart. An opposite group, forming the " antipodal cone," extend from the centrosome to the cell-periphery, the base of the cone forming the " polar circle." These rays, opposing the action of the principal cones, not only hold the centrosomes in place, but, by their contractions, drag them apart, and thus cause an actual divergence of the centres. The remaining astral rays are attached to the cell-periphery and are limited by a subequatorial circle (Fig. 48). Later observations indicate, however, that this arrangement of the astral rays is not of general occurrence, and that the rays often do not reach the periphery, but lose themselves in the general reticulum.

precisely like that of muscle-fibres; and it is difficult to study Boveri's beautiful figures and clear descriptions without sharing his conviction that "of the contractility of the fibrillæ there can be no doubt."[1]

Very convincing evidence in the same direction is afforded by pigment-cells and leucocytes or wandering cells, in both of which there is a very large permanent aster (attraction-sphere) even in the resting cell. The structure of the aster in the leucocyte, where it was first discovered by Flemming in 1891, has been studied very carefully by Heidenhain in the salamander. The astral rays here extend throughout nearly the whole cell (Fig. 49), and are believed
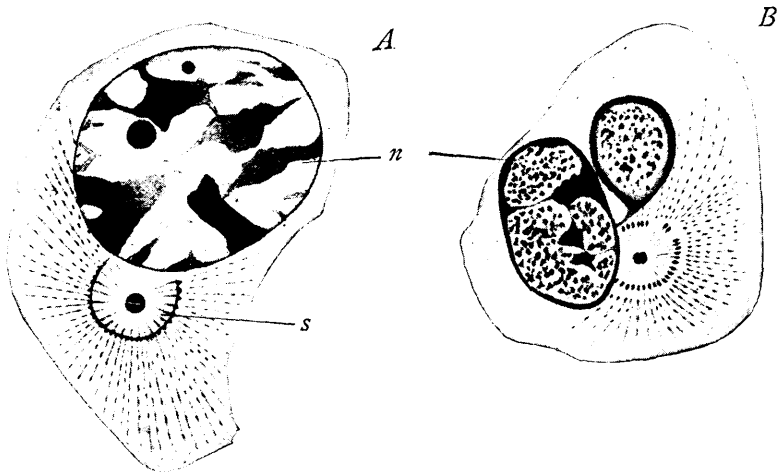


Fig. 49. — Leucocytes or wandering cells of the salamander.  [HEIDENHAIN.]

*A*. Cell with a single nucleus containing a very coarse network of chromatin and two nucleoli (plasmosomes) ; *s*. permanent aster, its centre occupied by a double centrosome surrounded by an attraction-sphere.  *B*. Similar cell, with double nucleus; the smaller dark masses in the latter are oxychromatin-granules (linin), the larger masses are basichromatin (chromatin proper).

by Heidenhain to represent the contractile elements by means of which the cell changes its form and creeps about. A similar conclusion was reached by Solger ('91) and Zimmermann ('93, 2) in the case of pigment-cells (chromatophores) in fishes. These cells have, in an extraordinary degree, the power of changing their form and of actively creeping about. Solger and Zimmermann have shown that the pigment-cell contains an enormous aster, whose rays extend in every direction through the pigment-mass, and it is almost impossible to doubt that the aster is a contractile apparatus, like a radial muscular system, by means of which the active changes of form are produced (Fig. 50). This interpretation of the aster receives additional support through Schaudinn's ('96, 3) highly interesting dis-

[1] '88, 2, p. 99.

covery that the "central granule" of the Heliozoa is to be identified
with the centrosome and plays the same *rôle* in mitosis (Fig. 41).
In these animals the axial filaments of the radiating pseudopodia con-
verge to the central granule during the vegetative state of the cell,
thus forming a permanent aster which Schaudinn's observations prove
to be directly comparable to that of a leucocyte or of a mitotic figure.
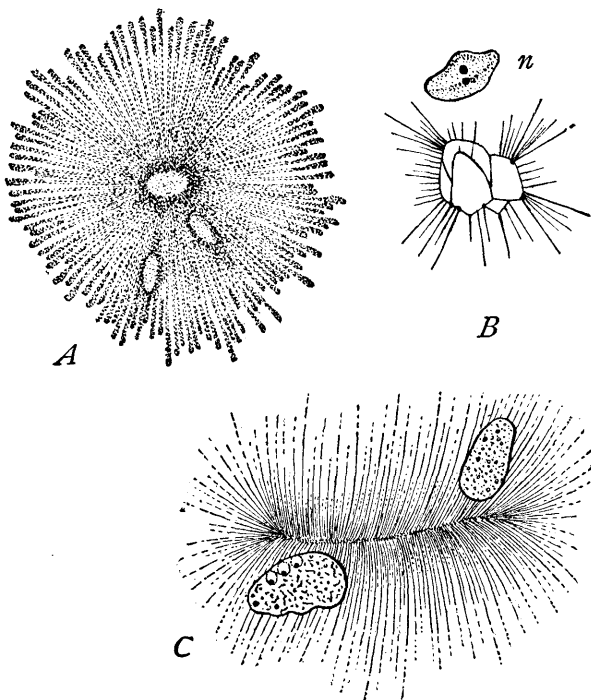There is in this case no doubt of the contractility of the rays, and a



Fig. 50. — Pigment-cells and asters from the epidermis of fishes.  [ZIMMERMANN.]

*A*. Entire pigment-cell, from *Blennius*.  The central clear space is the central mass of the aster
from which radiate the pigment-granules; two nuclei below.  *B*. Nucleus (*n*) and aster after ex-
traction of the pigment, showing reticulated central mass.  *C*. Two nuclei and aster with rod-
shaped central mass, from *Sargus*.

strong, if indirect, argument is thus given in favour of contractility in
other forms of asters.[1]  The contraction-hypothesis is beautifully
illustrated by means of a simple and easily constructed model, devised
by Heidenhain ('94, '96), which closely simulates some of the phenom-
ena of mitosis.  In its simplest form the model consists of a circle,
marked on a flat surface, to the periphery of which are attached at equal

