Wellcome Prize Essay

AN HISTORICAL SURVEY OF OUR KNOWLEDGE CONCERNING THE STRUCTURE AND GENERAL FUNCTION OF THE CELL.

# ESSAY.

(1). GENERAL OUTLINE. pp 1-24

(2). ESSAY.

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SCHEME



*Presented by:-*



*Edin.*

## TABLE SHOWING SCOPE OF BIOLOGY.

- **ANATOMY.** usually applied to structure of the more obvious parts.
- **HISTOLOGY.** microscopic Anatomy optical analysis.
- **CLASSIFICATION.** based on structure.
- **DISTRIBUTION.** position of living things in space and time.
- **EMBRYOLOGY.** development from germ.
- **PHYSIOLOGY.** Sc. of Function in health and disease. (PATHOLOGY.)
- **PSYCHOLOGY.** Sc. of mental phenomena .
- **SOCIOLOGY.** Social life.

Anatomy, Histology, Classification, Distribution and Embryology come under:

- **MORPHOLOGY.** Sc. of form.

Embryology, Physiology, Psychology and Sociology come under:

- **PHYSIOLOGY.** Sc. of function.

Morphology and Physiology come under:

- **OGY.** all things atter in iving te.

Anatomy through Sociology come under:

- **BOTANY.** Sc. vegetable living matter.
- **ZOOLOGY.** Sc. of animal living matter.

Botany and Zoology come under:

- **BIOLOGY.**

General Outline of ideas and theories leading up to the Cell-theory - 400 B.C. - SCHLEIDEN and SCHWANN. (1835).

To study the cell and its activities , is to study life, and to the scientist ,life means something more than mere static aggregations of molecules , even if they can grow and divide (1) ; it is an actual flux or continuous change of substance in a specialised unstable state of motion , and once this flux ceases , the organism is then considered as having lost its vitality , that is ,as having lost the close relationship which existed between its internal processes and its external environment (2) .

Primitive man's speculations upon life have naturally been influenced by his mode of life in various climes and under varying conditions . But,common to them all ,however,and probably the first thing that has induced man to reflect upon life has been its cessation death. To the Aborigines a natural death was something wonderful :; that a man should fall in battle against his enemies was part of a natural order ,but that the powers of a sound and healthy man should suddenly and without reason ,begin to fail and life to cease with or without pain ,appeared to be beyond their understanding. They had also various methods of dealing with bodies , some were cremated,others were elaborately cared for by preservation of the skeleton , or by embalming.

(I)Prof Pflüger Bonn's Expts.Radiates.-''Semi-living''Substances.

(2) Spencer BIology andSociologyThis idea means runs through all of Spencers works.Huxley takes a for more general and more practical view -Gives life an external and internal form, gives it position in space and time - it is a subject of operation of forces ,in virtue of which it undergoes internal changes ;modifies and is modified by externa objects .

From such manipulations as these, arose the first knowledge of human anatomy, and the observations made no doubt created certain physiological ideas. They learnt to observe the heart-beat and to connect life with its continuance, or cessation. They also observed, that breathing was an essential factor of life, and the deep expiration, which so often attends the actual moment of death, gave rise to the idea of life as being something in the nature of air, being dependent on the respiratory organs, and leaving the body through them.

Passing over the Babylonian and Egyptian collection of facts of science - primitive surgery and medicine, their knowledge of the anatomy of the sacred animals, and their conception of nature- we enter into the realms of the Greeks - a nation which was politically divided, yet capable to deduce from the facts handed down by the primitive peoples, a fairly consistent conception of nature. The earliest of these Greek philosophers, were those of the Ionic colonies founded on the coast of Asia Minor. Through trading with the Orient, they came into contact with the more highly cultivated peoples of the East, and there arose a keen desire for more knowledge, until finally nature, (φυσις) became the one great problem.

A survey of this period shows that there was a serious attempt made to discover a natural connection in the events of earth, in the existence origin, and decay of matter.

(I) In Mediaeval Church paintings -the idea reappears -the soul is depicted to leave the body in the form of a child through the mouth.
(2) Thales Ca650-580 Bc was probably the earliest natural philosopher together with Anaximander who wrote (περι φυσεως - on Nature) Diogenes and Hippo during Ist half of 5 th century.

Side by side with these ideas ,and perhaps having a deeper vision of the phenomena of life , yet not free from mysticism, there grew up in western Greece the Pythagorean philosophy , which played an important part in the history of culture in general .

With PYTHAGORAS?? western Greece[1] assumes a place in s scientific history , and they founded philosophic schools of a more superior character than their Ionian predecessors .At the end of the sixth century B.C. there appeared in Elea (S.Italy) a man whose name was X E N O P H A N E S .He was born at Colophon in Asia Minor, and had been a disciple of ANAXIMANDER . He based his theory of origin of the world, on that of his old master - the condensation of water and primardial mud- and in addition pointed out the foasilised appearance of marine animals high up in the mountains , which he declared to be a proof that the mountains were at one time under water.But these ideas were neglected chiefly because ARISTOTLE and his school , at a later period , regarded fossilisation as" lusus naturae "( freak of nature )

XENOPHANES' theory has been briefly stated here, because, when we come to study the Renaissance theories, it will be seen that his more correct views once more come into their own . He and his disciples , of whom PARMENIDES was the most famous ,continued to develop their theories further, and further, until finally ,they became purely theological problems ,wherein he expresses ,abstract conceptions of existence ; hot as opposed to cold,light as opposed to darkness.

Of far greater importance than the Eloeatics for the development of science ,was EMPEDOCLES a philosopher of Acragas in Sicily .

(I) Southern italy and Sicily had been colonised by Greeks at an early period .

Basing his theories on those of PARMENIDES -uniformity and immutability - he advanced further by stating that certain, however, do take place which he explained by movements in existingmatter and by alternaiing commixture and dissolution of its component parts . He postulates the four elements , fire, air, water and earth, as the fundemental material causes. He conceives Living creatures -Life of any description ,as having arisen out of the earth .Respiration he beléeved to be effected,not only through the windpipe ,but as also through the pores of the skin ;as the blood is conveyed ,alternately to and from the skin ,the air is inhaled in conjunction with it .The perception of the senses are to due to the objects which are perceived giving off five particles which unite themselves to the corresponding components in the sense-organs - water to water ,air to air, He explains sound as being created by air brought into motion , being forced into the auditory tubes as blowing into a trumpet .

From this brief synopsis of his career it will be seen that his speculations on the constituition of matter ,and its changes are worthy of attention . He also comes forward with a doctrine of affinnity ; though crude , nevertheless contains a nucleus of many ideas ,which could only be understood by later philosophers .

With the passing of Empedocles , the western Greek school made their last and most important contribution to science . Returning ,therefore,to the Asiatic or Eastern Greek school ,we discover observations of great importance were made and developed on entirely new ideas by Heracleitus (510-450 ) - In contrast to the Eleatics ' assertion of immutability , he states that everything is mutable , and that mutability is the essence of existence - He regards "fire as the casual principle of the universe - everything has arisen" "from a primordial fire ,to which everything returns - fire is the soul" "of man ,fire is inhaled in breathing and its cessation is identical" "with death .Disease arises mostly through water ,the enemy of ~~death~~ fire"

The service which he rendered to science lies in his general view of existence ; in his constant efforts of modification of the principle, thereby exerting a great influence upon the natural philosophy of succeeding ages.

Contemporaneous with Heracleitus ' idea there appeared another line of thought ,which was concerned with a much closer study of nature and formed the basis of the whole cosmic system .This was the Atomic Theory ,the founder of which is said to ~~hax~~ have been LEUCIPPUSa Sage of whom little is known except that he was the teacher ofDEMOCRITUS(ca470) The latter adopting Leucippus' Materialistic theory -that the universe was composed of a quantity of particles, moving in empty space -developed it still further, and thus achieved important work in the science of biology.A review of his general principles when compared with modern ideas appear surprisingly sound :-

" Out of nothing comes nothing ; nothing which is cannot be" "reduced to nothing . All change is merely an aggregation or separation" "of parts.Nothing happens by chance , everything through cause and of" "necessity . There is nothing but the atoms and space ; all else is" "an impression of the senses ."

He was the first to differentiate between the higher and lower animals according to the quality of their blood ,and his principle of classification was adopted and further developed by his successor Aristotle, thought the latter held different views on other matters. For example ,Democritus maintained that the spider's web is produced from inside the body ,wheras Aristotle declared it to be a cast-off skin . They were at variance over many points ,but modern research has proved the former correct in many respects .

The main object of Democritus' studies were the CONSTRUCTION AndX FUNCTIONS , of the human body. He conceives man to be a world in himself, a microcosm in which every kind of atom is represented . He regarded the brain as the centre of thought , while Aristotle believed it to serve the purpose of cooling the blood ; life and Soul he considered to be one and the same thing, and that Necessity which according to him governed the universe ,was purely impersonal .

Reviewing Democritus' theory as a whole we find that it represents the climax of the endeavour of Greek philosophy to arrive at an explanation of existence . Hitherto , it had been a series of heterogenous explanations with Anaximander as instigator but Democritus achieves results which, if primitive ,run parallel in many respects with those that have been attained by natural research in our own day .

But , however, this promising idea was not pursued by succeeding generations , because , it was not accompanied by material investigations , which therefore made it difficult to follow up the principle of causation . Chemical association and affinity , were xxxxx unknown to antiquity , and therefore these ideas could not be utilised as basis for the changes which occured in nature , xxx and the dogmatic theory of whirling motion ,therefore proved a poor substitute . They had no ideas of force and energy , but had to be content with motion as an explanation of all changes . They considered the whole cosmology as purely dogmatic , and it was therefore condemned ,and curiously enough ,condemned to give way to other similar dogmatic explanations.

The oldest Greek medical science ,also emanating from the shrines of Asia Minor , felt the influence of the Orient , and posterity received the benefits of the Hippocrates ~~ar~~ the Second or the Great (Ca460) . They give evidence of a close study of anatomy ,and physiology ; of bones and their construction, examine d from the skelëtons , and also the musculature , especially the external layers . These treatises assume with Empedocles that the human body is composed of the four elements already stated , which elements according to Hippocrates correspond with four "juices " in the body :- blood, phlegm, yellow, and black bile . Little was known concerning the internal organs , and the nervous system ,but the various glands had come under their notice ,and their function was considered to be to segregate water from the body.

After Hippocrates , the scientific world became acquainted with ,and influenced by the teachings of SOCRATES and PLATO, the latter laying down the foundation of biological systematisation . But later, there appeared among Platos disciples, one, ARISTOTLE (384B.C.) who began to discard their prevailing ideas, and offered guidance in a new direction.His sphere of activity was extensive ,and equally universal has been his influence throughout the succeeding ages . His first important contribution to Science was the classification of animals , the and the . He also occupied himself with the anatomical,and morphological structure of animals and states that anatomical research should be comparative ; he describ the asexual and sexual reproduction , and advances his evolution theory.

When Aristotle fled from Athens ,he left his school in the hands of THEOPHRASTUS , who had been his faithful friend, ever since his student days with Plato . Already, whilst under Aristotle , Theophrastus had paid special attention to the study of botany, and he continued to work in this science, in the spirit of his master.His treatises on plants were to botany, what Aristotles works were to Zoology.

The teachings of the Lyceum , which had already been firmly established ,were next carried on by STRATO ,who appears to have been a truly independent thinker . In contrast to Aristotle he denied the existence of a dominant power outside the universe ; he imagined that the forces which govern the course of events dwell in "things " themselves and operate by natural necessity .

Strato's successors appear to have been men of little importance ,and although Aristotles School survived down the sixth century after Christ, it nevertheless ceased to act as a guiding light in science ; its teachers became involved in specialised investigations into literature and ethics ,and interest in natural sciences waned.

But in the year 342 B.C. another school of thinkers began to flourish ,and under its guidance the atomic theory was given a fresh lease of lifeand it survived ,not only the classical period ,but also through the Middle Ages until the Renaissance.This new school was directed by EPICURUS, whose teaching-Epicureanism -

when brought to Rome ,degenerated into an unbridled worship of pleasure . In Rome ,however , it gained several adherents ,the most important being,LUCRETIUS CARUS (99-55 B.C.) whose enunciation of the atomic theory is the most detailed of its kind that has been handed down to us,from antiquity ,and as such ,it is also of interest on the grounds of the biological particulars which it contains .Lucretius'influence on posterity was both lastingand important ,, and although he did not succeed in improving the atomic theory ,nevertheless,it was due to him that atomism survived the Middle Ages .

After the death of Aristotle , there developed ,on the foundations laid by him ,a specialised form of biological research , with Alexandria the purely Greek capital of Egypt as its centre.Under the patronage of the refined and educated kingsof the Ptolemaic dynasty ,there was here established a scientific institute ,the like of which ,the ancients had never seen.It was conducted on the lines of an academy ,with the high priest of the MUSES as its religious head. All branches of science known to antiquity were studied ,and biology was pursued in connexion with medicine , like anatomy and physiology. Despising the traditional fear of dissecting human bodies , HEROPHILUS, one of its founders. became the most prominent anatomist of the time.

Contemporary ,and probably in competition with Herophilus was ERASISTRATUS ,of Cheos a small island in the Aegean- Whilst . still a court physician in Syria he was called to Alexandria and there founded another school of medicine . He,too, became a great anatomist, and controversies arose between him and Herophilus. This hostility had fateful consequences for science and it was all the more disastrous, because the enlightened Ptolemaic kings were followed by a line of degenerates .The Museum declined, the learned often fell victims to the whims of tyrants ,and finally Alexandria became a provincial town, within the great Roman Empire.

In Rome ,which in time assumed Alexandria's position as supreme capital ,there arose no equivalent to the Museum . But as time passed on two biologists of importance appeared . They were COLUMELLA, and PLINY ,and the latters "natural history "played an important part in the development of science .Nevertheless ,there was a decline of learning ,and the philosopher was no longer a lover of wisdom ,as the name implies, but a lover of piety ,and as such retained but little interest in natural phenomena .But during the second century of this era ,signs of revival of learning became evident , At this time lived the last great biologist of the age ,the physician Galen (CAI3I-2IO) who in his writings combined the many-sided biological teachings of antiquity, with the trend of thought of the new era. From his general conception of life we may gather, that he stood on the border-line between antiquity and the Middle Ages . But with regards to his knowledge of anatomical details, he was the foremost philosopher of the classical period, and as such remained the undisputed authority, in his own branch of learning ,up to the Renaissance and probably, up to the time, when HARVEY discovered the circulation of the blood ,thereby destroying one of Galens' foundation-stones .

Of the scientists of the Middle Ages none has won greater fame than ALBERTUS MAGNUS (I200-I280) and his whole object in life ,was to harmonise the teachings of Aristotle, with that of the Church .As a natural philosopher ,he is chiefly a chemist and it was he who introduced the chemical term"affinnity ".

Comtemporary with Albertus, were CANTIMPRATENSIS, and VINCENTIUS , both chiefly concerned with mediaeval descriptions of nature ,which scarcely can be called natural research .

But during this period ,when mediaeval scholastécism was at its zenith ,hostile movements were afoot ,partly by way of logic and partly by exhortations to empirical observations , The most important pioneer in the latter direction was BACON (1214-1294).Though no great scientific discovery can be attributed to him ,nevertheless,he introduced new scientific ideas which opened the way for the development of biology

What Bacon had theoretically conceived,and insisted upon, was brought into practical realisation by GALILEO (1564-1642),the founder of the whole modern natural research.

Biological research under the Renaissance considerably widened the knowlegemf of animate nature .The works of GESNER (1516-1605 RONDELET,BELON, renewed by BUFFON two centuries later,and eventually further developed by CUVIER,proved to be of great importance to biology.

Int the field of medical science the influence of the Renaissance was similarly felt. The human body was dissected with great care and attempts were made to study muscles ,nerves,and blood-vessels. But differences of opinion arose amongst the leaders with the result that that no great biological development occurred until VESALIUS ,appeared in 1514 . He at once led anatomical research into a completely new direction ,and thus started a new era in the history of science .He was at first ,a faithful follower of Galen ,but it soon became apparent to him that the work of his predecessor was incomplete . In his book "De humani corpis fabrica",he discusses bone and construction ,muscle blodd-vessels and nerves ,together with the various organs ,and in almost every sphere of human anatomy he made important discoveries in matters of detail and corrected old fallacies .

His successors in Padua was COLUMBUS (CA1559) who published "de re anatomica",in which he shows himself a well informed anatomist . He,however ,was called away and was succeeded in Padua by a man of far higher qualities , GABRIELE FALLOPIO (1523).He made observations upon , and increased the knowledge regarding the sexual organs,.and his contributions to the knowledge of the structure of bone and of the organ of hearing were of considerable value .

After the death of Fallopio ,another branch of biology namely embryology was developed by a scientist named FABRIZIO, usaally called after the place of his birth ,Fabricius Aquapendente, to distinguish him from the German anatomist Fabricius. His treatises and illustrations on the evolution of the ovum and the embryo ,present in consise form ,the process of embryonic development, in a large number of vertebrates .Adopting Aristotle's idea of comparitive research ,he describes the anatomy of the embryo ,and the shape and appearance of the placenta ,pointing out the similarities and differences between the various animal forms.But of more definite value to posterity ,however, was his observations on the venous valves,which he discovered experimentally ,through binding the limbs of live subjects. In spite of this discovery ,which was so obviously at variance with the Galenian theory of circulation he could not abondon the latter;he explained his discovery and no more ,and it was left to Harvey ,one of his pupils , to formulate a true conception of the circulation of the blood.

Biological research ,under the Renaissance considerably widened the knowledge of animate nature ,the greatest achievement being so far ,in the anatomical sphere.

The next pioneer in the field was Cesalpino(1519-1603) who was a man of many interests,and was a natural philosopher of the true Aristotle spirit. From his treatises on the heart, we learn that this organ is the actual centre of the vascular system . And in regard to the relation of the lungs to the heart ,he maintains that the blood passes through the lungs from the right to the left side of heart - a process ,which he for the first time calls circulation .

During Renaissance there were many writers who made a study of the construction and function of vascular system ,in vain attempts to bring order, out of the chaos which existed through the innaccurate conception of animal biologist. The necessity of a solution was generally acknowledged .Then WILLIAM HARVEY 1578-1657), took the decisive step, and solved the problem . He also gives a comparative account of the embryonic development in higher and lower animals ,and quotes as his precursar his old teacher Fabricius. Also following along Aristotlean lines,he endeavours to find a formal unity in the manifold aspects of phenomens ,and he believes that he has discovered such unity in the ovum,out of which all living creatures are evolved. His dictum "All animals ,even those that produce their young out of the egg " is well known.

Harvey is without a doubt ,one of the most remarkable figures in history .His work is the most revolutionary that development of biology has to show ,for it undermines the foundations of the ancient conception of life and its manifestations. He thus brings to a close, the great epoch in the history of biology, which is governed by the ancient conception of nature, and he initiates the modern development in the sphere of biology.

The seventeenth century has been called the period of great systems of thought ,during which all the knowledge that the Renaissance brought to light was summarised and classified.

The pioneer amongst the systematic philosophers of this era was Rene Descartes (1596-1650),who introduced a new explanation of the cosmos -cartesianism - which had the advantage over the old in,that it rendered possible the application of the newly -achieved results of research in the various fields of science .He explained life-phenomena to be purely mechanical -the human body as a machine - and this theory may be regarded as the foundation of modern physiology Other thinkers ,during this period ,who held a mechanical view of existence were HOBBES1635-1679) and SPINOZA (1632-1677) also LEIBNIZ (1646-1716) who introduced the theory ,and BOYLE (1627-91) who broke away from the mystical speculations of alchemy by splitting up the complex substances into their simplest elements.

Far more renowned and of far greater infleunce were ISAAC NEWTON 1642-1690) who formulated the theory of gravitation , and VOLTAIRE 1694-1778).

The foundations of the mechanical view of natural phenomena already laid down by Harvey continues to develop and influence the succeeding decades. The mystery of the already discovered "chyle vessels" by Aselli(1581-1626) and Pecquet (1622-74) was cleared up by Bartholin, and Rudbeck, in 1653, also observations were carried out by GLISSON, X WHARTON, and WILLS. The observations of the latter on the brain and nervous system, are worthy of notice, in as much as he forestalled SWEDENBORG'S deeper investigations, into the localisations in the brain.

Also, during this period the phenomenon of movements of animals came under the notice of BORELLI (1608-79). He perceived that the muscles, were the principle organs of motion, and he began to study their structure, parts and visible actions -he observes the contraction which occurs in muscle, and explains the "swelling" thus caused to be a process of fermentation. Similar observations were made by PERRAULT and STENO, and thus experimental biology became universal. During the seventh century the construction of microscopes was considerably improved, with the result, that scientists were greatly assisted in their investigations.

Foremost among those who systematically based their research on magnifying apparratus was MALPIGHI (1628-1694). He published his observations in the form of letters, which he sent to the Royal Society London. He first investigated the structure of the lungs, which hitherto had been considered as "fleshlike". He declares it to be "network of thin-walled CELLS-UTRICULI-, which are connected with the finest ramifications of the wind-pipe." He next discovered the pyramid-cell of the cerebral cartex, which, he believed to be glandular elements that secrete the "fluidum". Malpighi, was also a pioneer in vegetable anatomy, which can be considered as the real starting point for the study of the elementary nature of living matter as a whole.

He described the different parts of plants also as being composed of small cells, which, in their turn form a larger connective group.

At the same time as Malpighi ,but quite independent ,another scientist named GREW(I628-I7I2) made observations on the same subject - vegetable anatomy- He describes the plants ,organs by organ ,and the cells and vessels of the stem ,which he discovered independently of Malpighi.

Through these two scientists ,biology acquired its knowledge of organised matter, as being something peculiar in its structure the ideas of tissue and its simple element -CELL- were established. But,however, nearly two centuries passed, before the fundemental value of these achievements was fully appreciated .Although their contemporaries ,and the immediately ,succeeding age ,admired the exacture of Malpighi,and Grew's investigations ,they considered the results more from the point of view of curiosity.

Biology, has to thank another investigator of this period in the person of LEEUWENHOEK(I632-I723).He explained and completed the knowledge of the cappillary system which Malpighi originated .He also for the first time, clearly recognised the blood corpuscles,which Malpighi thought to be fat globules;To him may also be attributed the discovery of spermatozoa's association with the ovum;the stripes of the striated muscle ,and the construction of optic lens in man; and the difference between the structure of the stem of monocotyledons and dicotyledons .Other investigators in the same field, were SWAMMERDAM (I637-80) who introduced the preformation theory,GRAAF (I64I-I673) who made observations on the sexual human organs, and described the "protuberances" in the ovary ,already observed by Versalius and Follopio,as being comparable with the ovum of the bird ovary.

During the first part of the eighteenth century, the theoretical speculations of SYDENHAM , HOFFMAN ,and SWEDENBORG, lead to no great discoveries ,and apparently did not succeed in satisfying humanity's craving for knowledge. These are followed by the icthyology of ARTEDI (1705-1&35) LINNAEUS (1700-78) first important work :- "Systema Naturae" and BUFFON(1707-1788).Histoire Naturelle. The latter, has played a fundemental part in the history of biology ,not on account of his discoveries ,but of the new ideas which he produced . Those ideas which he could only imperfectly realise have since, been taken up by others who ,having better opportunities and means of investigations ,have applied them in a wider sense : CUVIER'S comparative anatomy, BICHART'S tissue theory and LAMARCK'S evolution of living organism ,all show the adoption of Buffons'ideas.

The eighteenth century displays a great activity in the sphere of natural sciences,especially the latter half ,which represents a period of decisive preparation for the development that took place during the following century .It will be seen , that we have now arrived at a stage in biological science ,where it is possible for us to choose, a more direct path, towards our objective namely the - CELL.

Of the various pathways which the biological field now offers ,that of botany, seems to take precedence in this respect but we must not altogether ,overlook men like HUNTER, CUVIER, BICHAT, HALLER, and MULLER, who made great progress in other spheres xxx such as comparative anatomy, and physiology.

The progress of botany from LINNAEUS(1707) to SCHLEIDEN(1840) may be briefly summarised thus :-The pre-Linnaeun, workers toward a natural classification are represented by CESALPINO, (1583)BAUHIN(1623) JUNG (1678) RAY(1686-8.9).[1] during this time, some of these, by philosophical reflections, attempted to determine the relationship among plants, but since the discovery of natural affinities must be based on objective study, their methods were inadequate. Ray, however, gave the first carefully considered definition of species, and thereby, probably laid the foundation of the origin of species, which became the burning question of the 2nd half of the 19 th century.

Of Linnaeus, it is said that he marks the beginning of a new epoch in botany ; but Sachs, however, makes the point, that Linnaeus is the last link in the chain of development formed by the work of his predecessors, transmitting the work of these men, and in many cases their errors;-But the overwhelming importance of his work lies in the skilful way he gathered and fused into one, the scattered fragments of the past. The most important post-Linnaen workers in the same field were CANDOLLE(1778-1841) and BROWN(1773-185 -1858), and with the latter we come to the threshhold of an new kind

(1). Date when their respective works were published.

of botanical investigation ,inaugurated by the work of HOFONEISTER, of Schleiden, and many others, such as MOHL,(I805-I872 ) NAGELLI, (I8I7-I89I) SCHWANN,(I8IO-I882) SACHS,(I832-I897) and SPRENGEL,who made plant physiology an independent study.

Concurrent progress in these different lines is confusing if treated as a whole,and for clearness it becomes necessary to separate the advance under three sub-heads:

(1).The progress in reference to classification .

(2). Knowledge of the inner structure of plants.

(3). Progress in vegetable physiology.

In the first division,we find Linnaeus,using the work of his predecessors, Cesalpino,Bauhin ,and Jung.After him Candolle,and Brown,the latter, bringing this aspect of botany, into its highest development.In the 2nd. division we find men of penetrating insight devoting themselves to investigations of a different type .Using the microscope , Mohl,and Nageli ,investigated the structure of plants. This work,so different from that of Linnaeus ,opened numerous questions of general biology . Through their researches, and those of their contemporaries ,arose the CELL-THEORY,the PROTOPLASM doctrine, FERTILISATION, and a host of other observations ,which would never have arisen from the systemisation of LINNAEUS and his school.

In the 3rd, division we have work beginning with the investigations of Stephen Hales on vegetable physiology (I727) followed by INGEN-HOUSZ, Saussure, and VON SACHS.

We have now followed the stream of biological progress, to a period which is full of discoveries in every branch ,therefore,

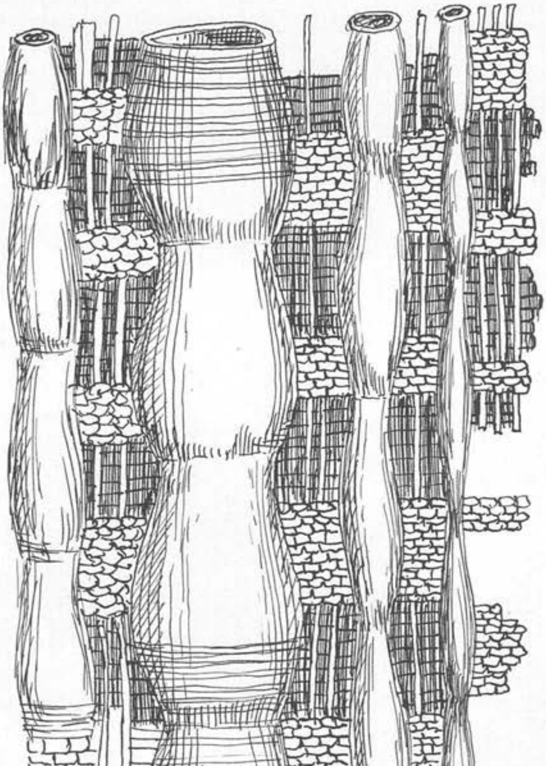

FIG. 1. Microscopic Structure of Oak Wood.

Malpighi. 1679.

leaving the more general field of investigation ,we will endeavour to trace the steps by which our present knowledge of the CELL ,has been acquired .

## REVIEW OF THE INVESTIGATIONS LEADING UP TO THE CELL-THEORY-

## LINNAEUS TO SCHLEIDEN.

As will be seen from the foregoing ,the foundation of microscopic anatomy of plants was laid by Malpighi ,and Grew,in the last quarter of the I7 th century . We pass over Hooke's observations on the cellular structure of cork published in I665. He was not so much concerned with plants ,but the books of Malpghi -"Anatome -phantorum," and of Grew ," The anatomy of Plants. By means of diagrams ,MALPGHI ,illustrates cells(utriculi),and vessels of plants, but he considers the cells as a massed matrix rather than as elementary units of structure

See Fig.(I).

His diagrams are suggestive of the beginning of cell-theory, but an examination of the text shows that he is more concerned about the vessels and fibres of plants ,and their course ,and we must guard against the idea that he was on the verge of conceiving the cell-theory.

Grew is far more elaboratein his sketches ,filling in the entire surface of a cross-section. (I64I-I7I2).

These writings of these two scientists appeared almost simultaneously[1]. These men were independent workers, and it seems difficult to account for Schleiden's caustic accusation that Grew plagiarised from Maplghi.[2] Also Lamarck (1809), and his colleague Mirbel, both gave expressions to general ideas about cells, but it is a mistake to consider either one as a presumptive founder of that great generalisation.

During the 1st half of the 19 th century the study of the inner structure of plants had been resumed, and the work of Van Mohl, and Nageli, so greatly surpassed all other investigators in the same field, that we may well confine attention, to their scientific works. But it must not be overlooked, that Schleider in 1838, had raised embryological study to a high standard, but in the same year his free-cell formation was shown to be faulty;

Mohl (1805-1872) laid the foundation for future work. By exact observations, he showed that the cell is the individual elementary unit of structure; he was the first to explain (1831) the formation of vessels in plants, as produced by the union of elongated cells - he analised the cell-contents, he recogonised the protoplasm as the source of the movements in plant cells - found and named the "primardial utricle" (1844). He observed the behaviour of protoplasm in cell-division, and helped to overthrow Schleiden's theory of free-cell formation - and brought the word protoplasm into general use (1846).

(1). Dec 7, 1671. The Royal Society received Grew's first essay and also Malpghi's Anatomy of vegetables begun both of which deal with the same subject. (2). Grew in the preface of his extended work 1682 tells how the MS of Malpghi's, first memoir was received by the Royal Socy.

Nagelli, I8I7-I89I), investigated the nucleus of plants, tissue -formation, and carried further the work of Von Mohl. Sach says", he "devoted himself with enenrgy, and sound reasoning to important, and "difficult question, how cells are formed, in reproduction and growing vegetative organs, and how far the processes are the same in the lower Cryptogams and Phanerogams -" He formed a theory of cell- formation, opposed to Schleiden's theory of free-cell -formation, and showed that the phenomena of cell-formation, are similar in the lower and higher plants, and that they agree in essential particulars, with the cell-formation of animals, as Schwann (I839) and Kolliker (I845) had already maintained. Nageli is also notable for the discovery of growth, from an "apical cell" in lower plants, and the formation of tissues from a "meristem" in the higher - explained the structure of starch grains (I858). Sachs says " Nageli arrived at clear ideas of the molecular structure of (Starch) Grains, and of their growth, by the introduction of new molecules between the old ones." Nageli lived in stirring times for the advance of biology. Intensive studies in related subjects -embryology, and histology ( Baer., Koelliker ) physiology ( MÜLLER ), taken in connection with the botanical investigations, provided constructive material.

Disregarding certain sporadic observations, the rise of vegetable physiology can be summed up by refernce to the works of HALES, INGEN-HOUSZ, KNIGHT and, SACHS-.

Hales (I677-I76I), was a pioneer in using instruments for the measurements of physiological activities.

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(I). Measuring root pressure of a 50 feet vine with mercury gauges; invented methods estimating transpiration of plants.

Sachs says " One of his (Hale's ) most important "discoveries has been generally overlooked ,even in modern times ," "because it was neglected by his successors in the I8 th century ," "he was the first to prove that air cooperates in building up the" "body of the plant --------- ".

Ingen-Housz ,discovered that the carbon of plants is derived ex carbonic acid of atmosphere -also that all vegetables give carbon dioxide etc - His work was considered as a standard and the results were passed on to later generations .

Sachs (I832-I897).He was the first to insist on the continuity of protoplasm throughout the plant organism -he advanced the physiology of nutrition -studied growth and development ,the relations of plants to stimuli,such as light.

Schleidin (I804-I88I) saw the imperative need of giving to botany another direction :- His book "Botany as and Inductive Science "- led investigators into the path .In I837 he published his investigation on the origin of cells ,and played a part in the formulation of cell theory. The study of botany in the light of species seemed to greatly annoy Schleiden ,and he remarks "Most " "people ,even the most enlightened are still in the habit of " "regarding the botanist as a dealer in barbarous Latin names,as a man" "who gathers flowers ,names them ,dries them,,and wraps them in paper" "and all of whose wisdom consists in determining ,and classifying " "this hay which he has collected ,with such pains ".

Hofmeister (I824-I877),owes his place in botanical history to his technical investigations -demonstrated the alternation of sexual with an assexual generation in plants -published a book entitled "Comparative Researches ",which revealed all plants as "genetically related ,which ultimately led to Darwins" origin of species " .

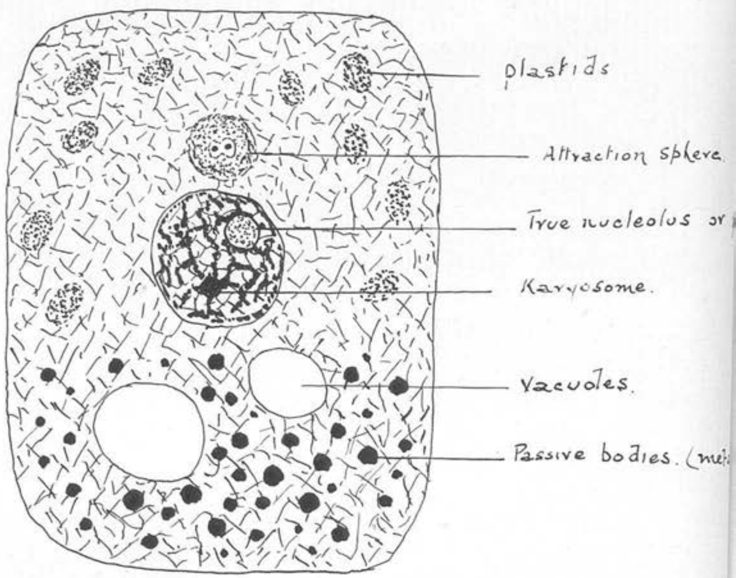


FIG. 2. Diagram of a cell.

In the foregoing general outline ,efforts have been made to show how the numerous investigations carried on throughout the past ages ,have served more and more to focus attention on the individual cell as an organic unit.

That the cell may be treated as an elementary organism was indicated in a general way by SCHLEIDEN ,SCHWANN and VIRCHOW; but like every other great generalisation, the theory was based, on a long series of earlier investigations ,beginning with the microscopical researches of Robert Hooke, who, in 1665, announced, that the vegetal tissue ,cork ,is made up of "little boxes or cells distinct from one another ;" Malpghi's diagrammatic representations of the "utricles" which he considered as a massed matrix ,as well as with the researches of LEEUWENHOEK and GREW.

Wolf also in his "Theoria Generationis "(1759), clearly recognised the"spheres " and "vesicles " composing the embryonic parts of animals and plants ,but he did not grasp their real nature or mode of origin ,and his conclusions were developed by the botanist Mirbel (1775-1854)

In the year 1805 OKEN foreshadowed the cell-theory in the form that it assumed with Schleiden and Schwann ,but his conception of "Urschleim " and Blaschen ,can hardly be regarded as being definite. ~~A still closer approximation to the truth is found~~

(1). See general outline page

in the works of Turpin I826 .Meyen I830 and Raspail I831, but, these ,like others of the same period ,only paved the way for the real founders of the cell-theory ,namely Schleiden I804-I88I and Schwann I8IO-I882.

The work which brought Schleiden fame was an essay in Mullers archives of I838, and the question he propounds is :How does the cell arise ? He takes as his starting point the English botanist Robert Browne's discovery of the cell-nucleus . From this nucleus ,or as he calls it ,the cytoblast , Schleiden sought to reconstruct the course of development of the cell,and selected for his study the embryonic cell of phanerogams, wherin he later discovered the formation ,that is now called the nucleolus.This discovery led him to form an errant doctrine of cell -development ,which will be further considered at a later stage.

In I839 Theodor Schwann, published his work on cell structure, taking as his starting point, Schleidens cell formation theory ,which he accepted in its entirity ,and expands into a general theory, of life-phenomena .He had discovered in the notochard of tadpoles ,cells provided with nuclei similar to the plant-cells, and both there and in the embryonic cartilage, he believed he saw a process of cell-reproduction ,such as Schleiden had described . This induced him to look for cells ,in all the tissues of the animal body ,and by examining these ,in their embryonic stage and

(I). See General outline for Schleiden and Schwanns' immediate predecessors and contemporaries, afterwards, following their development, he succeded in establishing the fact, of cell-structure in tissues, that in a state of full growth show little or no trace of any such structure. He states that, "one common principle of evolution is laid down for the most highly differentiated elementary parts of the organisms, and this principle of evolution is the cell formation." This conception of the cell as the common unit of life, and as the common basis, for the vital phenomena in both the animal, and the vegetable kingdom, was immediately, and universally accepted. Further, BRUCKE (1861) insisted, that cells must possess some kind of structure, or organisation, more complex by far, than any made visible, by the microscopes of the time. The study of cells, or Cytology, arose when the internal organisation of the cell, was made more accessible to investigation, by improvements in microscopical technique, and by the discovery of more favourable objects for study. Its beginning can be traced to a series of researches on the fertilisation, and cleavage of the animals ovum, which began in the early seventies, more than 30 years after the promulgation of the cell theory by Schleiden and Schwann (1838-39) Cell-study, therefore, may be said, to have taken its origin from embryology; its close association with histology in the narrower sense, first took place, when it was discovered that the apparatus[1] of cell division.

(1). Discussed later.

IN the tissue, cells is in every respect identical with that observed in the ovum ,and blastomeres, into which it splits up during the earliest stages of development .The work of these pioneers researches centred in the discovery of indirect cell division, or KARYOKINESIS , (Schleider), later known as MITOSIS (Fleming), a process, involving complexities which were unsuspected by earlier observers ;and down to our own day these phenomena ,together with the closely related ones displayed in the fertilisation of the ovum ,hace continued to hold a central position of importance, because of their fundemental significance for the principles of genetic continuity in living organism .

It may seem strange that the subject should so long have dominated by morphological studies ,when we recall the illuminating researches on living cells by Dujardin,Max Schultze, Kühl,and other pioneers ,which led to the general recognition of protoplasm, as the physical basis of life . The explanation lies partly in the failure of the earlier microscopes, to make visible in the living cell ,an organisation which would adequately explain the vital activities ,and partly, in the general technique of fixation .Improved methods were introduced during the 18 th .century which have played an indespensable part in the advance of modern study of the cell .From now onwards cell research entered upon a phase of new and broader activity in the course of which cell morphology ,and cell physiology ,tended more and more to amalgate . This led to the overthrow of certain of the earlier conceptions of protoplasmic structure ,such as the reticular theory ,which had been based on the study of fixed material .It also aroused a salutary sceptisism ,concerning the so-called "microchemical " methods in so far as the staining reactions of the cell components were employed, as a guide to their nature and origin;such methods were indespensable for certain purposes ,but unless used with caution ,they may be a source of numerous errors ,as the history of the subject abundantly demonstrates . Out of all this chaos , grew a more rational treatment of the whole subject ,and a gradual affiliation of cytological methods with those of the physiologist , the physicist ,and the biochemist . How this union came ,though an interesting and profitable study ,can hardly be considered within the scope of this work. In close connection with the foergoing has been the rapid development since 1900 ,of observations and experiments on living cells . These experiments have been purely mechanical, or physical ,such as the displacement of the cell components. by the centrifuge ,or by mechanical pressure ,and the actual dissection of the cells under the microscope . Studies along these lines have steadily tended to emphasise the conception of the cell, as a colloidal system, and have led to many interesting modern attempts, to imitate or model certain of the cell activities in artificial systems (1)

(1).Burkes'origin of life and Pfluger expts already given in the general outline .

as was long ago undertaken by Butscheli, and Pfluger .

The studies of effects of changed condition, in physical, or chemical, environment on living cells, are also of great importance, and it is here, that cell-study passes over into cell physiology . The starting point for the more modern work in this field, was given by studies, which culminated in the discovery by Bonnet of parthenogenesis, and from them, have branched out numerous lines of investigation . We cannot here attempt to follow in detail the general history of these various investigations -we have briefly indicated how the earlier study, cell-morphology has broadened out into a many sided science, which Carnoy has called "cellular-biology."

Now that the cell theory has been firmly established, it should be clearly recognised from the very beginning that the term " cell " is a biological misnomer ; for cells rarely assume the form implied by the word, that is, of hollow chambers surrounded by solid walls . The term is merely an historical survival of a word used by the botanist of the seveenth century to describe the honeycomb appearance of plant-tissues when viewed in section .

Both Schleiden, and Schwann, describe the cell-walls as being solid and conspicuous, in the cells which they examined, and they erroneously mistook them to be the essential parts .They both believed in a free cell -formation out of moisture . In fact, the latter carries the idea a stage further .He states that "out of moisture is concentrated, first the nucleolus, then the nucleus, and finally the cell, and he compares the process with crystallisation; his concluding remarks are concerned as to whether the hollow form of the cell might be accounted for by the " Imbibitious ". (fahigkeit ),of its component parts -ie what we would call today, its colloidal qualities.. According to him ,therefore,the cell--formation would be a kind of crystallisation in non-crystalline elements .For the essential part of the cell in Schwann's view , is its hollowness ;in its essence, a space surrounded by walls ; its contents is a moisture and its nucleus is a transitory formation, which disappears in later stages of development . These views however ,were corrected as time passed on.

The Schleiden- Schwann theory was followed up by other investigators and the most important contributions during the next few years were those of HUGO von MOHL .In his brief essays he analyses the different components of the cell. To him also it was still " a vesicle formed of a fixed membrane containing a moisture " . The character of the membrane is the essential thing ,and the shape ,consistency and interrelation of the cellular walls are discribed minutely . He also gives an account of the cell-contents . This, he calls ,protoplasm[1] ,(I846), a term which had already been used by PURKINJE (I840) to designate the formative material of animal embryos.

This "viscid moisture " which Schleiden Schwann had evidently looked upon as waste-product[2], Mohl describes carefully

(I). πρῶτος, first πλάσμα,something formed .The name has probably been based upon the assumption that all the component parts of the cell originate from it ,which is errant,

(2). The view was based upon the fact that in many plant -tissues it may wholly disappear leaving only lifeless walls.

and considers it to be the fundemental constituent ;its"currents", which were discovered by Corti, and rediscovered by Treviranus, are depicted in detail by him . Similarly ,the ~~evolux~~ evolution of the cell-content, is followed through its different stages of growth, and the secondary formations that accompany it -vacuoles,chlorophyll- and starch-granules are described .By describing the cell-contents and naming it protoplasm , Mohl established the fact, that this substance is an element in itself ,and not merely "slime " of some indeterminate kind, which Schleiden, and Schwann, suppossed . Also Mohl, describes the nucleus in greater detail than his predecessors, and he referred to it as a derivative of the protoplasm ,coming into being through an accumulation of a granulate substance in young cells, and disappearing in the older ones ,but the precipitation -theory of his predecessors was accepted with reserve.