[1] For an interesting discussion and development of the contraction-hypothesis see
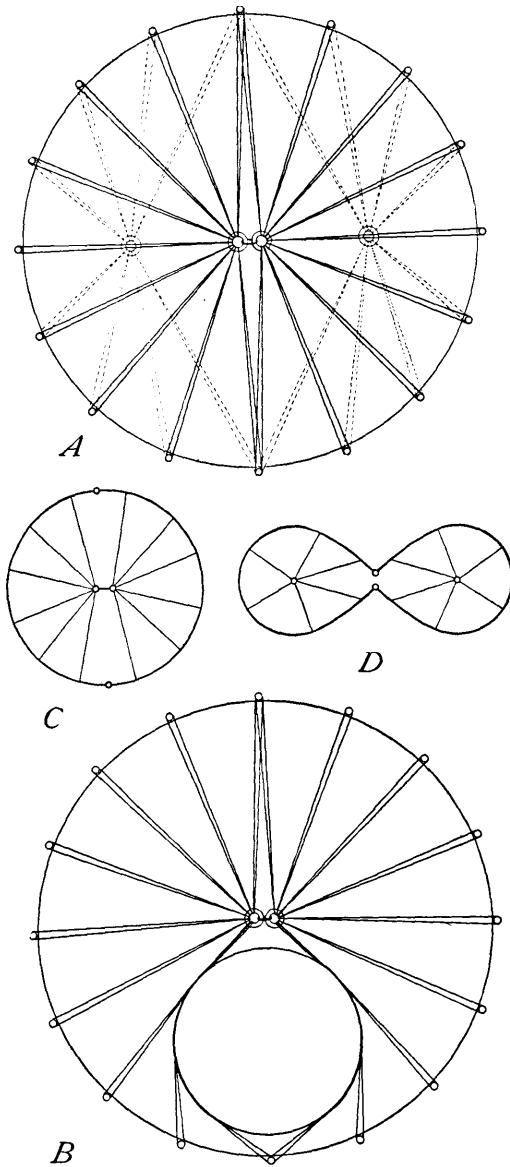Watasé, '94.

Fig. 51. — Heidenhain's model of mitosis (mainly from HEIDENHAIN).

*A.* Dotted lines show position of the rays upon severing connection between the small rings. *B.* Position upon insertion of "nucleus." *C. D.* Models with flexible hinged hoops, showing division.

intervals a series of rubber bands (astral rays). At the other ends these bands are attached to a pair of small rings (centrosomes) fastened together. In the position of equilibrium, when the rays are stretched at equal tension, the rays form a symmetrical aster with the centrosomes at the centre of the circle (Fig. 51, *A*). If the connection between the centrosomes be severed, they are immediately dragged apart to a new position of equilibrium with the rays grouped in two asters, as in the actual cell (dotted lines in Fig. 51, *A*). If a round pasteboard box of suitable size (nucleus) be inserted between two of the rays, it assumes an eccentric position, the cell-axis being formed by a line passing through its centre and that of the pair of small rings (*cf.* the epithelial cell, p. 57), and upon division of the aster it takes up a position between the two asters. In a second form of the models the circle is formed of two half rings of flexible steel, joined by hinges; the divergence of the small rings is here accompanied by an elongation and partial constriction of the model

in the equatorial plane; and if, finally, the hinge-connection be re-
moved, each half of the ring closes to form a complete ring.[1]

Heidenhain has fully worked out a theory of mitosis based upon
the analogy of these pretty models. The astral rays of the cell
("organic radii") are assumed to be in like manner of equal length
and in a state of equal tonic contraction or tension, the centrosome
forming the common insertion-point of the rays, and equilibrium of
the system being maintained by turgor of the cell. Upon disappear-
ance of the nuclear membrane and division of this insertion-point, the
tension of the rays causes divergence of the centrosomes and forma-
tion of the spindle between them, and by further contraction of the
rays both the divergence of the daughter-chromosomes and the division
of the cell-body are caused. A new condition of equilibrium is thus
established in each daughter-cell until again disturbed by division of
the centrosome.[2] In some cases (leucocytes) the organic radii are
visible at all periods. More commonly they are lost to view by
breaking up into the cell-reticulum, without, however, losing their
essential relations.

No one who witnesses the operation of Heidenhain's models can
fail to be impressed with its striking simulation of actual cell-division.
Closer study of the facts shows, however, that the contraction-hypothe-
sis must be considerably restricted, as has been done by the successive
modifications of Hermann ('91), Drüner ('95), and others. Hermann,
to whom the identification of the central spindle is due, pointed out
that there is no evidence of contractility in the central spindle-fibres,
which elongate instead of shorten during mitosis; and he concluded
that these fibres are non-contractile supporting elements, which form
a basis on which the movements of the chromosomes take place. The
*mantle-fibres* are the only contractile elements in the spindle, and it
is by them that the chromosomes are brought into position about the
central spindle and the daughter-chromosomes are dragged apart.[3]
Drüner ('95) still further restricts the hypothesis, maintaining that the
progressive divergence of the spindle-poles is caused not by contrac-
tion of the astral rays ("polar fibres"), as assumed by Heidenhain
(following Van Beneden and Boveri), but by an active growth or
elongation of the central spindle, which goes on throughout the
whole period from the earliest prophases until the close of the ana-
phases. This view is supported by the fact that the central spindle-

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[1] In a modification of the apparatus devised by Rhumbler ('97), the same effect is pro-
duced without the hinges.

[2] *Cf.* p. 57. For critique of this hypothesis, see Fick ('97), Rhumbler ('96, '97), and
Meves ('97, 4).

[3] Belajeff ('94) and Strasburger ('95) have accepted a similar view as applied to mitosis
in plant-cells.

fibres are always contorted during the metaphases, as if pushing
against a resistance; and it harmonizes with the facts observed in
the mitoses of infusorian nuclei, where no asters are present. This
view has been accepted, with slight modifications, by Flemming,
Boveri, Meves, Kostanecki, and also by Heidenhain. A nearly
decisive argument in its favour is given by such cases as the polar
bodies, or the mitosis of salamander spermatocytes as described by
Meves ('96, '97, 3), where the spindle-poles are pushed out to the
periphery of the cell, the polar astral rays meanwhile nearly or quite
disappearing (Fig. 130). This not only strongly indicates the push
of the central spindle, but also shows that the assumption of a pull
by the polar rays is superfluous. But beyond this both Drüner and
Meves have brought arguments against contractility in the other
astral rays, endeavouring to show that these, like the spindle-fibres,
are actively elongating elements, and that (Meves, '97, 3) the actual
grouping of the rays during the anaphases is such as to suggest that
even the division of the cell-body may be thus caused. A pushing
function of the astral rays is also indicated by infolding of the nuclear
membrane caused by the development of the aster as described by
Platner, Watasé, Braus, Griffin, and others.[1] The contraction-hypothe-
sis is thus restricted by Drüner and Meves to the mantle-fibres
alone, though many others, among them Flemming and Kostanecki,
still accept the contractility of the astral rays.