At this time there were numerous investigators carrying out observations on the cell-contents ,and probably, priority should be given to the French Zoologist ,Dujardin. (1801-60). It was he who first distinctly called attention to the importance of the "primary animal substance" or "Sarcode " which forms the bodies of the simplest animals . Without clearly recognising this as the seat of life,or using the word protoplasm , he nevertheless described it as endowed with the powers of spontaneous movement and contractility . Cohm another scientist of the same period ,maintained not only that animal sarcode, and vegetal protoplasm, were essentially the nature ,but also that this substance is the real seat of vitality and hence to be regarded

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as the physical basis of life . Barry showed this identity further in his work on the myxomycetes. But to Max Schultze, (1860) is generally assigned the credit of having finally placed this conclusion upon a firm basis ; and by him the meaning of the word protoplasm was extended so, that there was a union established between the cell-theory, and the protoplasm-doctrine. Closely associated with these were KOELLIKER the embryologist, and histologist, Müller the physiologist. Nageli (1817-91), the Swiss botanist, who investigated the chemical nature of the same. Virchow (1821-1902) the founder of cellular pathology, a theory of the cells, as the true cause of disease -has compared the whole organ " to a free state, containing individuals, endowed with equal priveleges, if not with equal power ". He for the first time, definitely established the cell's character, as being an independent life-unit. He draws out the distinction between the animal, and the plant cell, and states that the "cartilage cells of animals are the closest related to plant cells." The comparison between animal, and plant cells, previously expounded is, according to him, inadmissible, " because the cellulose membrane of the vegetable cell does not correspond with the membrane of the animal cell. The so-called cell-membrane of the vegetable cell is only met"

(1) Feb 10 1858.

with in a few animal tissue e.g.cartilage cells.The ordinary membrane of the animal cell corresponds to the primoidial utricle of the vegetable cell[1] " ,and at the same time he submits his aphorism , " Omnis cellula ".He denies any form of spontaneous generation whether within the organism or without ,in nature.

In the year 1781 Fontana, described a rounded body- the nucleus- lying within the protoplasm ,but this was not considered as a normal element of the cell,until 1833 ,when it was discovered by the Scottish botanist ROBERT BROWN. In his book on " OBSERVATIONS of the organs and mode of Fecundation in Orchidae and Asclepiadae " Brown states :-"I shall conclude my observations on Orchidae,with a notice of some points of their general ~~internal~~ structure which relate to the cellular tissue In each cell of a great part of this family especially of those with membranaceous leaves a single circular areola ,generally somewhat more opaque than the cell-membrane ,is observable . This areola ,which is more or less distinctly granular,is slightly convex,and although it seem s to be on the surface is in reality covered by the outer lamina of the cell . There is no regularity as to its place in the cell ; it is not infrequently , central or nearly so .... it is not confined to the Orchidae , but is

(1).Discovered by Virchow in 1847 .

Equally manifest in many others .... The few indications of its presence ,that I have hitherto met with in the publications of botanists ,are chiefly in some figures of epidermis ,in the recent works of Meyen, and Purkinje ,and in one case in Brogniart's memoir on the structure of leaves . But so little importance seems to be attached to it ,that the appearance is not always referred to in the explanations of the figures in which it is represented."

We see therefore,from Brown"s remarks that some of the earlier observers looked upon the nucleus ,as they did upon the cell-wall,as something of secondary importance . But Stricker in his work quotes Lionel Beale's explanation of the "significance of the nucleus" ,but at the same time does not seem to accept it. Beale, he says applies the term germinal layer "both to it and to protoplasm " and places them in opposition to formed material which constitutes the investing membrane . He ( Stricker ) however, admits that this view contains "an indication that the nucleus and protoplasm possess certain characters in common". "That the nucleus was something of secondary importance, was further impressed upon the scientific minds of the period by HAECKEL'S (1834-1919) discovery of cells which he called cytodes .Haeckel was interested in a group of life-forms called the Monera ,and to

(1).Comparative histology p.33.

this order he refers single-celled organisms without nucleus ,that is, those formed of only a homogeneous mass. He has described many of these, generally amoeboid organisms and many of them with systematic validity . But the greatly improved microscopy of modern times has actually discovered in the majority of these ,a nuclear substance ,either in the form of a single nucleus or divided into minute particles ,and modern scientists, who have learnt by greater experience to count the nuclear substance among the essential components in a cell capable of life ,have in general, presupposed the existence of the nucleus ,even in cells in which ,owing to its minimal dimensions or indistinct contents ,it has not been possible to confirm its existence . Haeckel ,however ,stubbornly held to his non-nuclear Monera ,the existence of which he regarded ,as an essential qualification of that spontaneous generation by which he believed life to have arisen ,and which he looked upon as " a logical postulate for philosophical natural science , " a theory which later culminated in the formulation of his natural - -philosophical speculation which gave him both fame and ill fame .

From these deductions Leydig defined the cell as a " mass of protoplasm containing a nucleus . "

Schultze ,however, has probably laid the foundation of the modern idea of cell in his essay published in 1861 . At the beginning of his essay he asks " what is the most essential thing in a cell ? " The old theory which ,as we have seen Virchow still embraced would answer " A vesicle surrounded by a membrane with a nucleus and fluid contents " . Schultze refers to the embryonic cells and points out that these consist of a mass of protoplasm,with nucleus ,but without any surrounding walls ; the membrane which had previously been supposed to surround these cells ,and which certain investigators had brought out by chemical means ,he proves to be an artificial product.

No general statement can be made respecting the form of cells ,especially the amoeboid ,since the mutability of their shape is their distinguishing characteristic . In places,where numbers are accumlated together they become flattened . Thus,the segmentation spherules ,whilst still in their natural position ,are polyhedral with flattened sides,which are mutually opposed to the similar surfaces of others. Similar appearances are presented in most instances where soft and yielding cells completely fill a given space ; but one axis may be longer than the other ,as is the case in the inferior layers of laminated epithelia ,where they generally form prisms ,or are arranged in the form of palisades . The cells which are superjacent to them, on the other hand ,are polyhedral, without any one axis being longer than the other . Cells which line the interior of cavities as a single layer ,appear either in the form of plates of different shape - the endothelial cells of His - or of cells in which the long axis is predominant - cylindrical epithelial cells .

Remak and Duncan investigating the cells lining the renal capsules of some amphibia describes a form of cell which to them apeeared"as quite peculiar " - the ciliated cell- . They state that this form varies to a considerable extent ,but the cilia are always limited to one portion of the surface ,and constantly project with their free extremities,into the interior of the cavity , of the organ they line.

The cilia they state as being of various length ,and may on the one hand considerably exceed the long diameter of the cell,as occurred in the organ they examined .

From time to time the form of the cell has been looked upon as approximately ,spherical ,but this is seldom realised, except in isolated cells,such as the unicellular plants and animals or the egg-cell of the higher forms . In the majority of cases the typical spherical form is modified by unequal growth and differentiation ,by active movement of the cell-substance ,or by the pressure of surrounding structures ,and the true angular forms are rarely assumed, except by cells surrounded by hard walls .

The physiological peculiarities of cells, have been studied throughout the ages, and the early observers were practically unanimous in their descriptions . They described the contractile substance ,or protoplasm, as being homogenous ,or destitute of structure (1). It rarely occurred ,however ,in a pure state ,for small "particles" were usually embedded in it ,which have either been taken up from without ,or have formed in the interior ,as a consequence of chemical processes . If the protoplasm contains many coloured corpuscles they called the cell a pigment cell ; if it contained fat ,a fat or granule-cell ,and they indicated the presence of small colourless ,dull or shining granules ,by the term "granular" applied to the whole cell ,and of such cells they distingushed two kinds ,those that are coarsely, and those that are finely granular .

The researches of Haeckel, have shown us that foreign matters can penetrate into the interior of the protoplasm . Whilst injecting Thetis fimbria with indigo ,he discovered that fine particles of coloring matter could penetrate into the interior of blood corpuscles. Suspending the cell in a medium ( e,g. blood plasma ) he introduced a finely granular colouring matter into the

(I). Virchow and Stricker .

latter ,and soon found that the particles adhered to the cell--surface and gradually passed into the interior .

Further investigations were then made to determine whether a body which lies within the cell is the result of some chemical process in the interior of the protoplasm or whether it has been introduced from without. There were many investigators in this field . RECKLINGHAUSEN . SCHULTZE ? and COHNHEIM . and the question as to whence the colouring matter proceeds, was answered by the experiment itself . But it was more difficult to decide from whence those bodies found imbedded in the cells ,without the agency of an experimenter,proceed .

Before considering the origin of these bodies ,we should first turn our attention to the protoplasm in greater detail . We have already learnt, that it forms the active basis of the cell ; sometimes apparently homogeneous ,more frequently granular ,giving the appearance of a mesh-work ,and also that it contains various , "lifeless " bodies suspended in meshes . Virchow had clearly shown , that it was difficult to distinguish between the active and the passive contents of the cell . He states"that the chief point is to obtain a recognition of the fact that the cell is really the ultimate morphological element in which there is any manifestation of life and and that we must not transfer the seat of real action to any point beyond the cell.

Much discussion has been given to this question as to which of the visible elements should be regarded as " living " substance proper ,and the diversity of opinion may be judged ,by the fact that altho' many earlier observiers identified the "reticular" as the living element ,and the ground substance as lifeless ,others such as Leydig ,and Schafer ,held exactly opposite views ,while Aalltmann insisted ,that only the"granules" were alive .

Protoplasm, deprived of its nuclear element has lost one of the most characteristic vital properties ,namely :- the power of synthetic metabolism ,yet it is referred to as"living" because it still retains for a longer or shorter period ,such properties as irritability ,and the power of coordinate movement . Some adopted the views of Sachs,Kolliker, and Verworn, life can only be properly regarded as a property of the cell-system ,as a whole ,and the separate elements of the system would ,as Sachs points out ,better be designated as " active ", or passive ,rather than"living or "lifeless ". Thus regarded ,Virchow's difficulty in deciding which were active ,and which were passive elements , together with the "protoplasmic ,and " metoplasmic " ideas which followed later -though a real problem -becomes one of degree- Sachs sharply distinguishes between the "energid " (nucleus andxprm protoplasm ) which forms the living unit ,and the passive energid

" products ",pāacing in the former the nucleus, nucleolus ,general cytoplasm centrosome and plastids ,and in the latter ,the starch grains, aleurone -crystals and membrane . Meyer howerer,carries the analysis further ;he classifies the active energid -elements into protoplasmatic ,and alloplasmatic organs ,the former (nucleus cytoplasm chromatophores ,arising only by division ,and the latter (cilia,muscle ,and nerve -fibrillae ) formed by differentiation from the protoplasmic elements .The passive energid -products i.e. the ergastic structures or "forɱed material " of Beale - are formed , according to him ,as "enclosures " (starch -grains etc ) or excretions .

Hanstein and Kupffer , however have distinguished between these ; the passive contents have been designated by the former as metaplasm,and latter calls it paraplasm;in contradistinction to the active propoplasm. But later researchers state, that it is often difficult to distinguish between the "protoplasmic " and "metaplasmic" elements ,because as it will be shown later ,there is reason to believe that these bodies cannot be definitely separated but are connected by various gradations .

These investigations led to confused ideas as regards the use of the word protoplasm .When Leydig ,Schlutze, Brucke ,Barry and others earlier writers spoke of "protoplasm" they had in mind only the substance of the cell-body .STRASBURGER, however , in 1882 , extended the term so as to denote the entire cell-substance ,including the nuclear material ,suggesting that the latter be called "nucleoplasm " and that of the cell-body "cytoplasm These terms have been adopted by many,but not all later writers the word ,"nucleoplasm " having at the suggestion of Flemming , been changed into Karoyoplasm . Butcheli , Hertwig ; and Kolliker, use the word protoplasm in its original narrower sense equivalent ,therfore, to Strasburger's cytoplasm - while the majority of later writers have accepted the terminology of Strasburger, and Fleming, cytoplasm, and karyoplasm .

The differentiation of the active cell-substance into a nucleus and cell body was considered as a fundemental character of the cell, because of its almost universal occurrence , and because there was reason to believe, that it was in some manner an expression of the dual aspect of the fundemental process of metabolism that lies at the basis of cell life .

In the field of Zoology , Butcheli , Hertwig , and Flemming ,during the same decade ,made decisive contributions to our knowledge of the nuclear division .[1]

(I). Discussed elsewhere.

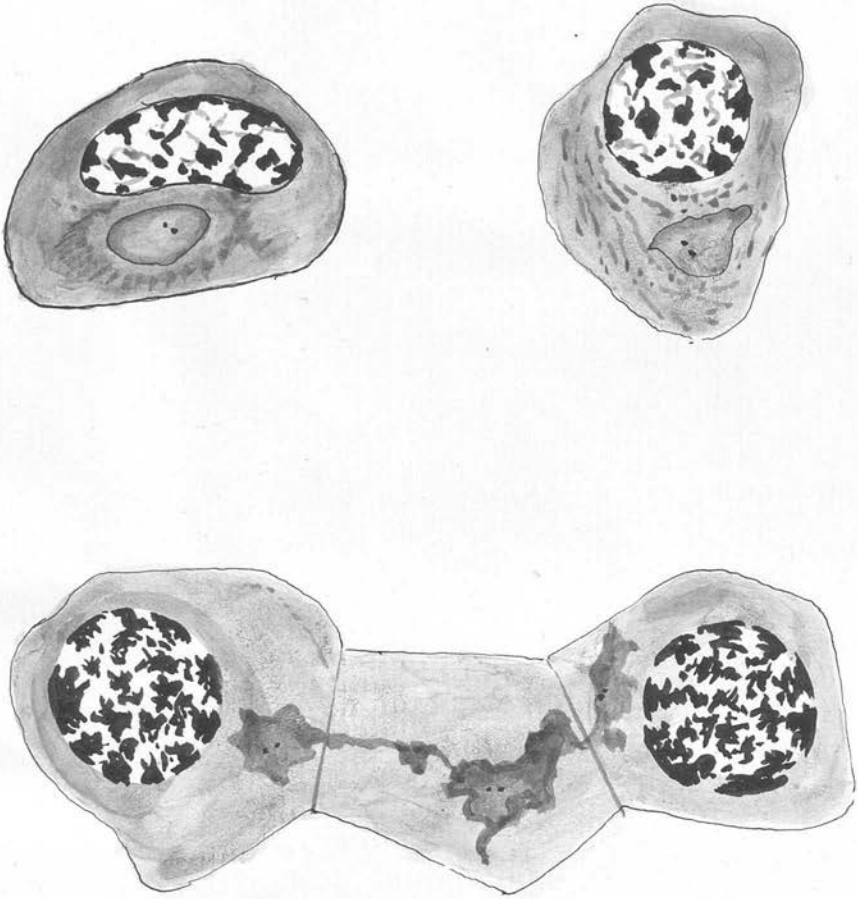

FIG. 2(A). Spermatogonia of salamander. [MEVES]

Above. two cells showing large nuclei, with linin threads & scattered chromatin-granules.

Below. Three contiguous spermatogonia, showing chromatin reticulum, centrosomes, spheres and sphere-bridges.

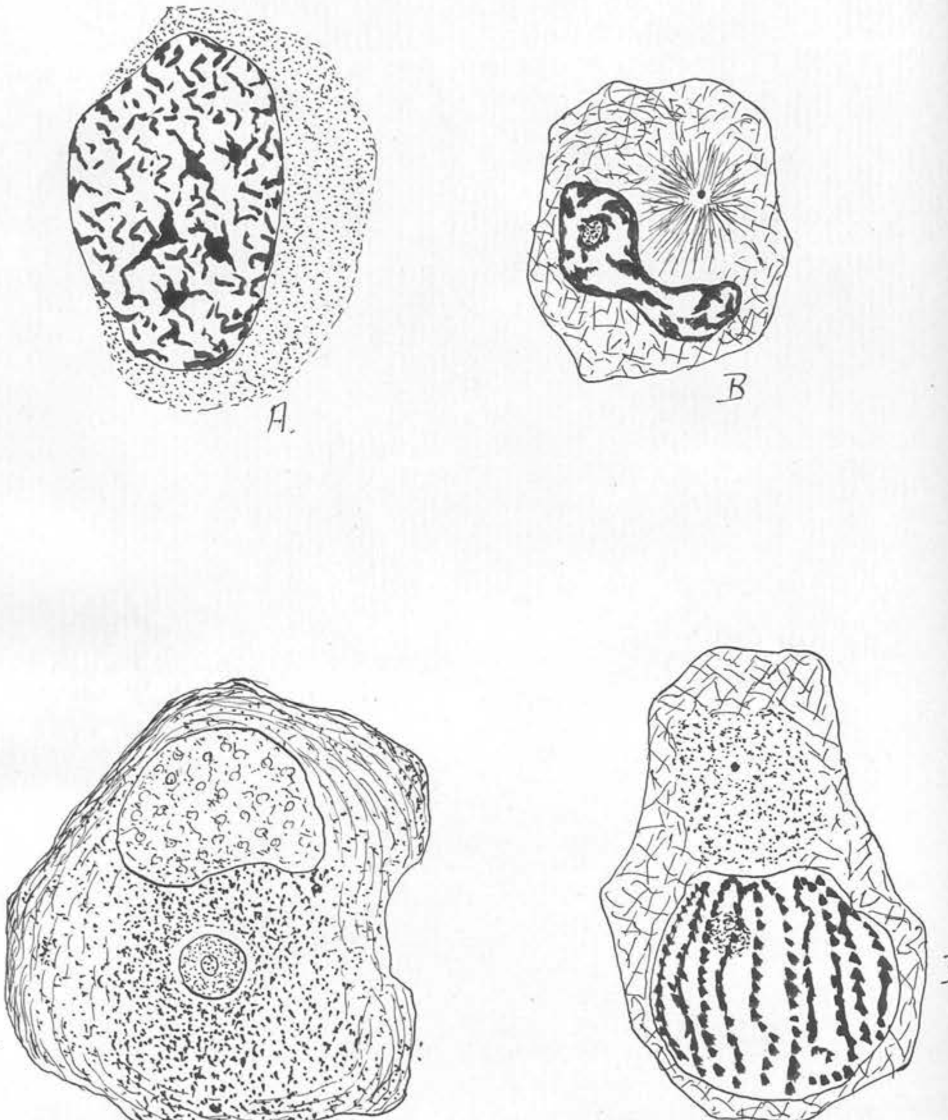

FIG. 2(B). VARIOUS CELLS. SHOWING TYPICAL PARTS.

A. peritoneal. Epithelium. of Salamander. Two centrosomes on rig
Nucleus. showing net. Knots. [FLEMMING]

B. spermatogonium of frog. - Attraction-sphere, single centrosome.
Nucleus with a single plasmosome. [HERMANN]

C. Spinal. ganglion-cell of frog. Attraction sphere. near centre.
single centrosome. with many centrioles [LENHOSSEK].

D. spermatocyte. of Proteus. Nucleus in spireme stage. -
Single centrosome. - attraction. sphere. - containing rod. shaped.
bodies. [HERMANN]

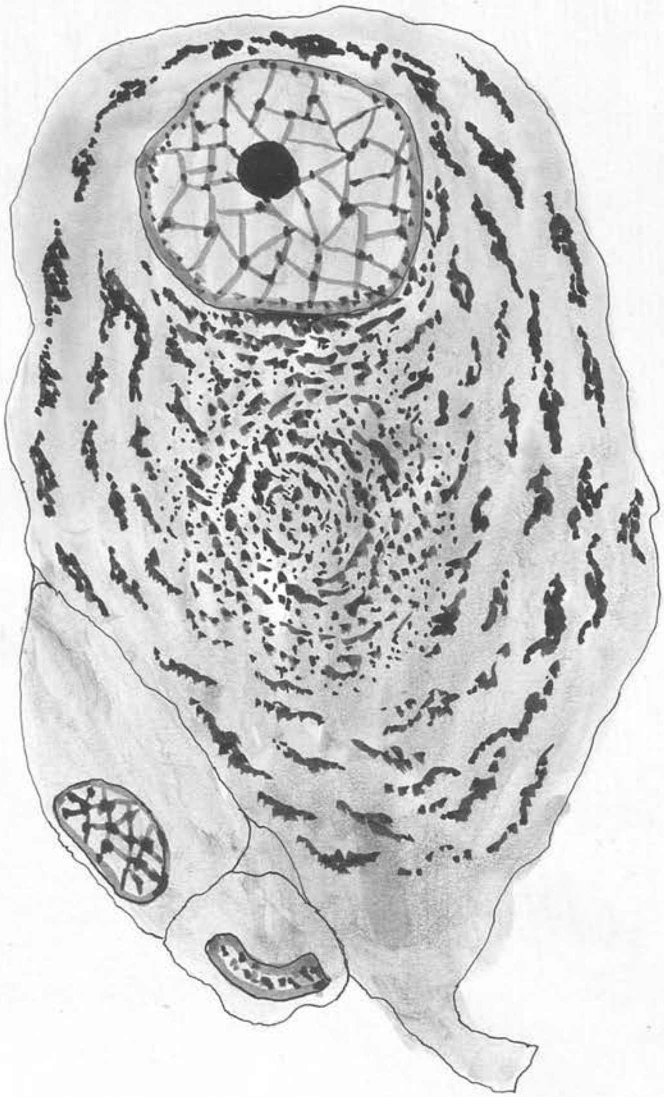

FIG 3. Spinal. Ganglion-cell. of FROG.
(Lenhossek.)