(b) *Other Facts and Theories.* — Even in the restricted form indi-
cated above the contraction-hypothesis encounters serious difficulties,
one of which is the fact urged by me in an earlier paper ('95), and
subsequently by Richard Hertwig ('98), that in the eggs of echino-
derms and many other dividing cells the daughter-chromosome
plates, extending through the whole substance of the spindle,
wander to the extreme ends of the spindle — a process which
demands a contraction of the fibres almost to the vanishing point,
while in point of fact not even a shortening and thickening of
the fibres can be seen (Fig. 52). Moreover, in these cases, no
distinction can be seen between central spindle-fibres and mantle-
fibres, and we can only save the contraction-hypothesis by the
improbable assumption that fibres indistinguishably mingled, and
having the same mode of origin, structure, and staining-reaction, have
exactly opposite functions. The inadequacy of the general theory
is sufficiently apparent from the fact that in amitosis cells many

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[1] *Cf.* p. 68. It should be pointed out that the originator of the pushing theory was
Watasé ('93), who ingeniously developed an hypothesis exactly the opposite of Van Bene-
den's, assuming both astral rays and spindle-fibres to be actively elongating fibres, dove-tailing
in the spindle-region, and pushing the chromosomes apart. This hypothesis is, I believe, in-
consistent with the phenomena observed in multiple asters and elsewhere, yet it probably
contains a nucleus of truth that forms the basis of Drüner's conception of the central spindle.

divide without any amphiaster whatever. In Infusoria mitosis seems to occur in the entire absence of asters, although the cells divide by constriction, and the analogy with Heidenhain's model entirely fails.
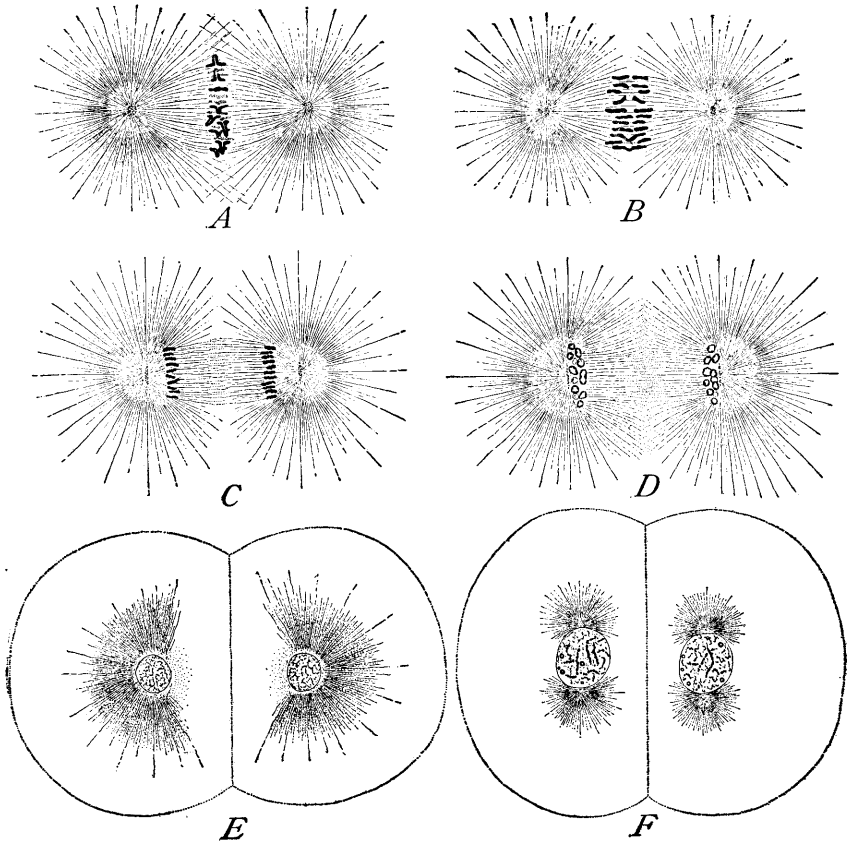


Fig. 52.— The later stages of mitosis in the egg of the sea-urchin *Toxopneustes* (*A–D*, × 1000; *E–F*, × 500).

*A*. Metaphase; daughter-chromosomes drawing apart but still united at one end. *B*. Daughter-chromosomes separating. *C*. Late anaphase; daughter-chromosomes lying near the spindle-poles. *D*. Final anaphase; daughter chromosomes converted into vesicles. *E*. Immediately after division, the asters undivided; the spindle has disappeared. *F*. Resting 2-cell stage, the asters divided into two in anticipation of the next division.

In Figs. *A* and *B* the centrosome consists of a mass of intensely staining granules, which in *C* and *D* elongates at right angles to the spindle-axis. In *F* the centrosome appears as a single or double granule, which in later stages gives rise to a pluricorpuscular centrum like that in *A*. The connection between *D* and *F* is not definitely determined.

In *Euglypha*, according to Schewiakoff (Fig. 39), division of the cell-body appears to take place quite independently of the mitotic figure. Again, a considerable number of cases are now known in which during the fertilization of the egg a large amphiaster is formed, with

astral rays sometimes extending throughout almost the entire egg,
only to disappear or become greatly reduced without the occurrence
of division, the ensuing cleavage being effected by a new amphiaster
or by the recrudescence of the old.[1]   For these and other reasons we
must admit the probability that contractility of the astral fibrillæ, if
it exists, is but the expression or consequence of a more deeply lying
phenomena of more general significance.   The subtlety of the prob-
lem is strikingly shown by Boveri's remarkable observations on
abnormal sea-urchin eggs ('96), which show (1) that the periodic
division of the centrosome and formation of the amphiaster may take
place independently of the nucleus; (2) that the spindle, as well as
the asters, is concerned in division of the cell-body; and (3) that an
amphiaster without chromosomes is unable to effect normal division
of the cell-body.   The first and third of these facts are shown by eggs
in which during the first cleavage all of the chromatin passes to one
pole of the spindle, so that one of the resulting halves of the egg
receives no nucleus, but only a centrosome and aster.   In this half
perfect amphiasters are formed simultaneously with each cleavage in
the other half, *yet no division of the protoplasmic mass occurs*.[2]   The
second fact is shown in polyspermic eggs, in which multipolar astral
systems are formed by union of the several sperm-asters (Figs. 53, 101).
In such eggs *cleavages only occur between asters that are joined by a
spindle*.   Normal cleavage of the cell-body thus requires the complete
apparatus of mitosis, and even though the fibres be contractile they
cannot fully operate in the absence of chromatin.