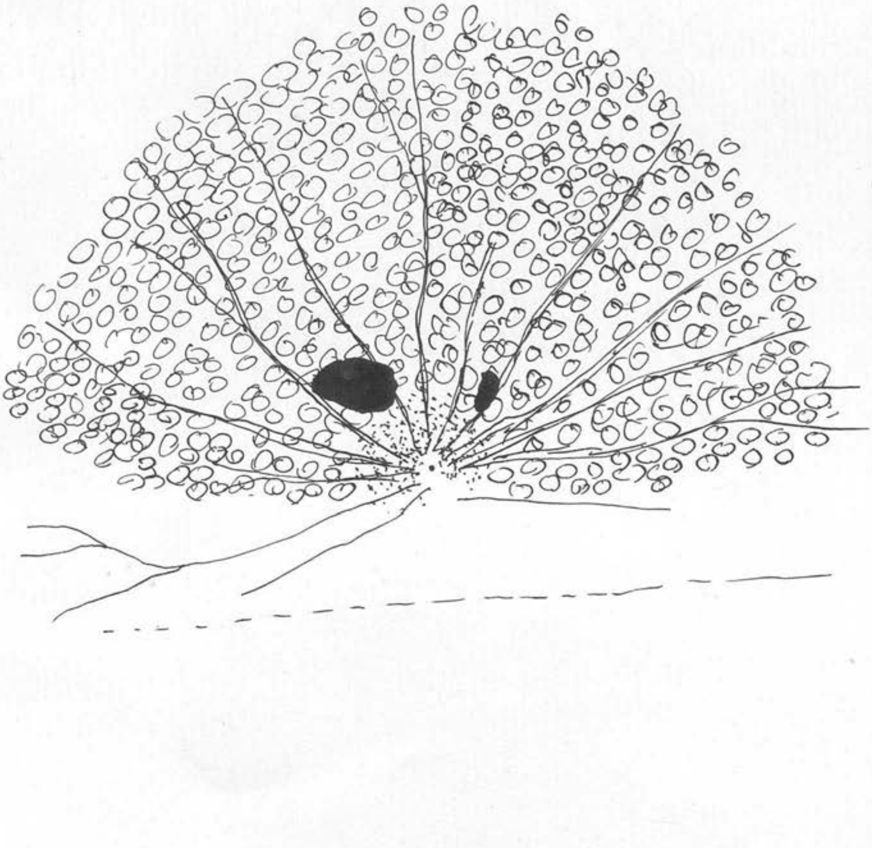

FIG. 4. Section of Sea-Urchin egg. 1½ minutes after entran
spermatozoon. Showing alveoli and microsomes

As a result of this research work, the elements composing the nucleus, were also investigated : the filament substance and nucleolus, nuclear juice, and nuclear membrane, were the constituents first distinguished .

FLEMMING ,BOVERI ,and Van BEVEDEN , carrying out further investigations of the achromatin filaments during division discovered the minute centre body -the centrosome , which was also considered as a third eseential element of the cell. ( See Fig 27 and 28 ).

The protoplasm of the cell, and its many and various derivities, have offered fresh problems for every generation . the actual basic substance has been investigated by a vast number of scientists, and has called forth many attempts at an interpretation of its essence . Some of these attempts have never been considered as worthy of notice ,and consequently have been lost in the sea of science, like the receding wave is lost in the ocean . But , however , there are three different theories based on observations which have been handed down to us and they are named after their founders :- Bucheli's froth, or alveolar theory ,Flemming's filament theory, and Alltman's granule theory . The chief difficulty that revealed itself in these explanations, and that brought out

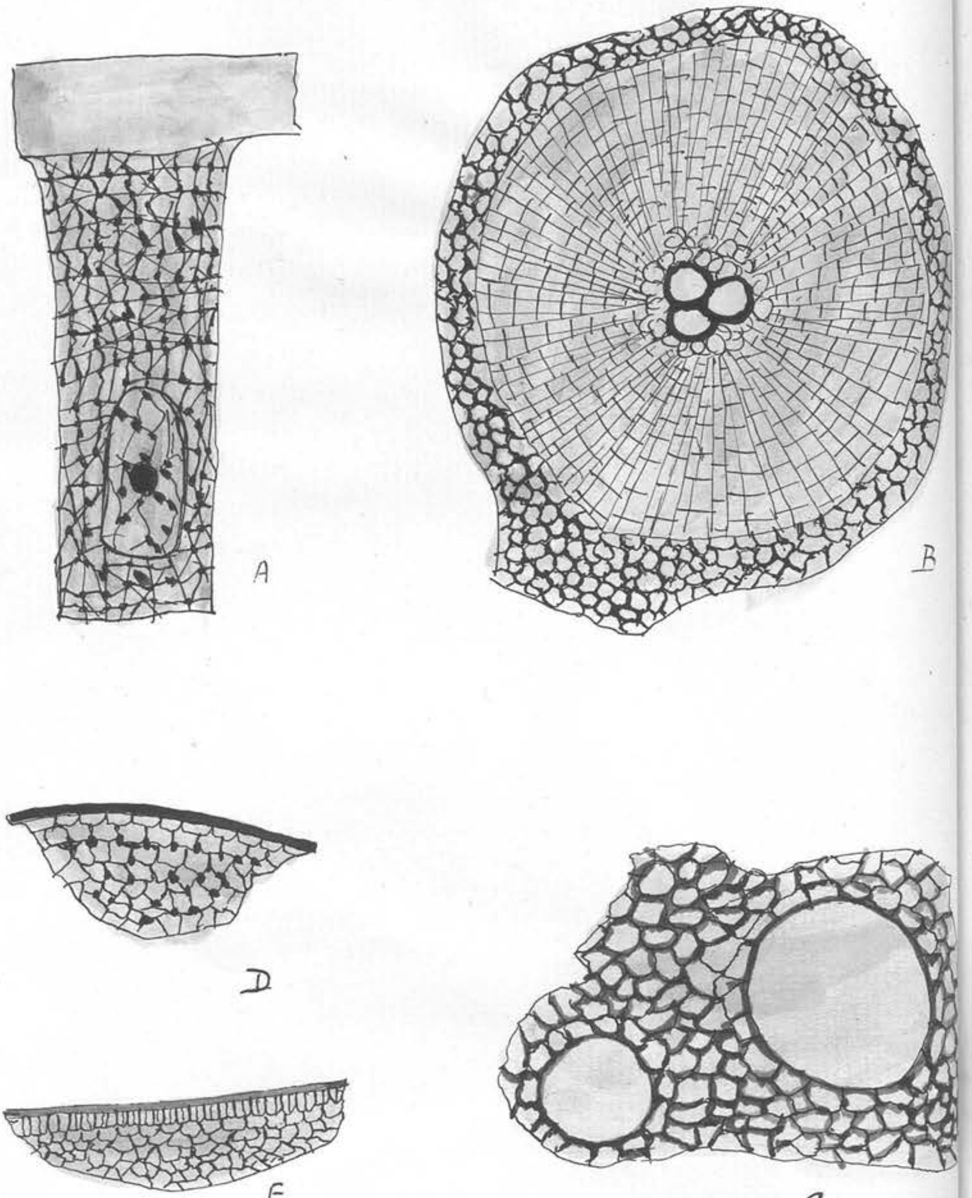


FIG. 6. Alveolar or foam-structure of Protoplasm. (according to B

A. Epidermal cell. (earthworm).
B. Aster, attraction sphere, & centrosome. (Sea-urchin egg)
C. Intrascapular protoplasm of a radiolarian with vacuoles.

D. Peripheral cytopl
E. Artificial emuls
Nacl. + $H_2O$.

their mutual contradictions, is actually caused by the inconstantcy which the living protoplasm always displays, and which is a necessary consequence of its rolê, as a bearer of all metabolism, in the cells and the organisms composed of them .

Butcheli's froth theory is a purely physical attempt, to explain the structure of propoplasm , He certainly points outk the chemical reactionary phenomena of the cell ,but pays very little attention to them . He regards the protoplasm as having a foam-like alveolar structure ( Wabenstruktur )(See Fig 5 ) Taking as his basis the strongly vacuolised substance of the lowest Protozoa,especially the amoeba ,with the current-phenomena visible therein ,he conceives the living protoplasm as a fluid mass, identical in its structure with the emulsion that is obtained when oil and soda-solution are shaken together . (See Fig 6 . ) This purely mechamical emulsion-theory ,he afterwards elaborated , after making a series of experiments of an ingenious character . By mixing variously composed liquids, he succeeded in imitating in a surprisingly natural manner, a great many of the most complicated movements, and structures, of the living protoplasm . But, as a reproduction of the phenomena of life, these experiments possess the fundemental error of entirely disregarding the chemical reaction

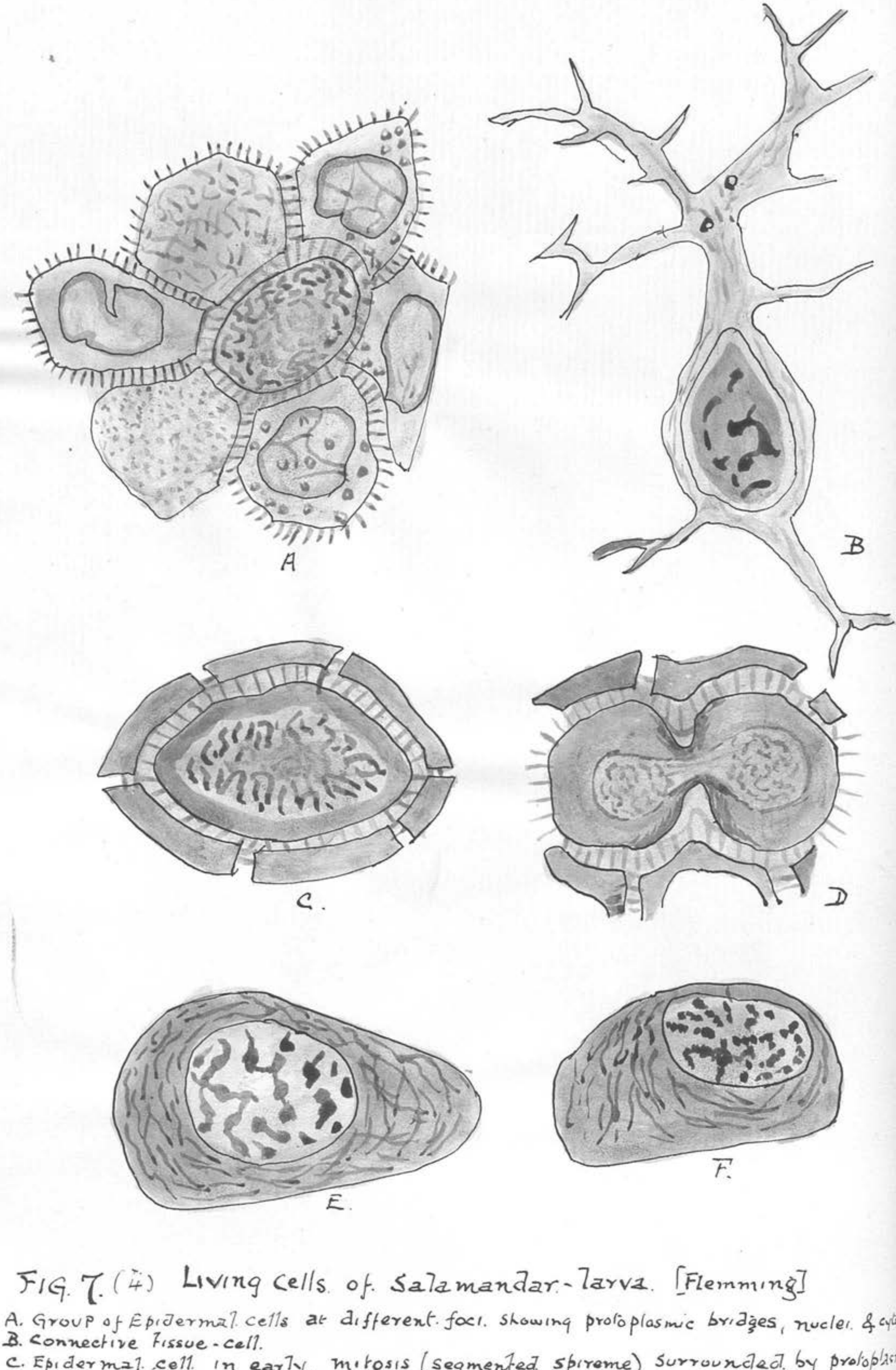


FIG. 7. (4) Living cells of Salamandar-larva. [Flemming]

A. Group of Epidermal cells at different foci. showing protoplasmic bridges, nuclei & cytop
B. Connective tissue-cell.
C. Epidermal cell in early mitosis (segmented spireme) surrounded by protoplasm
D. Dividing cell.
E. F. Cartilage-cell with cytoplasmic fribrillae

that is incessantly going on in living substance ;the mobile oil-emulsion remains chemically what it was ,whereas as a creeping amoeba is continually changing its chemical composition ,so that the movement,and the chemical reaction,are indissolubly dependent upon each other . Associated with this,we find a belief, which is wholly unsatisfactory from the very beginning ,that the fundemental substance of life is fluid -a theory that has been considerably revised by modern colloid chemistry ,of which we shall have more to say presently .

Flemming's plasma theory- (reticular theory of Klein, Van Beneden ,and Heitzmann ) takes into account more chemical conditions . According to this theory ,the protoplasm consists of a network of fibres embedded in a homogeneous substance . These structures he found in the cellular mass in various tissue-elements , (See Fig.7 ) in egg-cells and in cartilaginous,and glandular cells in higher animals .He believes the phenemena of metabolism in the cell to be accompanied by changes in the filament mass ,and in the basic substance .The threads may sometimes be dissolved into canals and vacuoles ,and thereby convey the assimilation products not only to different places within the cell ,but also between various cells,for these latter in most cases demonstratly connected with one another by bridges of filaments ,so that the cells become the structural elements of the body,as well as elements incorparated in the same vital unit,and their independence need not be over-stressed as hitherto had been the case .

In oppssition to these theories ,which belong to the eighties ,there appeared somewhat later the granule theory of Alltmann of Leipzig (1852-1901). He devoted his attention chiefly to the fundemental substance in which the above described network of plasm lies embedded ,and with the aid of suitable colouring-matter he found in it a mass of grainlike formations -granulae of different kinds in different cells . In these he sees the true substance of the cell ,and he finds that the thread-like structures which can be produced by Flemming's method are composed of similar granular formations . Many of his observations have been confirmed ; in the glandular cells especially ,the forthcoming secretion first appears in the form of homogeneous granules ,which gradulaly increase in aize and assume the form of drops . Altmann calls these granules bioblasts (βίος -life βλαστος a germ ) and considers them to be the true elementary organisms of which cells and tissues are composed ,just as bacterial colonies are composed of various bacteria. Later writers state that Altmann is on firmer ground when he states that the living substance must be solid and not liquid -an assertion, he bases upon his granula theory in opposition to Butcheli'S above mentioned experiments , and speculations . These granular structures have been studied by recent investigators ,who have given them innumerable names , "chondriosomes "mitochondria " etc. They are brought to light by the special colouring-methods ,but in favourable circumstances they may also be visible in the living subject ,which justifies the assumption that theyare not purely artificial products .

The present drift of opinion is toward the conclusion that none of the above interpretations have succeeded in giving a universal formula for protoplasmic structure ,and many recent observers have arrived at the conclusion ,earlier advocated by Kolliker ('89 ) ,that the various type described above are connected by intermediate gradations ,and may be transformed one into another , in different phases of cell-activity . Unna ('95 ) ,for example endeavours to show how an alveolar structure may pass into a sponge-like or reticular structure by the breaking down of the inter-alveolar walls. Flemming now also admits that protoplasm may be fibrillar ,alveolar,granular ,or homogeneous ,and that we, therefore, cannot regard anyone of these types of structure as absolutely diagnostic of the living substances . In plant-cells ,Strasburger maintains that the"Kinoplasm" (κινεῖν = to move ) from which the spindle-fibres and astral rays are formed is fibrillar ,while the trophoplasm (τροφή = nourishment )forming the main body of the cell is alveolar ,the former ,assuming the fibrillar state structure as a rule ,only during the miototic activity of the cell . M. Heidenhain, points out the possibility of all the three structural forms existing in the one and same cell ,but this would also show, that none of these structural theories, are capable of forming the basis of a uniform conception of the composition of living matter. Heidenhain however goes further, and states, that the common structure of the living plasm must be sought beyond that which is microscopically visible -that it consists in a system of minute particles which possess the essential qualities of life ,principally those of multiplication by ~~fission~~ division ,and those that build up the structures of which the cell is composed. These particles he calls "plasomes" (πλασμα + σωμα = body) ,a term also adopted by Weisner about the same time (1890.) . It will be realised, that in this term we have a name for Haeckels' Plastidules, and Darwin's gemmules - unknown quantities, that can be used neither for the purpose of observation, nor for theoretical calculation, and are, therefore, automatically eliminated from the problem of life,but the facts regarding the cell -composition contributed by modern chemical research is no doubt of greater value.

Colloid chemistry ,with its own methods of investigations has made it possible for us to study far more closely than before, the structural details of the living substance. These accurate observations, and experiments, have given a more natural explanation of the granular ,and vacuolised structure of the plasm than Butcheli's froth theory . In many instances, it has been possible to compare the mutual interpenetration of the various structures, with physical, and chemical metabolistic phenomena, occurring in inaminate colloid substance, and the old dispute , and to the solid or fluid nature of plasm, has lost its force.

Reviewing briefly the plasma theories, we find, that Butcheli had always maintained that ~~ptmp~~ protoplasm obeys the fundemental laws of a fluid mass . He also attributed the lack of visible structure in hyaline protoplasm to the extreme attenuation of its alveolar walls' .

From a purely observational point of view, it can hardly be stated that Butcheli's theory stands on firmer basis than Altmanns theory (for granules in hyaline protoplasm may be as invisible, as colourless beads in oil ), nevertheless it has been more generally accepted because of its close analogy to our

~~(I).~~ 1894 Ed. p 264.

present conceptions regarding the structure of colloids . The great service which Butcheli has rendered to science, lies in the fact, that he firmly established that protoplasm is essentially a fluid .

In many forms of protoplasm ,both in life and after fixation ,the investigators of the period (Fromann and others ) had differentiated its structure to a more or less regular framework or meshwork ,consisting of the meshwork proper and the ground substance, which occupies the intervening spaces. This ground-substance is often referred to as cell-sap, enchylema, [1] Hanstein, and Carnoy (I880-) hyoloplasm (Leydig (I882) or interfillar substance . To these may be added the minute microsomes [2] ,or granules which are scattered sometimes quite regular other times irregular ,along the branches of the mesh-work and also the metaplasmic (passive ) substances already discussed.

It had also been recognised, that in the unicellular forms the gloplasmic substance is often differentiated into an inner medullary substance, or endoplasm, wherein lies the nucleus ,and an outer cortical substance, or ectoplasm, from which the more

(I).Enchylema (ἐν =in χυλος =juice );hyaloplasm (ὕαλος=glass ) para-
- mitone (μιτωμα from μιτος = thread)
(2) (μικρος =small; σωμα =body .

differentiated products of cytoplasm ,such as cilia, and membrane , ~~like~~ take their origin . Indications of these differentiation was first described by Küpffer (1875) whilst carrying out investigations, on tissue-cells of animals .

This cortical layer, Kupffer calls "paraplasm "and the medullary zone is termed "protoplasm",sensu strictu " . ~~Strax~~ Strasburger refers to the latter as Kornerplasma, and Nageli calls it polioplasma . To him it appears to be a general rule that the nucleus is surrounded by protoplasm of relatively slight differentiation ,while the more highly differentiated products of cell-activity are laid down in the more peripheral region of the cell ,either in the cortical zone or at one end of the cell .[1]- a fact, which, according to Kupffer, is of importance ,not because it is an expression of the adoption of the cell to its external environments ,but also, because of its bearing on problems of nutrition .

The most discussed question during this period, was whether the sponge-like ,fibrillar or alveolar appearance was a normal condition existing during life . They had discovered that there were many cases ,especially in plant cells,in which the most careful

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Cf. polarity of cell page .

examination had failed to reveal the presence of a reticulum, the protoplasm appearing only as a finely granular substance .

This, and the additional facts, that the cytoplasm may show active streaming and flowing movements led some authors , especially the botanists ,to regard the reticulum, as non-essential, and as being when present either a secondary differentiation specially developed to perform some particular function, of a mere congulation -product due to the action of fixatives.

Flemming in 1882 called attention to the danger of mistaking such coagulation -products for normal structures as seen in fixed and stained material ,and his warning ,was further emphasised by the later experiments of Berthold (1886 ) Schwarz (1887) and Butcheli (1892) and Fisher ('94-99) . Butceli's extensive studies of coagulation -phenomena show that coagulated albumin ,gelatin etc. show a fine alveolar structure .Similarly the experiments of Hardy and Fisher ('99) give strong evidence that not only the fibrillar and alveolar formations ,but also the microsomes observed in cell-structures ,are in part normal structures . Thes investigations state that the alveolar structure may be seen in Protozoa,living cells of cartilage and epithelium

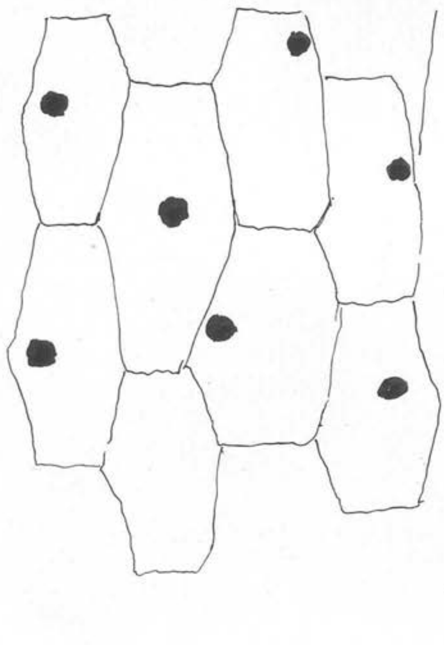


FIG. 8.

After. Balfour.

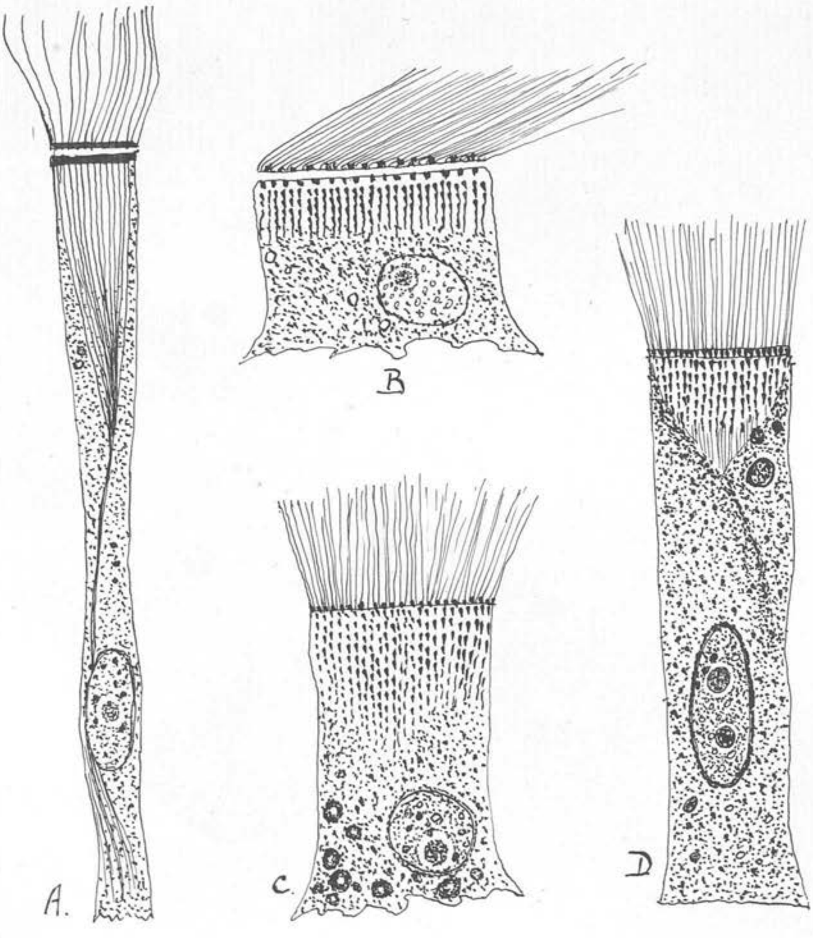



FIG. 9. Ciliated cells, showing cytoplasmic fibrillae terminating in a zone of peripheral microsomes, to which cilia are attached.

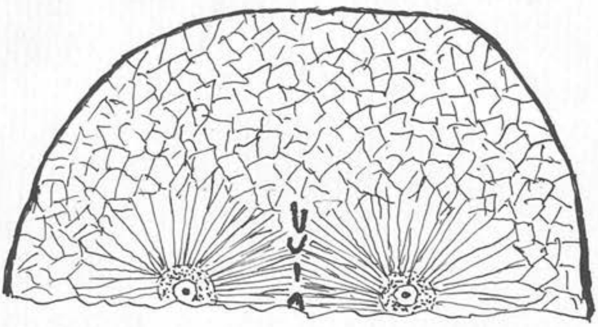
A. Intestinal epithelium of Anodonta.

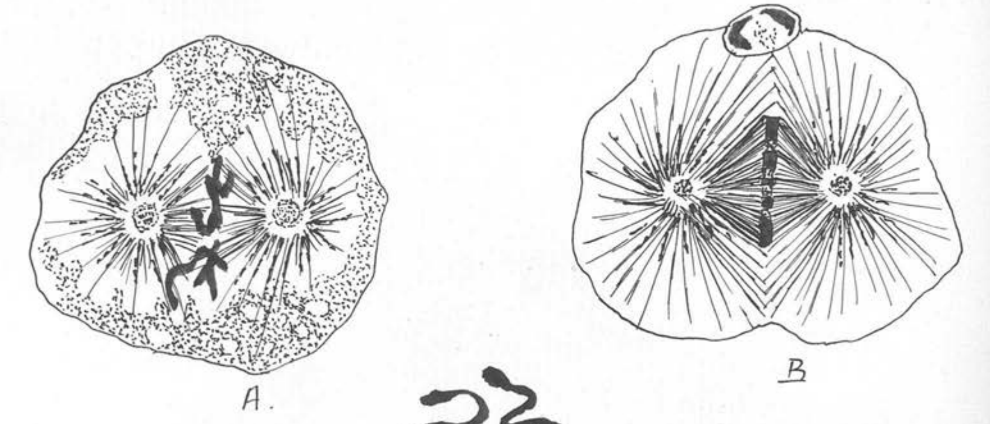
B From gill of Anodonta

C. D. Intestinal epithelium of Cyclas.

connective-tissue and other animal cells ( See Fig 7 .). Engèlman described the same structure in ciliated cells in muscle-fibres and neeve-fibres (See Fig.9.)and especially in the mitotic figure of dividing cellà ,Fig IO and II.). Mathews and other later researchers have the genesis of àlveolar structure in the living cells of exhinoderm eggs aad they state that her the protoplasm a appears at first almost like glass ,showing at the most a sparse and fine granulation ;but after fixing and staining it a mass of fine closely crowded grabules appears . This may indicate the existence of an extremely fine alveolar structure during life ,but after investigations however,consider the granulols as coagulation.--products because they closely resemble the coagulation granules found in structureless proteids.

Graf and Bolsius describe a form of cyto-reticulum which they became acquainted with in the nephridial cells of leeches (See Fig I2 ). The mess-worh here is distinct and regular and scattered microsomes are found along its threads . In cartilage cells and connective tissue-cells where the threads can be seen in life ,the net-work is described as being loose and open and to xpp appear as consisting of more or less ,separate threads (Fig (Fig 7) This is also clearly shown in ciliated epithelium ,the fibrillar corresponding in number with the cilia as if continuous with their






[ FIG. 3 A. also. ] Diagram of Dividing Cell.

FIG. 10 + 11. The middle phases of mitosis [BOVERI]

A. closing phase, equatorial plate forming. B. {Metaphase, Eq plate formed
& chromosomes split.

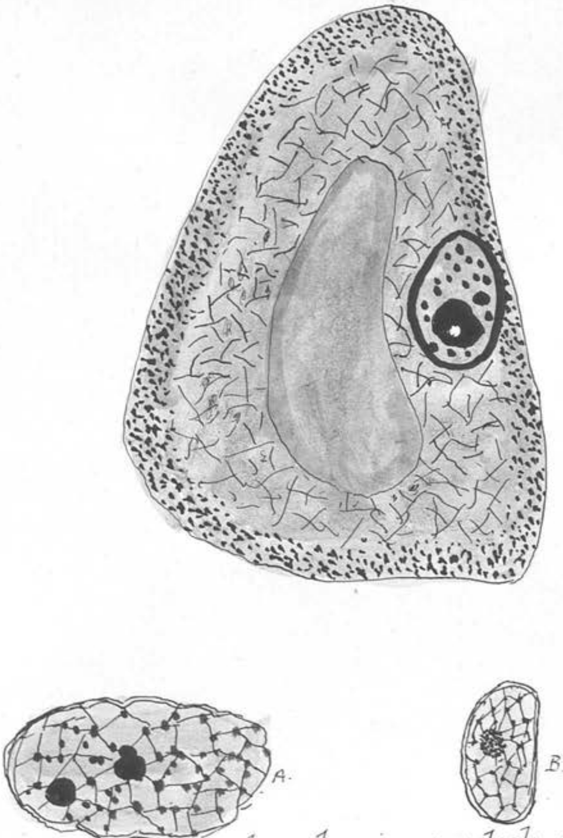
C. Early. Anaphase. - divergence of daughter - chromosomes. D. Later/an bases ( Fig 9).

Also in the nerve fibres already mentioned ,the threads form closely set parrelel fibrillae which may be traced into the body of the nerve cells ,where according to most authors they break up into a net-work in which are suspended numerous deeply staining masses "the chromophilic granules" of Nissl(seeFig I3) Also the remarkable researches of Apathy (1897)on the nerve cells of leeches have revealed within the cell the existence of complex and definite network bearing definite relations to incoming and outgoing fibrillae.

Ballowitz investigating contractile element in a smooth muscle ,and in tails of spermatoza, states that the threads are most conspicuous, and that they have a parrell course. Retzius, Carnoy, and Van Gehuchten ,state that the meshes in striped muscle-fibres (1) have a rectangular form ,and that the principle fibrillae ,having a longitudinal course

This peculiarity of the Cytoplasm has also been shown in the dividing cells (figIO andII),where, according to Engelman , the fibrillae group themselves in two radiating systems or "asters" which are considered in some manner the immediate agents of cell-division .Similar radiating systems of fibres occur in amoeboid

(I).Cf Sir E Sharpey-schafer Essentials of Histology.




A.B. - isolated nuclei showing nucleoli and chromatin-granules.

FIG. 12 Section through nephridial cell of Leech.
cytoplasm forms regular & distinct reticulum.
with scattered microsomes
Larger bodies within ground substance are metaplasm
The nucleus, on the right, is surrounded by a thick chromatic membrane, & contains numerous scattered chromatin-granules. [GRAF.]

cells such as laucocytes (FigI4) and pigment cells.

It will be seen that Butcheli's views differ considerably from the foregoing ,the fibrillae being regarded as the optical sections of thin plates which form the walls of closed chambers filled by a more liquid substance .Butcheli,followed by others such as Reinke,Eismonal and Erlonger ,interpets the astral systems, of dividing cells ,which are regarded as a radial configuration of the plates, around a central point (Fig6B), in the same sense .But Mathews and Wilson believe, that there is strong evidence against this view ,in the appearance of the spindle and asters in cross - sections .Investigating the egg of Nereis they state, that in the early stages the astral rays are coarse anastomosing fibres (FigI5) which stain deeply and are therefore favourable for observation . As proof, that these are fibres ,they state that the rays are cut at various angles by sagittal sections ; the cut ends of the fibres appearing not as plates ,but as dots from which the ray ,in oblique sections may be traced inwards . Drüner also states the spindle consists of rounded dots like the "end of a bundle of wires " when viewed in cross-section (Fig I6) .

A review of this period ,taking the structure of

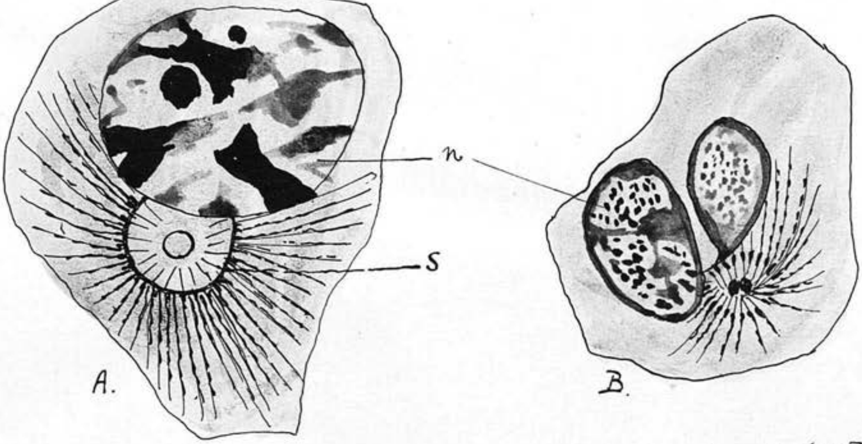



FIG. 13. Leucocytes. of the. salamander. [Heindenhain].

A. Cell with single nucleus. containing course network of chromatin., & two nucleoli. (S) permanent aster. & attraction-sphere.

B. Similar cell. with double nucleus. showing (large) basi- & [small] oxychromatin- granules.

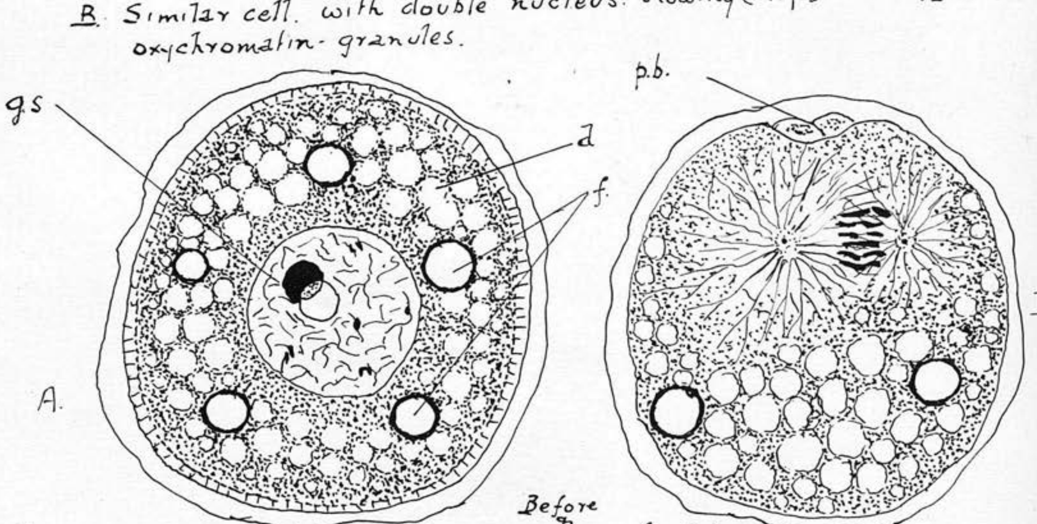



FIG. 14. EGGS of the Nereis Before & after. fertilisation.

A. before. fertilisation. Large germinal. vesicle with chromatin-network & the tetrads. (gs). double germinal spot (d) deutoplasm-spheres. (f). fat-drops.

B. Some time after. fertilisation and. about to divide. The deutoplasm is now concentrated. in the lower hemisphere Above, are the two polar bodies. (p.b.). Below them lies the mitotic figure, the chromosomes dividing cytoplasm in echinoderm-eggs as our point of departure ,we find that the alveolar structure in these eggs is entirely of secondary origin ,and that all the visible structural elements arise during the growth of the eggs ,by the deposit and subsequent enlargement of minute spherical bodies ,all having the appearance of liquid drops in a homogenous or finely granular basis which itself is a liquid . Some of these minute bodies enlarge to form alveolar spheres while the homogeneous basis or continuous substance remains as the inter-alveolar material .Others remain much smaller so as to constitute the "microsomes " scattered along the threads .It has also been pointed out that these microsomes ,like the alveolar spheres ,are perfectly visible during life ,as well as in section ; they are therefore not coagulation-products . From these three elements arise all the other structures observed in these eggs , deutoplasm[1] spheres and pigment bodies being formed by chemical alteration of the spheres ,while the astral rays and spindle-fibres are differentiated out of the inter-alveolar material and microsomes According to their theories ,these various elements show a continuous gradation in size from the smallest to the largest ,the former being the source of all the larger elements ,and emerging into view from the "homogeneous " basis . But the real question whethere the granules - ultra-microscopical bodies -exist as permanent organised bodies still remain to be settled. The question

(I). δευτερος) = second .

was then approached by an indirect method, that is ,through the study of the phenomena of nuclear division ,which will be further discudsed later.

By application of newer methods we have since ~~learne~~ learned that the alveolar structure observed by Butcheli is due in ~~mos~~ most cases to microscopic inclusions which can be eliminated without affecting the viability of the protoplasmic matrix. So far no structure has been revealed within this matrix and its colloidal nature is indicated more by its behaviour than by its general appearance. On the other hand, protoplasm is a cellular unit (I) which cannot exist, without its nucleus and its cortex and, therefore, must be regarded as a mechanism consisting of visibly differentiated and essentially inter-related parts.

From this time onwards numerous investigators such as Nemec, Heilbronn, Weber, Lyon and many others have devised new methods for ascertaining the physical nature of protoplasm and its constituents .

Considerable work has been done in detecting the effects of external agents on the streaming movements which normally occur in the protoplasm of certain cells but it is believed that

(I). As already stated it may continue to exhibit irritability ~~and~~ etc the continuance or cessation of movement does not necessarily imply viscosity changes . A surer method for detecting viscosity changes is that of Nemae (1901- 15 ) and Webers (1916) used as their test the effect of gravity on the dislocation of starch granules ,in plant cells . Lyon (1907) and Morgan (1910) and others have used the centrifuge method . Other valuable adjuncts for studying the physical nature are Heilbronn's electiomaquet method (1922) ,the detection of Brownian movement by means of a dark filled illumin--ation . It was in this manner that Robert Brown himself discovered the movement . Experience had taught the majority of investigators that protoplasm is usually too viscid,to exhibit a movement of the ordinarily visible granules ,but some have recorded that it may occur . In 1912 Kite and Chambers introduced micro-dissection and their methods were improved upon by Peterfi in 1923 . Many of these delicate experiments conducted at various research centres [1] have given fruitful results .

In order to understand and appreciate the investigatio[n] of these modern scientists we must first realise that protoplasm exists only within the confines of a cell . In plants the cell is usually separated from its neighbour by rigid walls of cellulose . On the other hand animal cells are not as a rule confined within rigid walls so that in most cases they are packed together more closely

(1).Elli Lilly Research Div.,Woods Hole;-Weir Mitchell Station Salisbury Cove.

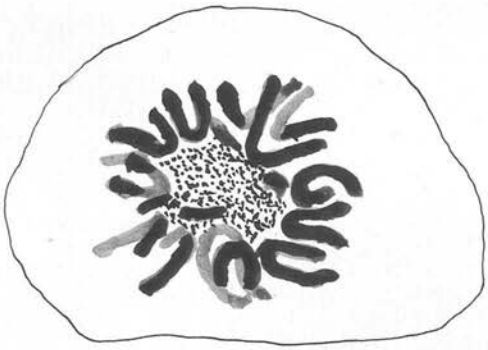


FIG. 15. TRANSVERSE. Section. through the mitotic figure. showing the ring of Chromosomes surrounding the central spindle, the cut fibres of the latter appearing as dots.

than is possible in plant cells .But ,however,it is not correct to consider the typical animal cell as being actually "naked " . If it does not possess an extraneous membrane of some kind ,it is usually surrounded by a cement-like substance which serves to hold contiguous cells together ;and it was a question of importance whether protoplasmic bridges between contiguous cells -a feature already well known in plants ,are also common in animals .

In plants cell-division usually occurs by the deposition of separate granules which subsequently coalesce to form a wall between the two daughter-cells. Frequently this union of the wall substance is incomplete thus leaving small pores , through which the daughter-cells remain connected by protoplasmic bridges.

The animal cell on the other hand ,divides by an equatorial constriction which clearly cuts the cell into two . Sometimes the division is incomplete so that the two daughter--cells remain connected by a bridge of protoplasm . But it is considered ,by these investigators ,that this method ,offers no opportunity for the formation of the numerous bridges which have been described as occurring in many tissues ,that if they do exist, they must be formed after the cell has divided . Farr I9I8 and Sharp I92I point out that the furrowing process typical for *

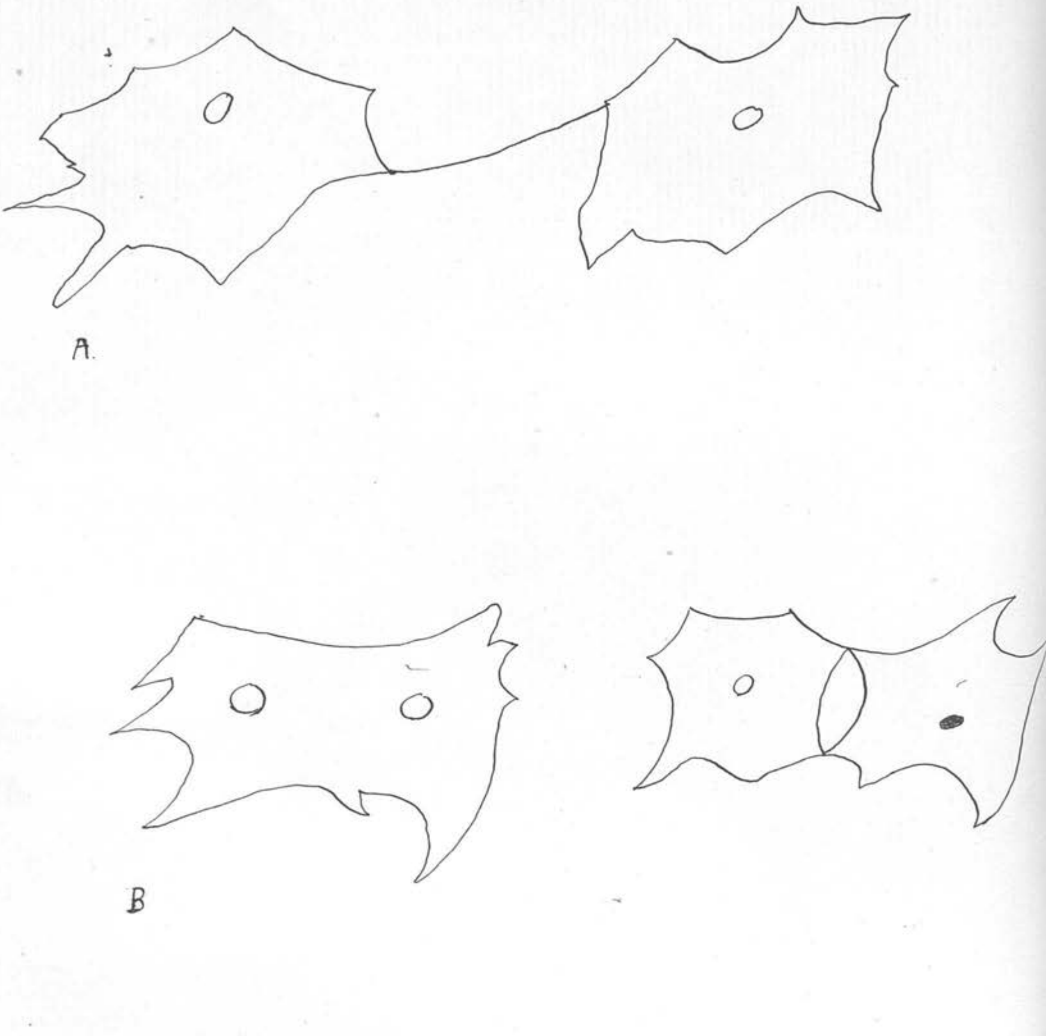



FIG. 16 A. Two cells CONNECTED BY BRIDGE.
B. Two contiguous cells, ONE of which is injured.

animal cells ,is frequently met with in plants ,in cases where a completely separated ~~xxxx~~ spare cells are to be produced .