   We may now turn to theories based on the hypothesis, first sug-
gested by Fol in 1873, that the astral foci (*i.e.* centrosomes) represent
dynamic centres of attractive or other forces.   It should be noted that
this hypothesis involves two distinct questions, one relating to the
origin of the amphiaster, the other to its mode of action; and we have
seen that some of the foremost advocates of the contraction-hypothesis,
including Van Beneden and Boveri, have held the centrosomes to be
attractive centres.   Apart from the movements of the chromosomes,
the most obvious indication that the centrosomes are dynamic centres
is the extraordinary resemblance of the amphiaster to the lines of force
in a magnetic field as shown by the arrangement of iron-filings about
the poles of a horseshoe magnet — a resemblance pointed out by Fol
himself, and urged by many later writers,[3] especially Ziegler ('95)

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   [1] *Cf.* p. 213.

   [2] This result is opposed to Boveri's earlier work on *Ascaris* (p. 355), and is modified by
Ziegler ('98), who observed in a single case that an irregular cleavage occurred in the
enucleated half after two or three divisions of the centrosome.   On the other hand, it is sup-
ported by Morgan's convincing experiments on the eggs of *Arbacia* (p. 308).

   [3] *Cf.* the interesting photographic figures of Ziegler ('95).   A still closer *simulacrum* of
the amphiaster is produced by fine crystals of sulphate of quinine (a semiconductor) sus-

and Gallardo ('96, '97). It is impossible to regard this analogy as exact; first, because it is inconsistent with the occurrence of tripolar astral figures; second, as Meves has recently urged [1] the course of the astral fibres does not really coincide with the lines of force, the most important deviation being the crossing of the rays opposite the equatorial region of the spindle, which is impossible in the magnetic or electric field. We must, however, remember that the amphiaster is formed in a viscid medium, that it may perform various movements, and that its fibres probably possess the power of active growth. The
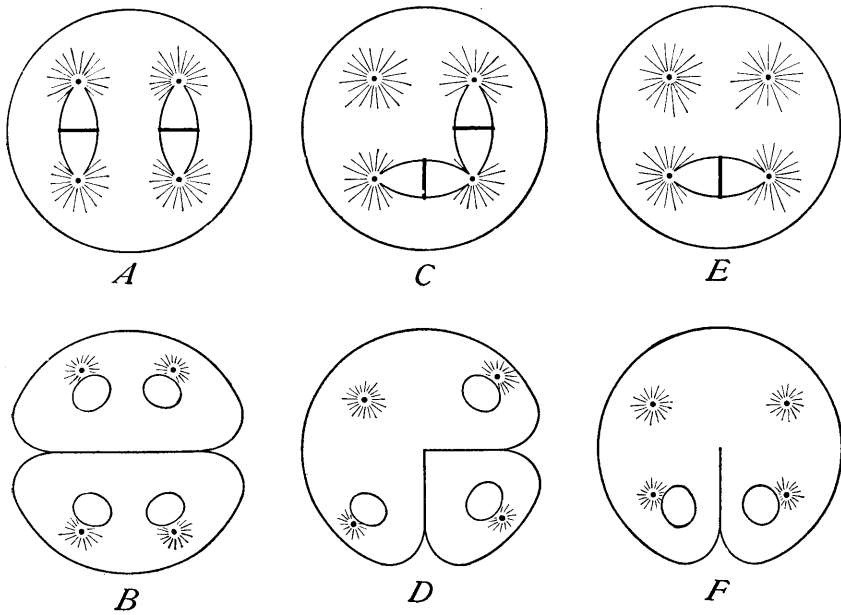


Fig. 53. — Division of dispermic eggs in sea-urchin eggs, schematic. [BOVERI.]

*A. C. E.* Eggs before division, showing various connections of the asters. *B. D. F.* Resulting division in the three respective cases, showing cleavage only between centres connected by a spindle.

physical or chemical effect of the centres, through which the amphiaster primarily arises, may thus be variously disturbed or modified in later stages, and the crossing of the rays is therefore not necessarily fatal to the assumption of dynamic centres. Bütschli ('92, '98) has, moreover, recently shown that a close *simulacrum* of the amphiaster, showing a distinct crossing of the rays, may be produced in an artificial alveolar structure (coagulated gelatine) by tractive forces cen-

pended in spirits of turpentine (a poor conductor) between two electric poles. This experiment, devised by Faraday, has recently been applied by Gallardo ('96, '97) to an analysis of the mitotic figure. [1] '96, p. 371.

tring in two adjacent points. This result is obtained by warming and
then cooling a film of thick gelatine-solution, filled with air-bubbles,
and then coagulating the mass in chromic acid. Such a film shows a
fine alveolar structure, which assumes a radial arrangement about the
air-bubbles, owing to the traction exerted on the surrounding structure
by shrinkage of the bubbles on cooling. The amphiastral *simulacra*
are produced about two adjacent bubbles, — a " spindle " being formed
between them, and the " astral rays " sometimes showing a crossing
like that seen in the actual amphiaster (Bütschli is himself unable to
explain fully how the crossing arises). The protoplasmic asters are
maintained by Bütschli to be, in like manner, no more than a radial
configuration of the alveolar cell-substance caused by centripetal
diffusion-currents toward the astral centres.[1]   The most interesting
part of this view is the assumption that these currents are caused by
*specific chemical changes taking place in the centrosome* which causes
an absorption of liquid from the surrounding region. " The astral
bodies are structures which, under certain circumstances, function in
a measure as centres from which emanate chemical actions upon pro-
toplasm and nucleus; and the astral phenomena which appear about
the centrosomes are only a result incidental to this action of the central
bodies upon the plasma."[2]   Through centripetal currents thus caused
arise the asters, and they may even account, in a measure, for the move-
ments of the chromosomes.[3]   This latter part of Bütschli's conception
is, I believe, quite inadequate; but the hypothesis of definite chemical
activity in the centrosome is a highly important one, which is sustained
by the staining-reactions of the centrosome and by its definite morpho-
logical changes during the cycle of cell-division.

More or less similar chemical hypotheses have been suggested by
several other writers.[4]   Of these perhaps the most interesting is
Strasburger's suggestion,[5] that the movements of the chromosomes
may be of a chemotactic character, which I suspect may prove to have
been one of the most fruitful contributions to the subject. Beside this
may be placed Carnoy's still earlier hypothesis ('85), that the asters
are formed under the influence of specific *ferments* emanating from
the poles of the nucleus. Mathews ('99, 2) has recently pointed out
that there is a considerable analogy between the formation of the
astral rays and that of fibrin-fibrils under the influence of fibrin-fer-
ment, adding the suggestion that the centrosome may actually contain

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[1] Carnoy ('85) and Platner ('86) had previously held a similar view, suggesting that not
only the spindle-formation, but also the movements of the chromosomes, might be explained
as the result of protoplasmic currents.