The passage of an injury from one cell to another when a proliplasmic bridge exists has been shown by an experiment on chick mesenchyme tissue culture cells . (Fig16) - In. fig 16a the two cells are still connected by a slender strand of cytoplasm . One cell was injured by being torn with a needle ,whereby the nucleus immediately coagulated . After an elapse of several seconds the effect of the injury became apparnet in the other daughter -cells by the coagulation of its nucleus.

In contrast to this is fig 17b. where two interkinetie cells were so closely associated that the boundary between them could bet be seen . One of these cells was injured and both cells reacted immediately by partially withdrawing from each other ,but only the nucleus of the injured cell coagulated , while the other remained normal and alive . From this it is evident that the effect of mechanical injury ,can travel fromm one cell to another only when there is protoplasmic contiinuity between them.

Andrews in 1897 claimed that protoplasmic bridges exist between the blastomeres of segmenting echinoderm eggs - Chambers however, states that it is highly improbable ,because with a needle the blastomeres can be gently pushed apart or made to roll over one another within the investing egg membrane . The blastomeres have according to the latter ,perfectly smooth contours ,and they give no evidence of sonnecting strands . If the medium in which the eggs are examined axe is allowed to evaporate ,injury sets in ,and elevations appear on the surface .These grow out in slender filaments which soon produce the effect of bridges extending across the gap between the shrunken and maribund cells. It also maintained ,that these bridges are contained in many other cells especially in strati--fied epitheluin ,and they are general ly figured as fine strations extending across a narrow space between contiguous cells . Further investigations show that in the majority of the cells groups ,in the metazoan body ,there is no evidence for the existence of actual protoplasmic bridges between the cells and that the cytoplasm exists as a morphological and physiological unit in each cell of tak the body .They believe that some of its functions may be more highly specialised in one group of cells than in another ,and that the secretion of one group may effect another group of cells ; but as regards the vital phenomena ,each cell lives its own life ,a fact already shown by Muller 1835 and Stricker 1870 " the independence of cells "

Today the cytoplasm is described as being a colour-less ,translucent substance in which there may or may not be imbedded granules and vacuoles ,the matrix or hyaloplasm being transparent .

The presence of living granules ,fibrils and vacuoles in the hyaline matrix is such a universal feature that most of the older scientist conceived the idea that these inclusions form an integral part of the protoplasmic structure . But ,nowadays ,in view of the fact that these structures may vary in different cells, not only in form ,but also in number ,and may be entirely absent , or appear only at different stages in the cell life, they are regarded rather as specialised differentiations.

Lillie Mathews (1906) carrying out experiments[1] on the sea-urchins eggs ,state that the cytoplasm of the egg is normally crowded with visible granules which can be separated with-out impairment. The granular amoebae frequently send forth ~~pseudopo~~ pseudopodia which are entirely free from granules . These pseudopea can be cut off from the parent body and still maintain their integrity . They are irritable ,are capable of ingesting food and can move about in the typical ameeboid manner,and although lacking the visible granules of the parent ;they must be still regarded as masses of viable protoplasm.[2]

Gaidukov 1910 Mott 1912 and PRice 1914 ,and other dark-field investigators find that the cytoplasm is optically heterogeneous.

(1).centrifuging method .

(2). Chambers.

wheras the nucleus shows no structure ,but these were investigating cytoplasm which still contained inclusions already visible with ordinary illumination . Chambers in 1923 using the dark-field illumination examing the hyaloplasm of the amoeba and of the sea-urchin states that it shows no structure when freed of its visible granules of centrifuging.

Of the various kinds of visible granules to be found in the cytoplasm the modern scietnistts seem to agree with their older brothers ,that the microsome[1] appears to be almost univeraally present . According to the latest investigators ,it is somewhat less than one micron in size ,but is plainly visible owing to its high refrangibility ,and by means of the centrifuge they have been able to throw it out of suspension from the fluid protoplasm of mature echinoderm egg cells . They have observed too, that in the dark-field method it gives rise to "diffraction " disks ,and it is of great value for the detection of low viscosity ,as it readily exhibits Brownian movement when the cytoplasm in which it is suspended shows a more fluid-nature.

The other types of cell inclusions vary greatly in different cells and many of them vary in the same cell at diffeant periods[2]. Apart from the microsomes ,the most prominent are the macrosomes ,or alveolar spheres described by Wilson 1899.

(1). Already considered under general morphology.

(2). Chambers .

They are irregularly shaped and are closely packed together ; their index of refraction is so close to that of that of the hyoplasm in which they lie that their presence is somewhat betrayed ,and so far very little is known regarding their function. Wilson ('99) ,however, advances the theory that they are probably nutritive for they accumulate in the growing egg,and gradually disappearin the cells of the developing embryo. Mathews in 1906 stated that they are very susceptible to injury ,and quickly swell and run together when the egg cytolyses ,from which he deduces that they are quite fluid in nature ,and in the presence of neutral red, many of them will stain rose-red colour. In addition to these are minute globules ,possibly fatty in nature distributed throughout the cytoplasm and rodlike mitrochondia which collect chiefly in the cortex of the egg.

It has been the custom of medical historians to trace back our knowledge of mitochondria to the brilliant researchers of Altmann at Leipzig,between 1880 and 1890 but investigations show that they had been discovered ,but imperfectly described ,by Flemming before him. Possibly some of the bodies " Interstitial Korner " by Koelliker , Neurosomen " by Held , and"Cytomicrosomes " by Strasburger are identical with the mitochondria of Flemming and Altmann . Some of the later writers have introduced the name

(I). μιτος = thread χόνδρος = grain .

"chondriosomes " (Benda 1904) which was brought into more general use by Meves (1908) Cowdry(1918) on the other hand urges the desirability of replacing chrondriosome by the old term mitochondria ,and to use the former as a general term to include the granules mitochondria ,rods or filaments (chondriconts ), which were no doubt observed by the earlier observers ,and described as under the name of "granules " "microsomes " or "fibrillae" , all of which have already been discussed ,so that according to Retzius , " we are dealing here with new names for old things . "

Practically all the latest authors are unaminous in their definition of these bodies ,that is ;they are composed of material which exhibits the following general properties :-
It is of rather low refractive index ,but with care may be seen to occur in living unstained cells in the form of granules ,rods and filaments ,which vary in size and shape .
(b). It gives a characteristic colour reaction when very dilute Janus green B. is applied. At first it assumes a bluish green colour then on reduction ,turns pink,then bleaches .Janus green C. will not stain mitochondria though the dyes differ only in the substitution of an H2. and (CH3)2 group in place of the ($C_2H_5$)2. [1]

Very few animals or plants exhibit mitochondria of

(I). Cowdry 1918.Evans Scott 1921.

distinctive morphology; but if we compare the individual tissues of higher organisms we find considerable differences .In some filaments predominate in others granules of different sizes but in similar tissues of different animals ,they are much the same . Cowdry states that the cells of the liver pancreas ,lungs and other organs mitochondria which are alike in closely related animals This constancy in shape where function of organs is similar has led investdigators to consider that the morphology of the bodies is a fundemental property ingmained in the organisation of the cell ,and that it is not always a passing trivial affair which varies from moment to moment.

Mitochondria are often filamentous in gland celâs . and in most of the tissues of devebloping embryos of all vertebrates; their length and diameter vary ;they may be curved straight or twisted depending on their surroundings ,and have rounded ends . Cowdry and Lewis state that their uniformity in diameter must mean that interastions between the cytoplasm and the mitochondria can only profitably take place in a certain thickness of mitochondrial substance .Thus ,the scientists of today have two attributes - length and breadth -independently variable and probably influenced by different factors .

They have discovered that under normal conditions any increase in size occurs through the addition of material at their extremities .i,e . the accretion is lengthwise - never lateral

If foreign matter ,like starch ,pigment or fat is deposited within the bodies expansion is always provided for by increase in girth . So far no explanation has been given for the difference in the mode of addition ,nor have they yet been able to account for the two methods employed for increasing their surface ; that is by elongation into filaments ,and by frequent segmentation ,into rods and spherules of approximately the same diameter ,so that a cell may be packed with the filament ,or rodlike,or spherical mitochondria

Attempts have been made to explain these phenomena .It has been suggested that in some cases the filamentous mitochondria may be the result from streaming movements in the cytoplasm .e.g. in outgrowing nerve fibres and in gland cells .But they may be equally filamentous in bone cells and cartilage cells in which the cytoplasm is relatively stationary .

Rubaschkin in 1910 explained that the filamentous type are characteristic of specialised cells ,and granular forms of embryonic .Dubreuil's 1913 believed that the filamentous are indicative of rest and the granular forms of rapid multiplication by division but his views have not been substantiated by recent researchers ,because according to the description of Moreau (1914) they are granular in the spores of fungi in which cell activities are considered to be at a low ebb . conversely N.H.Cowdry ,has found that they are filamentous in the rather inactive cells of the dried seed pea.

Branching of the filamentous types is rare ,but when it does occur ,it gives rise to a more or less extensive networks arrange chiefly around the nucleus.

Their occurrence is practically universal .Guilliermond (1913.19.21) observed mitchondria in certain algae and diatoms ; Faure-Fremiet (1909) describes the same to be visible in certain protozoan ; in fact they have been found to occur in representative organisms ,ranging from man to the protozoa ,and from the angiosperms to the fungi and Myxomycetes, but according to the latest observers their existence in bacteria is somewhat doubtful .Also it may occur that in the near future some observer may discover that they do not occur in some lowly plants and animals ,or that if they do occur ,the bodies said to represent them may differ so widely from the typical mitochondria of vertebrates that the term cannot rightly be applied to them .For according to Velu(1923) the "piroplasmas "[1] in the protozoa pass through a stage of development within the red blood corpuscles of vertebrates in which the cytoplasm is very much reduced ,and the "anaplasma marginale "[2] is said to consist wholly of nuclear material during this phase. Here the arises a problem ,i.e. to ascertain whether with increase of cytoplasm ,

(I). Les piroplasmes et les piroplasmoses.
(2). Sir Arnold Theiler (1910).

mitochondria appear ,because if so it would be a clear case of their "de novo" origin. All the latest authors agree that the mitochondria have been found in the tissues of higher animals , except in cells, whose, activities are greatly reduced owing to the approach of senility.

Within the cells the mitochondria are usually distributed without definite order ,throughout the cytoplasm ,but Champy has brought forward some interesting exceptions .He states that in the epithelial cells of the intestine they tend to accumulate at both poles of the cell . Also in the kidney they are often most numerous in the basal region next to the blood vessels . N.H.Cowdry quotes a similar arrangement in all other glands with fixed polarity ,wherein the direction of secretion is proximo-distal, that is from the blood stream to the lumen of the duct. .Champy believes this accumulation around the poles to indicate the existence of a double polarisation in two directions ,for secretion , and for absorption .Bensley (1916) is of the opinion that the original proximo -distal polarity of the thyroid cells has been reversed and points to the heaping-up of mitochondria next to the lumen instead of near the peripheral blood vessels ,as one indication of a change in the direction of secretion . It is therefore possible that the mitochondria like the Golgi-apparatus ,may serve to some extent as indicators of secretary polarity.

According to perinuclear condensations of mitochondria occur in both plants and animals .In the early meristem they are usually found indifferently distributed in the cytoplasm . In older cells ,however, they seem to approach and come into actual contact with the nucleus, in which position they enlarge to form plasts.

.They then migrate from the nucleus ,and finally become more or less evenly distributed in the surrounding cytoplasm . Guilliermond has also described this migration ,and has found that they undergo a parallel increase in resistance to the solvent action of acetic acid . Regaud in 1910 investigating the later stages of spermatogenesis states that they leave the nucleus and become more resistent to acetic . W.H. and M.R.Lewis experimenting in 1915 with living cells of tissue cultures observed these mitochondria journeying to the nucleus, and back again. Perinuclear condensations are of rather frequent occurrence in pathological conditions .

They are always prone to gather in the peripheral cytoplasm especially in eggs (Strickt)and after a time they become redistributed just as in the case of perinuclear condensations, This peripheral arrangement has been produced experimentally in liver cells by Grynfeltt and Lafont(1921)

Kingsbury (1912)has suggested that the grouping of mitochondria about the centrosome ,which is so often met with ,may perhaps be interpreted on the supposition that, being reduced substances ,they carry a positive electrical charge ,and accumulate around the centrosome in order to deliver it . Childs (1915) states that it is also possible that the presence of an "axial gradient in metabolism ,may be part responsible for their distribution ,particularly in gland cells .They ,Gibb-Thompson ,principle tells us that any process which diminishes free energy at an interface will tend to take place .E.V.Cowdry ,and his pupils advance the supposition that mitochondria are lecithin-like and that lipoids decrease surface tension ,so therefore,it would be natural to expect them to be heaped-up at the nuclear and plasma membranes ,and that they might be dealing with a manifestation of the so-called electrical adsorption .On the other hand it is possible that the mitochondria may not be directive agents .They may be shifted from place to place by physico-chemical changes in the ground substance.

Thurlow in 1917 devised a method for counting the number of mitochondria present. By inserting in the ocular ,a glass disk with a ruled square of known dimensions ,and using sections of known thickness .She discovered that there is a fairly constant number per unit volume of cytoplasm ,in the cranial nerve cells of white mice ,and so constant is the number ,that certain groups of cells can be distinguished by the number of mitochondria within them .

In the human tissues in which there is considerable division of labour ,investigators have found many differences in the number ,because some cells are best fitted to perform their function with a large and others with but few. So far,it has not been ascertained that the cytoplasm of higher animals differ from that of the lower ,in the amount of mitochondria present .Neither is there any appreciable differance in the relative amount between animals and plants .In very young embryos of vertebrates most of the cells contain approximately the same number of mitochondria .As development proceeds tissues become specialised ,and distinctive differences in the amount often becomes apparent ,in fact these investigators state that they are more abundant soon after birth than in adults.

These investigations leave us with two lines of observations to harmonise ; the association of abundant mitochondria and the amoun of fat ; where fat is plentiful ,mitochondria are scarce.According to present ideas ,decreased axidation favours deposition of fat and increased axidation hastens its elimination ,which suggests the existence of some connection between the amount of mitochondria and the rate of oxidation .

Altmann (1890) believed mitochondria to be elementary micro-organisms embedded in lifeless ground substance .

Many later pathologists ,on account of their morphological resemblance to bacteria ,have exhibited a string desire to interpret the bodies as independent micro-organisms .And since the time of Altmann the idea that they are bacteria which have become completely adapted to an inter-cellular existence has been repeatedly advanced. Portier during 1917-18-19, wrote a book and several pamphlets supporting this contention ,but his view does not seem to have appealed to his comtemporaries , Regaud Laguesse ,Guilliermond , Rasmussen ,Van Gehuchten . In 1922 Wallin ,working quite independently of Pŏrtier ,has advanced a similar hypothesis ,which has likewise been questioned by Cowdry ,and Olitsky.

Wallin is of the opinion "that mitochondria are symbiotic "bacteria in the cytoplasm of all higher organisms whose symbiotic" "existence had its inception at the dawn of phylogenetic evolution" but his contention is not universally accepted .Woolbach and Nicholson (1923) investigating the same bacillus radicicola - have been able to differentiate between these organism and mitochondria lying side by side in the same cell.

The idea which has dominated most of the work on mitochondria.- that they are concerned in histogenesis -may thus be explained.They occur in all embryonic cells ,and in early stages of

(1) See also J. Am.Med .Ass.

development they are only formed elements in the cytoplasm . Meves conception that they are transformed into products of ~~xx~~ differentiation also falls in line with the view that they are in in part the material basis of heredity .The data bearing upon this theory is based upon the subsidiary hypothesis of mitochondrial continuity according to which they do not arise in the cytoplasm de novo ,but always through multiplication by division of pre--existing inits. While it cannot probably be denied from the evidence of tissue cultures (Lewis 1915) that in living cells some filamentous specimen do segment and break-up into granules ,it is still an open question ,they find very difficult to prove ,that all mitochondria arise exclusively from other mitochondria .

Van der Stricht (1923) has investigated their behaviour in oögeneses and Chambers (1914) has observed the presence in spermatocytes. During the metaphasi of the dividing cell they closely invest the spindle .He states that "when the cytoplasm is disintegrated the" "mitochondria adhere into a network which persists together with the" "spindle .The latter however,soon passes into solution leaving the " "the mitochondrial network about an area in which the chromosomes " "are irregularly dispersed. "

During the anaphase stage when the chronosomes migrates to the poles of the spindle,the mitochondria become converted into long strands .When the cell is torn the mitochondrial strands wrinkle and gradually anastomose into a gelatinous mass.

It has been claimed by Meves[1] and others that these bodies play an important role in fertilisation .They state that they are conserned in the transmission of hereditary characteristic basing this view on the part which they believe it to play in protoplasmic differentiation . The same author pursuing the matter further ,made a study of the fate of the middle piece of the spermatozoon in the ferilised eggs of echinids . This fragment he traced intact into one of the two cells ;in succesive cell divisions it passed intact into one of the daughter-cells only-thus he traced it to the thirty -two-celled stage ,unbroken ,and not yet transmitted to any one part of the egg,as the theory that it represents a subtratum for bearing heredity factors would require; neither does it according to him ,exhib any signs of activity . In the egg of an ascidian the same author (1913) could follow the sperm mitochondria through part of the fertilisation stages ,but afterwards lost sight of them . Stricht ,in the bat ,and Lam ,in the guinea-pig ,found that the tail of spermatozoon and connecting piece which carries mitochondria pass into one only of the first two cells . Finally in Nereos ,according to Lille (1912),the middle piece which is supposed to carry the mitochondria does not

(1). Meves calls mitochondria ,plastochondria.

enter the egg at all. Whatever may be the function of the mitochondria in cell physiology ,the study of fertisilation has evidently showm no reason for the assumption that their introduction into the egg by the sperm in certain species is concerned in the transmission of paternal characteristics . The variable quantity in different cases and the distribution to single blastomeres in certain cases ,exclude the hypothesis ,that they have any specific paternal hereditary effect . There is no reason yet to deny that sperm mitochondria function in the egg when presen ,but if so ,it is , according to Lille and Just,probable that they are not differentiated in their chemical composition or genetic behaviour from the mitochondria of the egg itself .

Regaud 1909 advanced a plausible electrosome theory according to which the mitochondria are said to play the part of plasts choosing and selecting substances from the surrounding cytoplasm ,condensing and transforming them in their interior ,into finely diverse products . He compares these bodies with the hypothetical side chain of Ehrlich ; Lille describes his theory as a modification of the lipoid membrane conception of Overton ,the difference being that the lipoid is considered to be scattered, throughout the cytoplasmic area,in the form of mitovhondria ,instead of being confined to a layer on the surface of the cell .

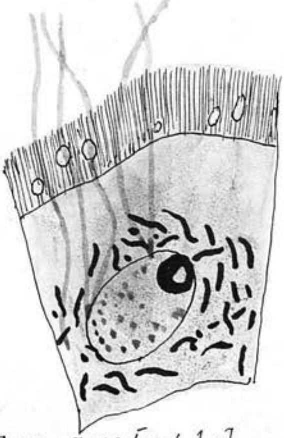


FIG. 17. [see below]

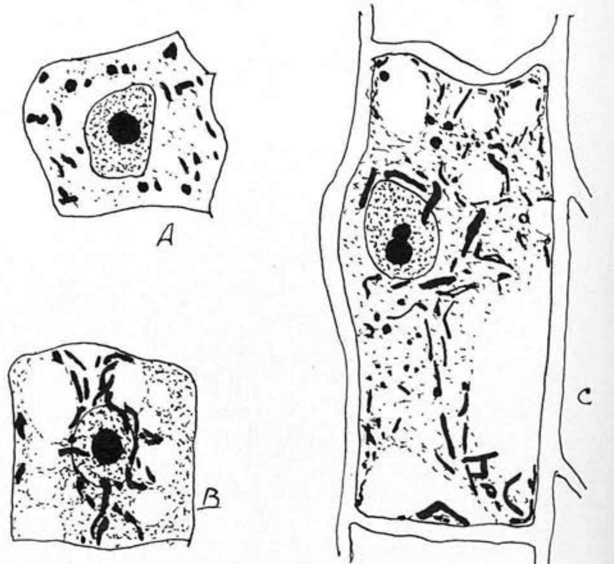



FIG. 18.
Meristem & young and old. cortical cells. showing
A). primary diffuse arrangement. of mitochondria.
B) condensation around nucleus.
c) Final. dispersal. throughout cytoplasm.

FIG. 19. Kidney cells with mitochondria in proximal. cytoplasm.

~~FIGS. 17. + 19. See. text~~.

FIG. 17. Diagram of Cell. from choroid. plexus. [after Grynfelt] illustrating perinuclear clumping of mitochondria.