[2] '92, 1, p. 538.

[3] '92, 2, p. 160 ; '92, 3, p. 10.

[4] *Cf.* the first edition of this work, p. 77, also Ziegler ('95).          [5] '93, 2.

fibrin-ferment. Attention may be called here to the fact, now definitely
determined by experiment,[1] that cell-division may be incited by chemi-
cal stimulus. In most of the cases thus far experimentally examined
the divisions so caused are pathological in character, but in others
they are quite normal, as shown in Loeb's remarkable results on the
production of parthenogenesis in sea-urchin eggs by chemical stimulus,
as described at pages 215 and 308. While these experiments by no
means show that division is itself merely a chemical process, they
strongly suggest that it cannot be adequately analyzed without reckon-
ing with the chemical changes involved in it.

*Résumé.* A review of the foregoing facts and theories shows how
far we still are from any real understanding of the process involved
either in the origin or in the mode of action of the mitotic figure. The
evidence seems well-nigh demonstrative, in case of the mantle-fibres
and the astral rays, that Van Beneden's hypothesis contains an element
of truth, but we must now recognize that it was formulated in too
simple a form for the solution of so complex a problem. No satisfac-
tory hypothesis can, I believe, be reached that does not reckon with
the chemical changes occurring at the spindle-poles and in the nucleus ;
and these changes are probably concerned not only with the origin of
the amphiaster, but also with the movements of the chromosomes. In
cases where the centrosome persists from cell to cell we may perhaps
regard it as the vehicle of specific substances (ferments ?) which become
active at the onset of mitosis, and run through a definite cycle of
changes, to initiate a like cycle in the following generation ; and it is
quite conceivable that such substances may persist at the nuclear poles,
or may be re-formed there as an after-effect, even though the formed
centrosome disappears.[2] In this consideration we may find a clue to
the strange fact — should it indeed prove to be a fact — that the cen-
trosome may divide, yet afterward disappear without discoverable
connection with the centrosomes of the succeeding mitosis, as several
recent observers have maintained.[3] When all is said, we must admit
that the mechanism of mitosis in every phase still awaits adequate
physiological analysis. The suggestive experiments of Bütschli and
Heidenhain lead us to hope that a partial solution of the problem may
be reached along the lines of physical and chemical experiment. At
present we can only admit that none of the conclusions thus far
reached, whether by observation or by experiment, are more than the
first *naïve* attempts to analyze a group of most complex phenomena
of which we have little real understanding.

[1] See pp. 306, 308.     [2] *Cf.* p. 215.     [3] *Cf.* p. 213.

## 2. *Division of the Chromosomes*

In developing his theory of fibrillar contractility, Van Beneden expressed the view — only, however, as a possibility — that the splitting of the chromosomes might be passively caused by the contractions of the two sets of opposing spindle-fibres to which each is attached.[1] Later observations have demonstrated that this suggestion cannot be sustained; for in many cases the chromatin-thread splits before division of the centrosome and the formation of the achromatic figure — sometimes during the spireme-stage, or even in the reticulum, while the nuclear membrane is still intact. Boveri showed this to be the case in *Ascaris*, and a similar fact has been observed by many observers since, both in plants and in animals.
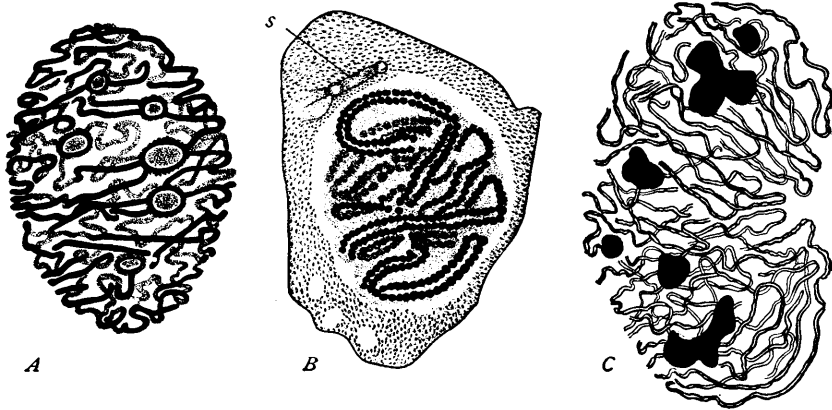


Fig. 54. — Nuclei in the spireme-stage.

*A*. From the endosperm of the lily, showing true nucleoli. [FLEMMING.]

*B*. Spermatocyte of salamander. Segmented double spireme-thread composed of chromomeres and completely split. Two centrosomes and central spindle at *s*. [HERMANN.]

*C*. Spireme-thread completely split, with six nucleoli. Endosperm of *Fritillaria*. [FLEMMING.]

The splitting of the chromosomes is therefore, in Boveri's words, "*an independent vital manifestation, an act of reproduction on the part of the chromosomes.*"[2]

All of the recent researches in this field point to the conclusion that this act of division must be referred to the fission of the chromatin-granules or chromomeres of which the chromatin-thread is built. These granules were first clearly described by Balbiani ('76) in the chromatin-network of epithelial cells in the insect-ovary, and he found that the spireme-thread arose by the linear arrangement of these granules in a single row like a chain of bacteria.[3] Six years later Pfitzner ('82) added the interesting discovery

[1] '87, p. 279.          [2] '88, p. 113.          [3] See '81, p. 638.