Kingsbury (1912). was the first to suggest that they function in protoplasmic respiration . He explains that osmic acid potassium bichromate and formalin are the chief ingredients of michondrial fixatives and that their value depends on the presence of reducing substance in the cytoplasm . These he believes to be the michondria because of their lipoidal properties ,but Mayer ,Rathery, and Schaeffer (1914) contend that the mitochondria are phosphatids containing unsaturated fatty acids with ethylidene groups ,and are, therefore, well adapted to function in oxidations and reductions. These investigations also advance that reagents which attack lipoid (like alcohol ,ether and chloroform )at the same time reduce respiratory oxidations (1). But although this view ,that mitochondria take part in protoplasmic respiration ,has been well received by cytologists ,it is still only a theory ,and up to the present , must be regarded as such .

Observations made on the behaviour of mitochondria in pathological conditions have been difficult to follow ,owing to the use of different terms ,to designate these bodies ,and also the confusion which has arisen from the fact that there are two theories -old and new - to be considered . The first developed as an outgrowth of Altmann's researches (already considered ).

(1) Janus Green reaction page

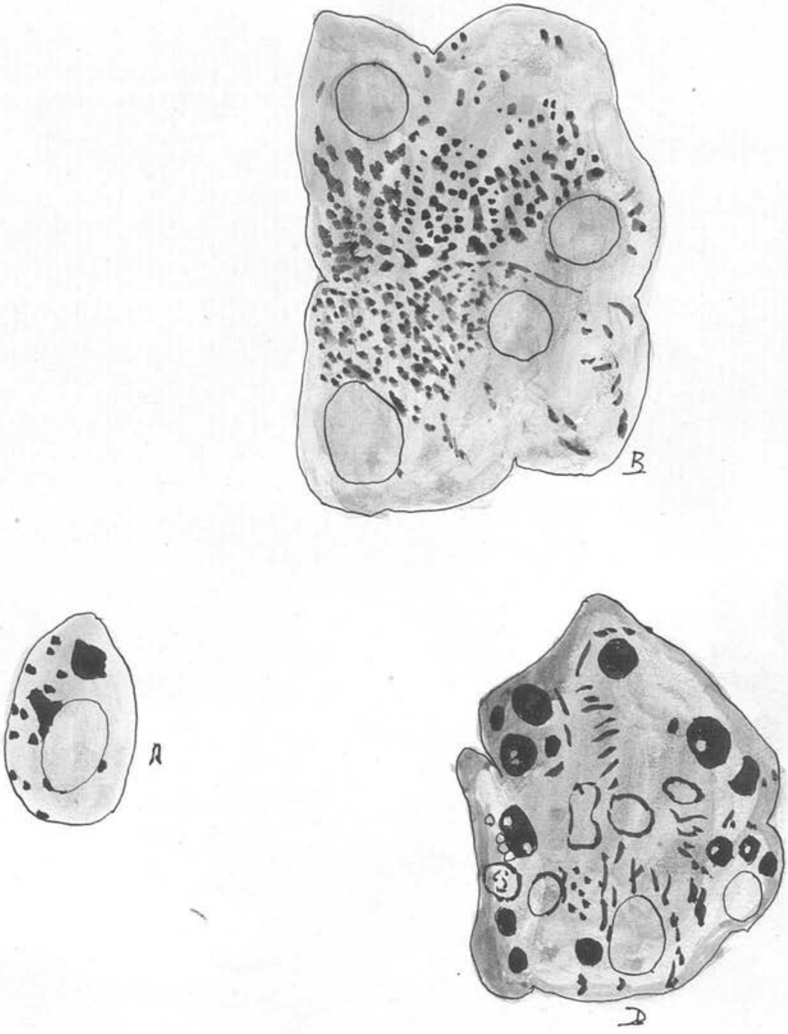



FIG. 22. A. B. & D.

Showing Effect of Phosphorus poisoning upon Mitochondria the Acinus cells of Guinea pig's pancreas. [Scott 1916]

The second in which we now find ourselves ,is a revival of interest in the study of cytoplasm ,which coincides with a tendency among biochemists and pathologists to become interested in the phospho-lipoids ,whereas their whole attention was devoted to proteins ; the latter being probably dominated by tremendous impetus of Emil Fisher's studies on protein synthesis ,based upon Kossel's theory and eventually involving the idea of building-up living substance [1].

With more satisfactory method for studying mitochondria it became apparent that a new criterion of cell activity and cell injury was inevitable ,and since they differ radically from the nucleus ,the belief has been expressed that their study will open a new chapter in cellular pathology . The cytoplasm ,being perhaps more directly concerned with adjustments between the living cell and its environments[2] ,will in all probability be very responsive ,and the possibilities involved are alluring .

Animated by the belief ,mitochondria have been studied by many investigators ,and Cowdry 1918 summarises the numerous[3] papers written on the subject . In 1916 Scott showed that whereas the mitochondria are exceedingly sensitive to any interference with the normal activity of some tissues ,they are also resistant in others .

Experimenting with pancreatic cells which had been

(1). C.F.General outline.
(2). C.F.Huxley's definition page
(3). J.Am.Med.Ass 1917.

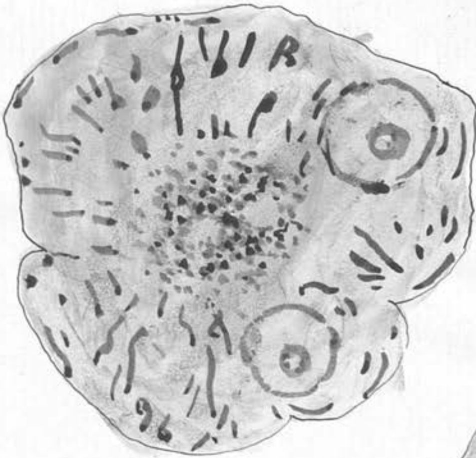


FIG. 20.

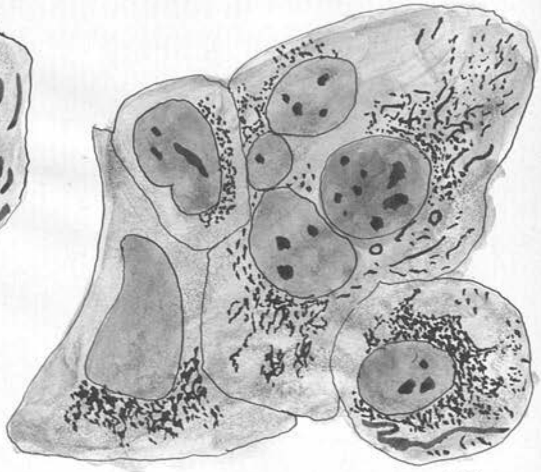


FIG. 22

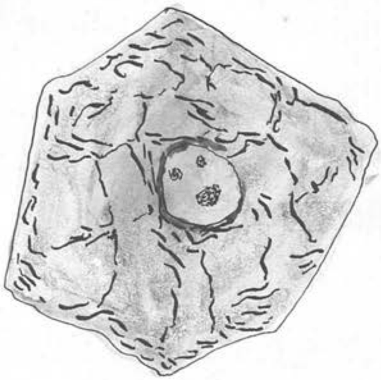


FIG. 21.

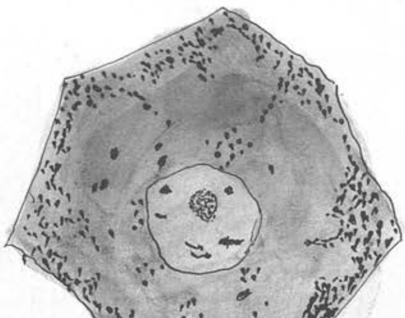


FIG. 23.

See text.

Fig. 20, 21 } Effect of Phosphorus poison upon mitochondria. Pancreas. Cells [Scott]

23. Shows rounding up of NORMAL filamentous mitochondria in Liver cells

poisoned by phosphorus ,he showed that they often respond by loosing their filamentous shape ,sometime before the nuclei show any modific-ation . Comparing B.and C with the normal A.it will be seen that they first lose their filamentous shape(B) then clump together and agglutinate (C). and finally fuse giving rise to droplets of fatty degeneration .(D). Nicholson (I923) has brought to light a variety of mitochondrial changes in the thyroid gland , and according to other observers these changes seem to be universal in gland cells .But this does not seem to be the case in the nervous system . Clark (I9I4) was unable to detect conspicuous changes in experimental beri-beri, Strongman (I9I7) in functional exhaustion ,or Rasmussen (I9I9) in hibernation ,and Mcann (I9I8) found normal filamentous mitochondria in nerve cells in fairly advanced stages of shromatolysis in poliomyetitis ; Also Cowdry and Nicholson (I923) were unable to observe any mitochondria[1] changes in nerve cells which were greatly plasmolised and exhibiting profound nucleolar alterations.

All the investigations in this field may be summed-up under three headings :- qualititive ,quantitative ,and topographical, which may occur singly or in combination.

The most delicate qualitative response is a change of filamentous mitochondria ,into granules ,but the method by which it is produced is not definitely known .But attention should be paid to the fact ,that granulation is often a manifestation of faulty technique ,it may be provoked by experimental injury ,such as phosphorus or sulphonal poisoning.

Lewis,Levi , Lafont ,and others have not yet been able to tell whether the poison ,or other injurious influence ,acts directly on the mitochondria,or whether the alteration therein is a visible expression of a long line of interdependent chemical reactions ,and we have still to explain why mitochondria ,existing side by side in the same cell ,and sharing many influences in common often differ so greatly in morphology.

The same difficulty is experienced with regard to quantitative changes .With the exception of a few ,observations recorded are based upon the general appearance of sections. Few investigators (Thurlow) and (Rasmussen) have availed themselves of the more logical method of actually counting the number present per unit area ,and of measuring the size of the cells (Noel 1923)

In practise ,a diminution in the number of mitochondria is commonly met with in pathological conditions ,but a definite increase above normal is rare . But Enderlen '08 Hirsch '10 and Nicholson 1923 , have reported an increase in compensatory hypertrophy ,and Goetch (1916) also discovered the same in toxic adenomata of the thyroid.

Changes in position have been reported in several conditions . Grynfalt and Lafont (1921) discovered the peripheral margination in sulphonal poisoning . and Sir E. Sharpey-Schafer points out that grouping about the nucleus is a fairly common occurren especially in pancreatic cells (1). This aggregation ,around the nucleus, Sir Edward ,refers to as paraneucleus.

The fact that mitochondria occurs in the vast majority of living cells ,opens up a new line of study in the re-examination of the genesis of cytoplasmic inclusions of doubtful origin. For example the large group of diseases of unknown etiology ,comprising , small-pox ,scarlet-fever ,rabies ,chicken-pox - offers numerous cytoplasmic inclusions concerning which further information is needed. We have a plethora of observations but so far no experimental method has brought us nearer to a solution of the problems.

Another important cytoplasmic component is the Golgi-Apparatus (2). This was discovered by the Italian neurologist ,Golgi in 1898. About the same time as this discovery Holmgren and Nelis found a system of clear canals within the cytoplasm of a large variety of cells belonging to the same categories in which the Golgi Apparatus was found . These exhibited the property of remaining unstained when the"rest"of the cytoplasm was coloured , Their close

(1). Essentials of Histology pp.6 and 371 .

(2). Synonyms : Golgi bodies Dictyosomes(Canalicular system or Trophospongium of Holgren. )

Their close resemblance in form abd position to the Golgi apparatus attracted widespread attention ,so much so that Cajol (1908) felt justified in proposing the name of Golgi-Holmgren canals so as to include both formations ,but this did not meet with a general approval Duesberg (1914-20) maintains that the Golgi apparatus and the clear canals are not identical in all cells . He is of the opinion that they are identical in neurones and non-nervous cells with a diffused trophospongium they cannot be the same ,because the Golgi apparatus on the contrary is restricted in distribution ,being localised at one pole of the nucleus. Penfield (1921) also has discovered changes in the Golgi-apparatus in injured cells ,and that when these cells were stained he observed a system of clear canals which in no way correspon-ded with the remants of the Golgi apparatus . From this he concluded that the clear canals and the blackened Golgi -apparatus were two different formations .

Bensley (1911) made a parallel study of the clear canals in plant and animal cells and he found a significant series of shanges in growing cells. In the younger cells he discovered a system of clear canals ,agreeing in many details with those seen in animal cells , With increase in age the canals enlarged and finally gave rise to the familiar plant-cell vacuole.On the basis of these observations he suggested "that the network of canals found in so "

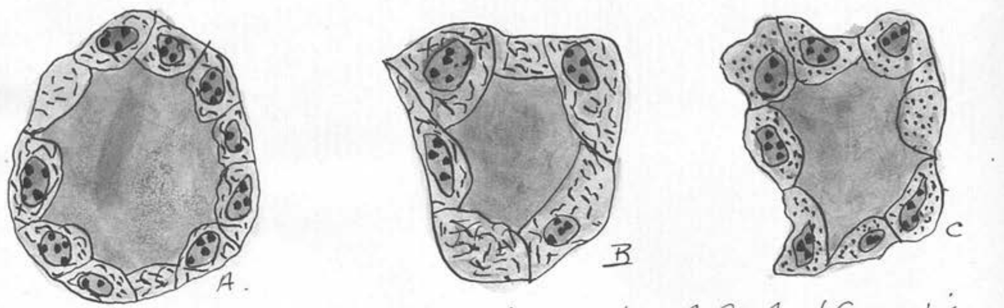



FIG 24. Reactions. of mitochondria. in thyroid. Gland. of Guinea-pig
A) Normal.. B) hypertrophy ~~after~~ of remaining portion, after removal.
of one gland. C) inhalation of Oxygen.

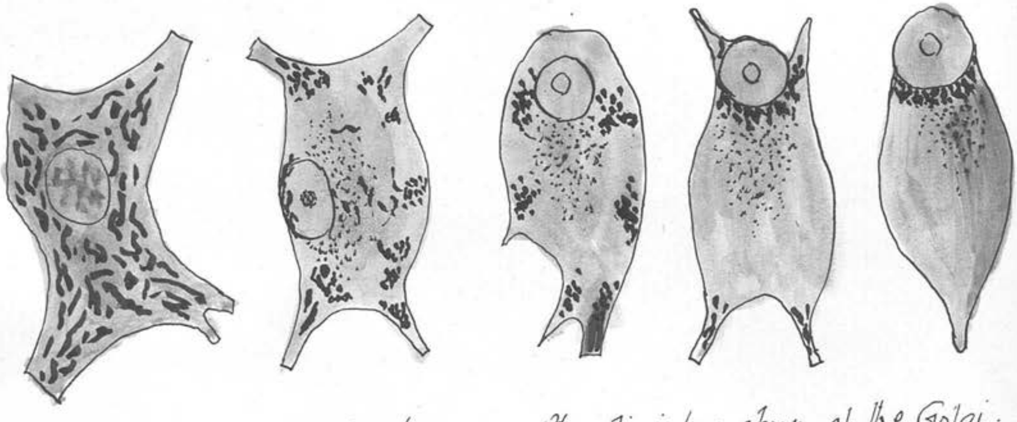


FIG. 24.(A). Different. phases in the disintegration of the Golgi.
-apparatus. in motor. neurons. (see. page 58).

"many animal cells is the physiologic and morphologic equivalent " " of the vacuolar system in the plant cell . " Guilliermond and Mangenot have also applied methods for the demonstration of the Golgi apparatus to barley cells ,and they seem to have confirmed Bensley's belief that there exists in animal cells an area corresponding to the vacuole in plants .

In addition to this view that the Golgi apparatus is the homologue of the plant -cell vacuole ,several other suggestions have been made . Hirschler's (1918 ) contention that it helps to isolate certain cell substances ,is supported by Hyman (1923). This theory recalls some point s in regaud's electrosome theory of mitochondria; function . In 192o Saguchi suggested that this Golgi apparatus (what he calls"intracellular network ") takes part in the act of secretion . At present no observer is specific with regard to its function .

Topographically the Golgi apparatus occupies a central position in the cell and its form is probably changing continually as it plays its obscure rolê in the cell . The fact that it is relatively larger in the most active stages of cytomorphosis is of some significance . Its activities may be bent in one direction during spermatogenesis and along entirely different lines in cells specialised to perform other functions.

Observations on the changes which occur in the Golgi-Apparatus. during pathological conditions, have been made by numerous researchers. Probably the first in the field was MOATI (1903) who investigated the effect of hibernation on intestinal epithelium and recorded that the clear canals disappear in hibernation.

Then follows HOLMGREN (1904) on metabolic activities of liver cells; result - clear canals more prominent after carbohydrate feeding; MARIANI (1904) - Human-breast carcinoma - perinuclear aggregations; VERSON (1908) - Tubercular lymph-glands and giant cells, hypertrophy of prostrate - Fragmentation; and many others.

It is believed that sufficient observations have been made to ~~those~~ show that in certain conditions the Golgi-apparatus is really very sensitive to pathologic change, while, like the mitochondria it is resistant in others.

Compared with the chondriosomes the Golgi-apparatus show some points of resemblance. Like the chondriosomes they are more or less polymorphic, though always consisting of the same specific material; also they show similar solubilities, being readily attacked by lipoid solvents; thus in these respects, they, like the chondriosomes, behave somewhat like lecithin compounds.

In addition to these the cystoplasm often contains a structure known as the central apparatus or microcentrum [FIG 13] of which the most essential component is the central body - the centrosome and centriole around which, as a centre, arise the asters that form a conspicuous feature of many forms of mitotic cell-division, and hence has often been referred to as the division-centre. In many cases this body persists during the vegatative or "resting" period of the cell, and is ~~hundred~~ handed in by division to the daughter cells without loss of identity. Much confusion exists concerning the terminology and relationships of this central body. Its discoverer, VAN BENEDEN (1876) first called it the "polar corpuscle", later (1887) "central corpuscle" - BOVERI applied to it the term centrosome, later describing it as consisting of a special centroplasm , and as forming the central point of attachment for the astral rays. Within it lies a much smaller body which GOVERI called the "centriole", which is first of all to divide", and thus to initiate division of the whole astral system and of the cell.

Boveri at first considered the centrosome as being separate and distinct from the aster, and held that both centriole and centrosome are persistent structures that "grow and divide without loss of identity".

Subsequent studies by MRAZEK ('03). YATSU ('09). + LAMS. ('10). demonstrated that in many cases the centrosome is but a transitory structure, which like the surrounding aster, may form, disappear, and re-form in successive places of mitosis.

Observers (1) describe the central body, in its simplest form, as a single granule of extreme minuteness, staining intensely, and often hardly distinguishable from a microsome, save by the fact that it lies at the focus of the astral rays. In this form it appears in the very young sperm aster during fertilisation, or in its early prophases during ordinary mitosis. At a slightly later period during prophases the centriole is found to be surrounded by a centrosome which steadily enlarges as mitosis proceeds, while centrioles remain minute.

At its highest development the centrosome is of several different types of which three are given.

(1) Simplest type described by Kostanecki (1897) and Boveri ('88) - is a spheroidal body, moderate size, and homogenous structure and is not ~~transversed~~ traversed by ~~artial~~ astral rays.

(2) In a second type - seen by Wilson in sea-urchin eggs, the centrosome offers a similar appearance, but contains a group of irregular granules, so as to give almost the appearance of a small

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1) Boveri, McFarland, Lille, Meves, and others.

nucleus in which the centrioles cannot be distinguished. Boveri considers these as artifacts, and describes the centrosome of sea-urchins approaching that of the first.

(3) Third type is where the centrosome is ~~transversed~~ traversed by the astral rays, so as to assume a radial structure. The "central corpuscle" was here described as being surrounded by two well defined zones, each bounded by a very distinct ring of microsomes and ~~transversed~~ traversed by astral rays. VAN BENEDEN designated these zones as medulliary (inner) and cortex, which to-gether form the attraction sphere. Boveri considered his "centrosome" to be the equivalent of Van Beneden's "central corpuscle". Braner ('93) suggests that the "central corpuscle" was in reality the centriole, and that Boveri's centrosome corresponds to Van Beneden's "medullary" zone of the attraction sphere and this view has been adopted by later observers.

Whether the central bodies may arise "de novo" as well as by division has proved a difficult question. Observers state that they are lost to view in the interphase or non-mitotic phase of the cell, re-appearing in the prophase of the ensuing mitosis, as if created "de novo" out of the protoplasmic substance.

Experiments carried out by Morgan and Wilson (1) show that

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1) Artificial Parthenogenesis.

division of the cytaster is initiated by that of the central body; and during mitosis the cytasters actually operate as centres of division, though the furrows around them are often not permanent.

These facts indicate, that the central bodies within these asters are true division - centres, and because, observers have often seen them ~~by~~ developing simultaneously and in large numbers in all parts of the egg, that they are formed "de novo". This conclusion, however, could not be accepted by many and Wilson carried out an experiment by which the "egg-fragments whether nucleated or not" were found to develop cytasters which are capable of multiplication by division and which contain central bodies.

The function of the central bodies is not confined to the part which they play in mitotic division. They may also be concerned with the formation of cilia and flagella, and with the more complicated basal apparatus often associated with the latter structures.

In animal spermiogenesis, investigators state that it is probable that in all cases the centriole is the lineal descendant of the centrioles of earlier cell-generations. On the other hand, in higher plants, division-centres seem to be absent in the somatic-cells and in those of earlier germ-line; nevertheless in the closing spermatogenous divisions the spindle poles are occupied by central bodies, which show all the characteristics of division centres. In this case, therefore, the law of genetic continuity as applied to these structures is of much more limited application, and the central bodies, considered as individuals must apparently be formed "de novo" at a late period in germ-line.

Another constituent of the cytoplasm is the chromidial group, under which heading the Nissl substance of nerve-cells, and the basophilic material of gland cells, as well as substances observed in Protozoa and plants are usually included. Delving deeply into medical history shows that up to the time of Hertwig the earlier observers were in the habit of confusing these with the microsomes, and also after Hertwig's (1908) announcement of the chromidial hypothesis, the term chromidia has very often been loosely used. Dobell ('09) understood it to mean "any fragments of chromatin" - irrespective of their shape or function - which lie freely in the cell, without being massed to-gether.