that during the mitosis of various tissue-cells of the salamander, the granules of the spireme-thread *divide by fission and thus determine the longitudinal splitting of the entire chromosome.* This discovery was confirmed by Flemming in the following year ('82, p. 219), and a similar result has been reached by many other observers (Fig. 54). The division of the chromatin-granules may take place at a very early period. Flemming observed as long ago as 1881 that the chromatin-
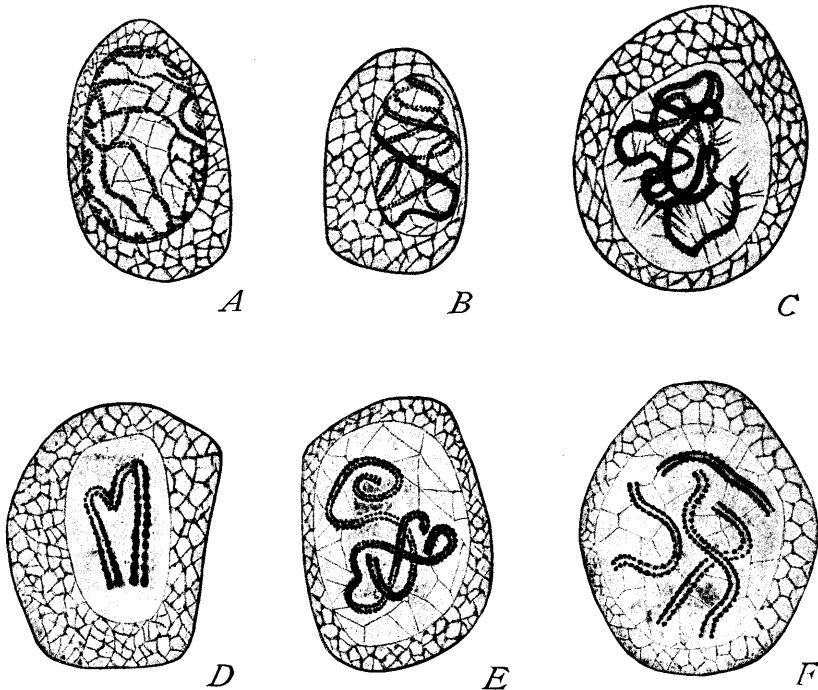


Fig. 55. — Formation of chromosomes and early splitting of the chromatin-granules in spermatogonia of *Ascaris megalocephala*, var. *bivalens*. [BRAUER.]

*A.* Very early prophase; granules of the nuclear recticulum already divided. *B.* Spireme; the continuous chromatin-thread split throughout. *C.* Later spireme. *D.* Shortening of the thread. *E.* Spireme-thread divided into two parts. *F.* Spireme-thread segmented into four split chromosomes.

thread might split in the spireme-stage (epithelial cells of the salamander), and this has since been shown to occur in many other cases; for instance, by Guignard in the mother-cells of the pollen in the lily ('91). Brauer's recent work on the spermatogenesis of *Ascaris* shows that the fission of the chromatin-granules here takes place even before the spireme-stage, when the chromatin is still in the form of a reticulum, and long before the division of the centrosome (Fig. 55). He therefore concludes: " With Boveri I regard the splitting as an

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independent reproductive act of the chromatin. The reconstruction of the nucleus, and in particular the breaking up of the chromosomes after division into small granules and their uniform distribution through the nuclear cavity, is, in the first place, for the purpose of allowing a uniform growth to take place; and in the second place, after the granules have grown to their normal size, *to admit of their precisely equal quantitative and qualitative division.* I hold that all the succeeding phenomena, such as the grouping of the granules in threads, their union to form larger granules, the division of the thread into segments and finally into chromosomes, are of secondary importance; all these are only for the purpose of bringing about in the simplest and most certain manner the transmission of the daughter-granules (Spalthälften) to the daughter-cells."[1]   " In my opinion the chromosomes are not independent individuals, but only groups of numberless minute chromatin-granules, which alone have the value of individuals."[2]

These observations certainly lend strong support to the view that the chromatin is to be regarded as a morphological aggregate — as a congeries or colony of self-propagating elementary organisms capable of assimilation, growth, and division. They prove, moreover, that mitosis involves two distinct though closely related factors, one of which is the fission of the chromatic nuclear substance, while the other is the distribution of that substance to the daughter-cells. In the first of these it is the chromatin that takes the active part; in the second it would seem that the main *rôle* is played by the amphiaster.

## E. Direct or Amitotic Division

### 1. *General Sketch*

We turn now to the rarer and simpler mode of division known as amitosis; but as Flemming has well said, it is a somewhat trying task to give an account of a subject of which the final outcome is so unsatisfactory as this; for in spite of extensive investigation, we still have no very definite conclusion in regard either to the mechanism of amitosis or its biological meaning. Amitosis, or direct division, differs in two essential respects from mitosis. First, the nucleus remains in the resting state (reticulum), and there is no formation of a spireme or of chromosomes. Second, division occurs without the formation of an amphiaster; hence the centrosome is not concerned with the nuclear division, which takes place by a simple constriction. The nuclear substance, accordingly, undergoes a divi-

[1] '93, pp. 203, 204.                    [2] *l.c.*, p. 205.

sion of its total *mass*, but not of its individual elements or chromatin-granules (Fig. 56).

Before the discovery of mitosis, nuclear division was generally assumed to take place in accordance with Remak's scheme (p. 63). The rapid extension of our knowledge of mitotic division between the years 1875 and 1885 showed, however, that such a mode of division was, to say the least, of rare occurrence, and led to doubts as to whether it ever actually took place as a normal process. As soon, however, as attention was especially directed to the subject, many cases of amitotic division were accurately determined, though
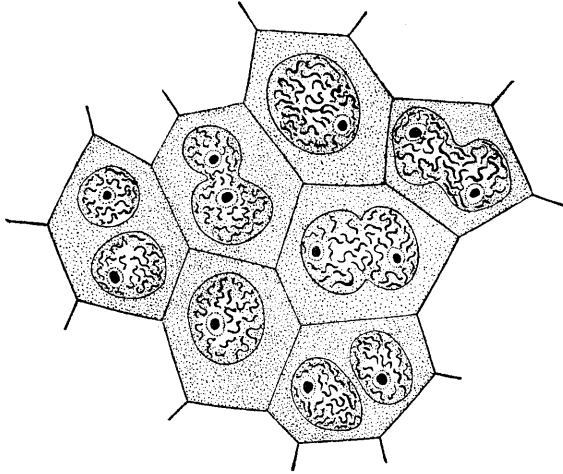


Fig. 56.— Group of cells with amitotically dividing nuclei; ovarian follicular epithelium of the cockroach. [WHEELER.]

very few of them conformed precisely to Remak's scheme. One such case is that described by Carnoy in the follicle-cells of the egg in the mole-cricket, where division begins in the fission of the nucleolus, followed by that of the nucleus. Similar cases have been since described, by Hoyer ('90) in the intestinal epithelium of the nematode *Rhabdonema*, by Korschelt in the intestine of the annelid *Ophryotrocha*, and in a few other cases. In many cases, however, no preliminary fission of the nucleolus occurs; and Remak's scheme must, therefore, be regarded as one of the rarest forms of cell-division (!).

## 2. *Centrosome and Attraction-sphere in Amitosis*

The behaviour of the centrosome in amitosis forms an interesting question on account of its bearing on the mechanics of cell-division. Flemming observed ('91) that the nucleus of leucocytes might in some cases divide directly without

the formation of an amphiaster, the attraction-sphere remaining undivided mean-
while.    Heidenhain showed in the following year, however, that in some cases
leucocytes containing two nuclei (doubtless formed by amitotic division) might
also contain two asters connected by a spindle.    Both Heidenhain and Flemming
drew from this the conclusion that direct division of the *nucleus* is in this case inde-
pendent of the centrosome, but that the latter might be concerned in the division
of the cell-body, though no such process was observed.    A little later, however,
Meves published remarkable observations that seem to indicate a functional activity
of the attraction-sphere during amitotic nuclear division in the "spermatogonia"
of the salamander.[1]    Krause and Flemming observed that in the autumn many
of these cells show peculiarly lobed and irregular nuclei (the "polymorphic nuclei" of
Bellonci).    These were, and still are by some writers, regarded as degenerating
nuclei.    Meves, however, asserts — and the accuracy of his observations is in the
main vouched for by Flemming — that in the ensuing spring these nuclei become
uniformly rounded, and may then divide amitotically.    In the autumn the attraction-
sphere is represented by a diffused and irregular granular mass, which more or less
completely surrounds the nucleus.    In the spring, as the nuclei become rounded,
the granular substance draws together to form a definite rounded sphere, in which
a distinct centrosome may sometimes be made out.    Division takes place in the
following extraordinary manner : The nucleus assumes a dumb-bell shape, while
the attraction-sphere becomes drawn out into a band which surrounds the central
part of the nucleus, and finally forms a closed ring, encircling the nucleus.    After
this the nucleus divides into two, while the ring-shaped attraction-sphere ("archo-
plasm") is again condensed into a sphere.    The appearances suggest that the ring-
shaped sphere actually compresses the nucleus and cuts it through.    In a later
paper ('94) Meves shows that the diffused "archoplasm" of the autumn-stage
arises by the breaking down of a definite spherical attraction-sphere, which is
re-formed again in the spring in the manner described, and in this condition the
cells may divide *either mitotically or amitotically.*    He adds the interesting observa-
tion, since confirmed by Rawitz ('94), that in the spermatocytes of the salamander
the attraction-spheres of adjoining cells are often connected by intercellular bridges,
but the meaning of this has not yet been determined.

It is certain that the remarkable transformation of the sphere into a ring during
amitosis is not of universal, or even of general, occurrence, as shown by the later
studies of Vom Rath ('95, 3).    In leucocytes, for example, the sphere persists in
its typical form, and contains a centrosome, during every stage of the division; but
it is an interesting fact that during all these stages the sphere lies on the concave
side of the nucleus in the bay which finally cuts through the entire nucleus.    Again,
in the liver-cells of the isopod *Porcellio,* the nucleus divides, not by constriction, as
in the leucocyte, but by the appearance of a nuclear plate, in the formation of which
the attraction sphere is apparently not concerned.[2]    The relations of the centro-
some and archoplasm in amitosis are, therefore, still in doubt; but, on the whole,
the evidence goes to show that they take no essential part in the process.


## 3.  *Biological Significance of Amitosis*

A survey of the known cases of amitosis brings out the following
significant facts.    It is of extreme rarity, if indeed it ever occurs in
embryonic cells or such as are in the course of rapid and continued

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[1] '91, p. 628.
[2] Such a mode of amitotic division was first described by Sabatier in the crustacea ('89),
and a similar mode has been observed by Carnoy and Van der Stricht.

multiplication. It is frequent in pathological growths and in cells such as those of the vertebrate decidua, of the embryonic envelopes of insects, or the yolk-nuclei (periblast, etc.), *which are on the way toward degeneration.* In many cases, moreover, direct nuclear division is not followed by fission of the cell-body, so that multinuclear cells and polymorphic nuclei are thus often formed. These and many similar facts led Flemming in 1891 to express the opinion that so far as the higher plants and animals are concerned amitosis is "a process which does not lead to a new production and multiplication of cells, but wherever it occurs represents either a degeneration or an aberration, or perhaps in many cases (as in the formation of multinucleated cells by fragmentation) is tributary to metabolism through the increase of nuclear surface."[1] In this direction Flemming sought an explanation of the fact that leucocytes may divide either mitotically or amitotically (*t.* Peremeschko, Löwit, Arnold, Flemming). In the normal lymph-glands, where new leucocytes are continually regenerated, mitosis is the prevalent mode. Elsewhere (wandering-cells) both processes occur. "Like the cells of other tissues the leucocytes find their normal physiological origin (Neubildung) in mitosis; only those so produced have the power to live on and reproduce their kind through the same process."[1] Those that divide amitotically are on the road to ruin. Amitosis in the higher forms is thus conceived as a purely secondary process, not a survival of a primitive process of direct division from the Protozoa, as Strasburger ('82) and Waldeyer ('88) had conceived it.

This hypothesis has been carried still further by Ziegler and Vom Rath ('91). In a paper on the origin of the blood in fishes, Ziegler ('87) showed that the periblast-nuclei in the egg of fishes divide amitotically, and he was thus led like Flemming to the view that amitosis is connected with a high specialization of the cell and may be a forerunner of degeneration. In a second paper ('91), published shortly after Flemming's, he points out the fact that amitotically dividing nuclei are usually of large size and that the cells are in many cases distinguished by a specially intense secretory or assimilative activity. Thus, Rüge ('90) showed that the absorption of degenerate eggs in the Amphibia is effected by means of leucocytes which creep into the egg-substance. The nuclei of these cells become enlarged, divide amitotically, and then frequently degenerate. Other observers (Korschelt, Carnoy) have noted the large size and amitotic division of the nuclei in the ovarian follicle-cells and nutritive cells surrounding the ovum in insects and Crustacea. Chun found in the entodermic cells of the radial canals of siphonophores huge cells filled with nests of nuclei amitotically produced, and suggested ('90) that the multiplication of

[1] '91, 2, p. 291.

nuclei was for the purpose of increasing the nuclear surface as an aid
to metabolic interchanges between nucleus and cytoplasm. Amitotic
division leading to the formation of multinuclear cells is especially com-
mon in gland-cells. Thus, Klein has described such divisions in the
mucous skin-glands of Amphibia, and more recently Vom-Rath has
carefully described it in the huge gland-cells (probably salivary) of the
isopod *Anilocra* ('95). Many other cases are known. Dogiel ('90)
has observed exceedingly significant facts in this field that place the
relations between mitosis and amitosis in a clear light. It is a well-
known fact that in stratified epithelium new cells are continually
formed in the deeper layers to replace those cast off from the super-
ficial layers. Dogiel finds in the lining of the bladder of the mouse
that the nuclei of the superficial cells, which secrete the mucus cover-
ing the surface, regularly divide amitotically, giving rise to huge mul-
tinuclear cells, which finally degenerate and are cast off. The new
cells that take their place are formed in the deeper layers by mitosis
alone. Especially significant, again, is the case of the ciliate Infu-
soria, which possess two kinds of nuclei in the same cell, a macro-
nucleus and a micronucleus. The former is known to be intimately
concerned with the processes of metabolism (*cf.* p. 342). During con-
jugation the macronucleus degenerates and disappears and a new one
is formed from the micronucleus or one of its descendants. The macro-
nucleus is therefore essentially metabolic, the micronucleus genera-
tive in function. In view of this contrast it is a significant fact that
while both nuclei divide during the ordinary process of fission the
mitotic phenomena are as a rule less clearly marked in the macronu-
cleus than in the micronucleus, and in some cases the former appears to
divide directly while the latter always goes through a process of mitosis.

These conclusions received a very important support in the work of
Vom Rath on amitosis in the testis ('93). On the basis of a compara-
tive study of amitosis in the testis-cells of vertebrates, mollusks, and
arthropods he concludes that amitosis never occurs in the sperm-pro-
ducing cells (spermatogonia, etc.), but only in the supporting cells
(Randzellen, Stützzellen). The former multiply through mitosis alone.
The two kinds of cells have, it is true, a common origin in cells which
divide mitotically. When, however, they have once become differen-
tiated, they remain absolutely distinct; amitosis never takes place in
the series which finally results in the formation of spermatozoa, and
the amitotically dividing "supporting-cells" sooner or later perish.
Vom Rath thus reached the remarkable conclusion that "when once
a cell has undergone amitotic division it has received its death-
warrant; it may indeed continue for a time to divide by amitosis, but
inevitably perishes in the end." [1]

[1] '91, p. 331.

There is, however, strong evidence that this conclusion is too extreme. Meves ('94) has given good reason for the conclusion that in the salamander the nuclei of the sperm-producing cells (spermatogonia) may divide by amitosis yet afterward undergo normal mitotic division, and Preusse ('95) has reached a similar result in the case of insect-ovaries. Perhaps the most convincing evidence in this direction is afforded by Pfeffer's ('99) recent experiments on *Spirogyra*. If this plant be placed in water containing 0.5 to 1.0% of ether, active growth and division continue, but only by amitosis. If, however, the same individuals be replaced in water, *mitotic division is resumed* and entirely normal growth continues. This seems to show conclusively that amitosis, in lower forms of life at least, does not necessarily mean the approach of degeneration, but is a result of special conditions. Nevertheless, there can be no doubt that Flemming's hypothesis in a general way represents the truth, and that in the vast majority of cases amitosis is a secondary process which does not fall in the generative series of cell-divisions.

## F. SUMMARY AND CONCLUSION

All cells arise by division from preëxisting cells, cell-body from cell-body, nucleus from nucleus, plastids (when these bodies are present) from plastids, and in some cases centrosomes from centrosomes. The law of genetic continuity thus applies not merely to the cell considered as a whole, but also to some of its structural constituents.

In mitosis, the usual and typical mode of division, the nucleus undergoes a complicated transformation, and, together with some of the cytoplasmic material, gives rise to the *mitotic figure*. Of this, the most characteristic features are the *chromatic figure*, consisting of chromosomes derived from the chromatin, and the *achromatic figure*, derived from the cytoplasm, the nucleus, or from both, and consisting of a spindle, at each pole of which, as a rule, is a centrosome and aster. There is, however, strong evidence that both these latter structures may in some cases be wanting, and the spindle is therefore probably to be regarded as the most essential element.

The chromosomes, always of the same number in a given species (with only apparent exceptions), arise by the transformation of the chromatin-reticulum into a thread which breaks into segments and splits lengthwise throughout its whole extent. The two halves are thereupon transported in opposite directions along the spindle to its respective poles and there enter into the formation of the two corresponding daughter-nuclei. The spireme-thread, and hence the chromosome, arises from a single series of chromatin-granules or chromomeres which, by their fission, cause the splitting of the thread.

Every individual chromatin-granule therefore contributes its quota to each of the daughter-nuclei, but it is uncertain whether they are persistent bodies or only temporary structures like the chromosomes themselves.

The spindle may arise from the achromatic substance of the nucleus, from the cytoplasmic substance, or from both. When centrosomes are present it is they, as a rule, that lead the way in division. About the daughter-centrosomes as foci are formed the asters and between them stretches the spindle, forming an *amphiaster* which is the most highly developed form of the achromatic figure. When centrosomes are absent, as now appears to be the case in the higher plants, the spindle is formed from fibrous protoplasmic elements that gradually group themselves into a spindle.

The mechanism of mitosis is imperfectly understood. Experimental studies give ground for the conclusion that the changes undergone by the chromatic and the achromatic figures respectively are parallel but in a measure independent processes, which are however so correlated that both must coöperate for complete cell-division. Thus there is strong evidence that the fission of the chromatin-granules, and the splitting of the thread, is not caused by division of the centrosome or the formation of the spindle, but only accompanies it as a parallel phenomenon. The divergence of the daughter-chromosomes, on the other hand, is in some manner determined by the spindle-fibres. There are cogent reasons for the view that some of these fibres are contractile elements which, like muscle-fibres, drag the daughter-chromosomes asunder ; while other spindle-fibres act as supporting and guiding elements, and probably by their elongation push the spindle-poles apart. The adequacy of this explanation is, however, doubtful, and it is not improbable that the centrosome or spindle-poles are centres of chemical or other physiological activities that play an essential part in the process and are correlated with those taking place in the chromatin. The functions of the astral rays are likewise still involved in doubt, the rays being regarded by some investigators as contractile elements like muscle-fibres, by others as rigid supporting fibres, or even as actively pushing elements like those of the central spindle. It is generally believed further that they play a definite part in division of the cell-body — a conclusion supported by the fact that the size of the aster is directly related to that of the resulting cell. On the other hand division of the cell-body may apparently occur in the absence of asters (as in amitosis, or among the Infusoria).

These facts show that mitosis is due to the coördinate play of an extremely complex system of forces which are as yet scarcely comprehended. Its general significance is, however, obvious. *The effect*

*of mitosis is to produce a meristic division, as opposed to a mere mass-division, of the chromatin of the mother-cell, and its equal distribution to the nuclei of the daughter-cells.* To this result all the operations of mitosis are tributary; and it is a significant fact that this process is characteristic of all embryonic and actively growing cells, while mass-division, as shown in amitosis, is equally characteristic of highly specialized or degenerating cells in which development is approaching its end.

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[1] See also Literature, IV., p. 231.