According to GOLDSCHMIDT they occur in the cytoplasm of the cells of Protozoa and bacteria in the form of irregular masses; and they seem to be derived from the breaking down of definite nuclei, as well as from chromatin extruded through the nuclear membrane.

When present in non-nucleated cells, CALKINS refers to them as constituting a "distributed" or "diffuse" nucleus.

Goldschhmidt's (1910) studies on "Ascaris" are probably the starting point of our knowledge of "chromidia" in multicellular animals.

The discovered filamentous bodies, often coiled and grouped about the nuclei, ~~which~~ he believed to be analogous to the chromidia first described by Hertwig in Protozoa. He advanced the theory that material of this kind is very widely distributed in animal cells, and attempted to include under that general category the Nissl bodies of nerve-cells, the basal filaments of gland cells and many other cellular constituents which we now know to be of a different nature. This generalisation gave rise to active controversy, the early phases of which have been summarised by Duesberg ('12).

Kulmatyeki (1922) studying the "Ascaris" advanced the conclusion that although chromidia are coloured by "chromatin" dyes they react differently from the nuclear chromatin and further, that there is no satisfactory evidence that they arise from the nucleus. More recent evidence, however, shows that in higher forms the Nissl bodies and basal filaments of Solger (but not Altmann) are, as Goldschmidt suggested, to be grouped among substances, formed at least in part, as a direct result of nuclear activity, and according to Tennent of the interaction between nucleus and cytoplasm.(1)

Much work has been done in the hope that a study of the Nissl bodies in nerve-cells would afford clues regarding the problem of the nature of mental activity, and though we seem to be far from solving it, results of real importance have been obtained. For instance MALONE ('13 & '23) has shown that not only are the larger groups of nerve cells characterised by the possession of distinctive Nissl bodies, but, that also, the Nissl bodies differ even in cells supplying heart muscle, smooth muscle, and striated muscle. Also NICHOLSON, CLARK, and others, state the Nissl bodies are still the most useful indicators of pathogenic change in nerve-cells, where they are apparently even more sensitive than the mitochondria. They undergo a definite series of alterations following

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1) See Cellulae Differentiation.

injury and functional exhaustion, characterised by loss of their distinctive shape (chromatolysis) and ultimate disappearance.(1)

MOTT concludes ~~that~~ from his ultramicroscopic studies that the fundamental substance in living cells occurs in a form wholly different from the distinctive Nissl bodies with which we are familiar, but, nevertheless, it does not follow that it actually exists in the particular state in which he observes it - that is, further proof of this appearance is necessary.

Like the Nissl bodies, the chromidial substance responds to microchemical tests for iron; is practically insoluble in alcohol and cannot be seen in the living cell. As revealed in fixed preparations, it is an equally good criterion of cell activity and cell-injury. But here, as in many other cytological problems, our functional interpretations must necessarily lag on account of the great difficulty of projecting accurate methods of chemical analysis into such very small units as the cells.

The discovery of the NUCLEUS has already been discussed under general morphology, and we may now proceed to study its

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1) SIR. E. Scharkey-Schafer's, Ess. of Histology p.158.

structure in greater details.

From the time of its discovery up to 1873 when SCHNEIDER discovered the chromosomes, very little was known regarding its structure and contents. BALFOUR (1) - (1849) states that "each cell, at some period of its existence contains a small body" "called the nucleus in which there are often found one or two", "rarely more, minute spots called nucleoli".

He described it as being round or oval in shape, granular and dark, homogeneous and transparent, bearing resemblance to a smaller internal cell. The nucleoli he states, "are not always present", that they are either vesicles and granules contained within the nucleus, or minute cavities in its substances. Barry also seems to have supported this view and holds that a peculiar substance called hyaline (ὕαλος = glass. ) is developed therein, which according to him, is the origin of the nucleus.

According to these two observers, the nucleus is situated in "different parts of the cell" (see fig.8); that it may be free in the cell cavity, or connected with its wall by mucilaginous threads, or imbedded in the substance of the membrane.

SCHULTZE in his essay (1861) takes the embryonal cell as

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1) Manual of Botany p.7.

the basis and starting point of his definition. "The most important cells" he remarks, "those in which the fulness of" "cell life, the unlimited power of tissue formation, is most" "distinctly evident, are the embryonal cells, which proceed" "from the division of the cell of the ovum. Both the nucleus" "and the protoplasm are products of the division of similar" " constituents of another cell. Such cells include a living" "force in their interior, essentially possessed by the proto-" "plasm, although it is true that the nucleus likewise plays an" "important part not hitherto known with sufficient accuracy.... "The protoplasm and the nucleus constitute a single whole".

Brucke, a contemporary, goes a step further in his definition. He maintained "that no proof has been given that the" "nucleus is indispensable to our conception of it." He basis his statement on the fact that cells were known to occur in the cryptogamia in which "no nucleus is visible.We have" he says, "no positive information either respecting the origin or the" "function of the nucleus; even the constancy of its occurrence" appears to be subject to certain limitations, especially if we" "consider the cells of cryptogams and do not start with the" "presumption that, even in those cases where no nucleus is" "visible, it must nevertheless be present". This opinion, according to STRICKER, undoubtedly gained weight, the more carefully the subject was considered, and it created a desire among the scientist of that era to carry out further investigations.

The outcome of all this was the discovery of non-nucleated Amoeba (Amoeba parrecta) in the Adriatic, by Schultze; HACKEL'S discovery of the larger non-nucleated Protista (Protogenes primoidialis) in the Mediterranean; and lastly, CIEN KOWSKI'S description of two non-nucleated monads.

BAER examining the germinal vesicle of the impregnated egg - that is, the nucleus of the ovum - discovered that it "vanishes" and that the further process of development commences with a new generation of nuclei. Stricker also investigating frog's eggs entirely agreed with Baer's opinion. Stricker also carried out a number of comparative investigations between fertilised and unfertilised ova, and stated that he found a germinal vesicle in the latter, whilst in the former there "is only a cavity left, or even a total absence of any trace" "of its existence".

Flemming in 1879, investigating the epithelial cells of salamander larvae discovered that the nucleus contains in addition to the nucleoli a net-like framework in which are suspended granules or irregular clumps composed of a substance that stains intensely with certain dyes, which he termed chromatin. But, a number of more recent investigators - (HAECKER, REINKE, WALDEYER) have followed Butcheli in the conclusion that the framework ~~in~~ is an alveolar structure, analogous to that so often seen in the cytoplasm, though often of different character. From this time onwards it is difficult to find that a consensus of opinion has been reached. Some Cytologists accept the earlier view of Flemming; others such as BECKWITH, RICHARDS, & GREGOÍRE, basing their assumption on the mode of formation of the nucleus, state that both types of structure may co-exist in the same nucleus; for after ~~all~~ cell - division ~~of~~ the framework is often produced by a process that involves not only a vacuolisation of the individual chromosomes, but also a formation of branches by which different chromosomes become connected to form a network, so that the nucleus becomes in the phrase of Gregoire a "network of networks", in which the boundaries of the original chromosomes can no longer be distinguished.

The staining properties of the nuclear contents had also proved an obstacle to the earlier cytologists and it was not properly understood until EHRLICH (1870-1880) advanced his theory regarding nuclear dyes. He showed that the nuclear dyes are basic, and the plasma dyes, acidic, and it was convenient for his contemporaries and successors to designate the various cell components as basophilic and oxyphilic according to their tendency to take up the basic or acidic dyes. This theory assisted the earlier observers to understand why only certain components of the nucleus were stained.

To this substance thus stained, Flemming as already stated, gave the name of "chromatin", and that which stains only slightly or not all, he called "achromatin". Chromatin as thus defined, Flemming considered to be composed wholly or in part, of the chemical substance nuclein and to form the more conspicuous part of the nuclear framework and also certain types of nucleoli. Under the conception of achromatin he included all the remaining nuclear substance except the enchylema.

STRASBURGER ('82) and CARNOY ('84) recognised that the framework itself appears to consist of two constituents, namely a continuous achromatic basis, and of a more or less discontinuous granules or clumps of chromatin suspended in it. The first of these was found to be oxyphilic and was accordingly designated by Strasburger as nucleohyaloplasm, by Carnoy as the plasmatic network (composed of plastin) and later by

Schwartz ('87) as linin, a term still in common use, and which has involved us in many difficulties. It was also discovered by RUCKERT & JARGENSEN in their studies of the elasmobranchs that the framework often undergoes great changes of staining-capacity in different phases of the cell-cycle, and that it may even lose its affinity for the basic dyes, becoming purely oxyphilic like the general cytoplasm. This led observers to the conclusion that the "chromatin" may completely disappear from the nucleus, and also that the nucleus, therefore, cannot be regarded as containing the basis of heredity. On the other hand, linin or plastin, is readily stained by acidic dyes; so that by using both a basic and an acidic dye of different colours, both chromatin and linin may thus be strongly stained but in different colours. Obviously therefore linin or plastin is no less chromatic than chromatin.

The confusion thus arising was wisely avoided by HEIDENHAIN ('90) who proposed to designate the baso - and oxyphilic nuclear materials as basichromatin (= Flemming's chromatin) and oxychromatin.

Heidenhain also, in harmony with an earlier suggestion of Van Beneden's (1880) further concluded that the two substances may be only different conditions of a single substance determined by comparatively slight chemical changes - e.g. by varying ratios between the percentage of nucleic acid and protein in the chromatin - substance. In this manner they explained the marked variations exhibited by the nuclear meshwork in different cells, or in different physiological phases of the same cells, and it also did away with the supposed consequences of the disappearance of "chromatin" from the nucleus already mentioned.

Many doubtful points still remained to be cleared. Heidenhain following the lines marked out by Flemming, Strasburger and Van Beneden, considers that both basichromatin and oxychromatin appear in the form of minute granules or chromioles and that both kinds of granules are suspended in a non-stainable, homogeneous substance or matrix, to which substance Heidenhain alone applied the term "linin". Thus the meaning of "linin" was greatly restricted for it appears that as originally used by Carnoy, Schwartz and their followers, the "linin" or "plastin" included also what is now called oxychromatin. Modern investigators, however, state that it is far from certain that these granules have a persistent identity, and that it is often difficult to distinguish them from artifacts produced by coagulation of reagents.

At the same time, they advise that we should not take too sceptical an attitude to-wards the question, since there are cases in which granules and other formed components in the nuclear substances and they are clearly visible in life. One of the best examples of this, is offered by the "spireme-nuclei" of the salivary gland-cells in Diptera described by BALBIANI, CARNOY and ALVERDES 1912. In this case the more solid part of the nucleus appears in the form of a long convoluted thread with a nucleolus attached to each end, and even in the living cell this thread is seen to be composed of denser-like bodies suspended in a clearer basis; in fixed preparations, these bodies are found to be strongly basophilic, while the lighter substance ("linin" or "plastin") is oxyphilic. These theories were further investigated by KITE ('13) and CHAMBERS ('14 - '18) who came to the conclusion that the ground-substance ("clearer basis") is in many cases of a much firmer consistency that was formerly believed. It was also shown (1) much more restricted after staining with a single "nuclear" or basic dye; for when staining with an acidic dye the spaces are often found to be occupied in greater or less degree, by oxychromatin granules, and the meshwork thus appears to be correspondingly extended at the expense of the enchylema.

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(1). that the spaces occupied by the enchylema may be

So far it has proved too difficult to determine definitely, how far these granules pre-exist in life. ZACHARIAS has shown in various plant cells, that during the early prophases of division, when the chromosomes are visible in fresh cells, a granular or net-like substance is immediately brought into view on treatment with alcohol, hydrochloric acid and other reagents. This material is dissolved by peptic digestion, while the basichromatin remains undigested. It may be that this material is precipitated from the enchylema; or perhaps it may correspond in part, to the linin and oxychromatin of HEIDENHAIN.

The earlier observers have described the form of the nucleus as rounded and oval, and generally speaking its contour is fairly constant as compared with that of the cytosome; but as their field of investigation increased they became familiar with other types - the elongated nuclei which are found in muscle cells, columnar epithelium, and certain forms of parenchyma, as well as the irregular type seen in cartilage cells, leucocytes and animal ova, which undergo slow amoeboid changes of form in the living cell.

According to CHAMPY (13) and CARLETON (21) nuclei of irregular or amoeboid form are frequent in cells characterised by very active metabolism, in which case the nuclei are often not only of large size, but show a marked further increase of surface, by the formation of lobes, sacculations, and of complex branches ramifying through the cells.

They report also other cases where the nucleus shows deep infoldings, and tubular ingrowths of membrane forming intra-nuclear canaliculi. Also in certain types of cells the nuclear surface may be increased by its breaking up into separate vesicles or Karyomerites (καριον = nut. μερος = part.)[1], thus forming "polymorphic" nuclear nests. But according to BECKWITH and Hargitt ('09)[2] these Karyomerites are partial structures due to incomplete union of the chromosomes after the cell division, or to amitotic fragmentation of the nucleus. Such facts as these add to the evidence that active exchanges of material between nucleus and cytosome take place during metabolism.

In respect of the relative VOLUMES of nucleus and cytosome, each type of cell tends to-wards a definite ratio - which Hertwig calls Karyoplasmic ratio. This quantitative relation between the nuclear and cytoplasmic masses was advanced

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(1) Used by some writers as equivalent to Karyomeres (Gregoire and Wygaerts '04) - by others, as above (Goldschmidt '02).

(2) On amitotic cleavage.

by Hertwig (1903), and the more recent investigators consider that his successors have carried the theory too far.

But there remain well-determined facts concerning this ratio that are of interest for many cell-problems. If permission to make a slight digression be allowed, we will consider briefly, the conclusion deduced by MORGAN and DRIESCH from their experiments on the larvae of sea-urchin. They discovered that the cleavage is so regulated as to produce a fixed or typical cell size at a given stage; this was afterwards confirmed by BOVERI. In all these cases the volume of the nucleus varies primarily with that of the cytoplasmic mass. Of equal interest, also is the reverse case in which the primary variable factor is the nuclear mass. Typical cases are offered by the giant forms of Spirogyra and Primola, in which the nuclear volume is doubled as a result of the doubling of the number of chromosomes and the normal Karyoplasmitic ratio is restored by a corresponding growth of the cytosome to twice its former size. BOVERI has clearly shown that the size of the nuclei at any given stage is directly proportional to the number of chromosomes that they contain; they are smallest in the haploid larvae, largest in the tetraploid, and variable in the dispermic larvae.

These various facts, show that the Karyoplasmic ratio is a real and important cell-constant, which may serve as a factor in age, cell-division, or as a guide to the number of chromosomes that have entered into the composition of the nucleus. The causes of senescence in higher organisms have long been a subject of inquiry. SPENCER has suggested that it arises from a progressive increase of protoplasmic stability, that is, "an approach to-wards molecular equilibrium",(1) in which condition energy is less readily liberated by chemical action. WEISMANN(2) ascribed senescence to progressive "differentiation" by which the cell gradually loses its plasticity and reproductive powers. MINOT and HERTWIG sought for a quantitative explanation of the phenomena, that is, to a disturbance of the Karyoplasmic ratio discussed above.

In a general way, it is possible to distinguish (a) vesicular, (b) massive and (c) chromidial or scattered nuclei; but they are all connected with transitional changes. The most common type is the vesicular, which is of general occurrence in the tissue cells of most multicellular animals and plants. It is usually bounded by a membrane and contains

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(1) Principles of Biology, 1866; It is interesting to note that he also emphasized the colloidal nature of protoplasm.

(2) Life and Death 1883.

the "chromatin" structure already described.

The massive type occurs in male germ cells and generally appears homogeneous, but it is connected by many transitional forms.

The third general type - the chromidial - is represented by small granules (chromidia or chromioles), or larger irregular clumps of chromatin scattered throughout the protoplasm, and which have been referred to, by earlier observers as nuclei, as a matter of convenience, since they are not properly individualised. But more recent morphological evidence shows that in some species - "Arachnula" etc. these scattered chromidia become aggregated to form a nucleus-like body in preparation for ~~these~~ spore - formation, division, or conjugation.

The nuclear membrane is a delicate film sometimes well defined, other times it can hardly be differentiated from the surrounding cytoplasm. According to VON BENEDEN'S ('83) investigations on the telophase of the cell division in "Ascaris", and also the chromonema - hypothesis of BENNEVIE ('08) and VEJDOVSKY ('12) it appears that this membrane arises from the "chromonema", a delicately coiled, convoluted thread [1]

(1) Schneider ((10).

formed within the telophase chromosomes.

They state "that the chromonema lies in an archomatic" "basis, by the swelling and liquefaction of which, arises the" enchylema of nuclear sap, while the nuclear membrane is" "formed from its periphery". Strasburger considered it to have arisen from the cytoplasm, a fact which led him to regard it as analgous to the outer cell-membrane and to designate it accordingly as the "inner cell-membrane".

It had long been disputed whether the membrane is continuous or interrupted, and whether it has any existence as a separate structure. Heidenhain ('07) described it as being continuous and this view is now rather generally accepted.

The earlier investigators, Heitzmann ('83) considered the nucleus as being only a localised area in a structural framework common to protoplasm as a whole, the nuclear membrane being considered no more than a denser region of the same structure; this view has also been advanced by STAUFFACHER ('10) and DERSCHAU ('11) and these two have gone so far as to deny the existence of a nuclear membrane as a definite structure, regarding it as only the "optical section of the peripheral zone of the nuclear framework where it comes into connection with that of the cytoplasm". The studies of KITE and CHAMBERS (1920) on living cells by means of the micro-dissection needle seem, however, to leave no doubt of the reality of the membrane, and they also show that it is in some cases of very tough and resistant nature. These two investigators, by tearing the cell-cytoplasm, have been able to remove the nucleus intact, which after removal, may swell up and eventually burst, or it may coagulate. They have also been able to throw the membrane into wrinkles by crushing the egg-cells between cover glass and slide - an experiment which had also been carried out by Albrecht (98).

The nucleoli are still imperfectly understood. There seems to be some forms of nuclei in which the nucleoli are entirely absent; but in the nuclei of higher organisms one, or a few such bodies are invariably present, and in extreme cases may be numbered by the hundreds. HAECKER ('95) recognised that the nucleolus commonly remains single in relatively small eggs while it is usually multiple in large eggs.

Like the nucleoli of tissue-cells, those of the germinal vesicle may be either basophilic or oxyphilic, or may even be of intermediate character. JORGENSSEN has advanced that in many cases both extremes may exist in the same germinal vesicle often being united to form amphinucleoli.

Morphologically considered, the nucleoli show so many differences of forms, staining capacity and behaviour, that classification is difficult. But OGATA ('83) suggested two general classes. (1) Plasmosomes or true nucleoli; (2) Karyosomes or Montgomery's chromatin-nucleoli - a distinction which he based on that of Flemming, who designated these respective classes as "true nucleoli" and "net-knots". The plasmosomes tend to be oxyphilic, while the karyosomes are basophilic, but their staining properties vary materially at different periods in the history of the nucleus. Such variations led HERTWIG and FARMER to form the idea that nucleoli consist essentially of a basis of oxyphilic "plastin" ("pyremin" of Schwarz) - But it is more in accordance with present conceptions, to think of these varying reactions as due to different phases of a single original substance which may assume either baso - or oxyphilic conditions.

The Karyosomes are, according to MONTGOMERY, basophilic and show a high degree of resistance to peptic-hydrochloric digestion. They contrast sharply with the true nucleoli in the fact that they contribute directly to the formation of the chromosomes during cell-division (1). These Karyosomes are of at least three well-marked types :-

(a) Net-knots, as originally distinguished by FLEMMING and later by Overton and Rosenberg - of more or less irregular

(1). See under Cell Division

form, variable in size and typically in direct continuity with the nuclear framework.

(b) Chromosome-nucleoli, known with certainty only in the nuclei of the gamete-producing cells - These are usually spheroidal, and are not continuous with the general framework. They either represent single chromosomes, or a small group of chromosomes which persist through the vegetative phase of the nucleus.

(c) Karyospheres equivalent to Carnoy's nucleoles-noyaux;- spheroidal bodies, of large size, which at certain stages contain all the basichromatin in the nucleus, and from these arise the entire group of chromosomes in mitosis.

The physiological meaning of the nucleoli still remains one of the most obscure questions of cell-study. In the case of the chromatin-nucleoli or Karyosomes, observers have been able to show that they are localised reservoirs of basichromatin. But concerning the true nucleoli or plasmosomes we are still, for the most part confined to indirect evidence and conjecture. In the later prophases of mitosis, these nucleoli most commonly disappear, often previously becoming reduced in size, on undergoing fragmentation.

In some cases they are cast out bodily (1) into the

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(1) See Sir E. Sharpey-Schäfer's Ess. of Histology p.10.

cytosome at the time the nuclear membrane disappears, and there, sooner or later degenerate; "but HAECKER ('92) KARSTEN ('93) WHEELER ('97) state that they persist for quite a long time. From this fact arose the view of Haecker, later held by many others, that the plasmasomes are accumulation of waste products or by-products of the nuclear action, derived from the chromatin either by direct transformation of its substance or as chemical cleavage products or secretions.

On the other hand many cytologists, from the time of FLEMMING ('82. '91) have considered the nucleoli generally as centres for the storage or elaboration of substances such as "linin", "plastin", or "chromatin", destined to play some definite part in the later operations of the nucleus. - ("transportation-hypothesis of HAECKER")

This view is obviously correct as applied to the Karyosomes. FLEMMING regarded the plasmosomes, likewise, as being somehow concerned with the storage of "nuclein" or "chromatin", or of materials necessary for the ~~preparation~~ production of these substances. STRASBURGER ('98) regarded the true nucleoli as storehouses of "kinoplasm", or material from which the spindle-fibres are formed during mitosis.

There is, however, little definite evidence in support of this, while it is opposed by the fact, later to be described, that in animal cells perfect spindles and asters may be formed in the entire absence of nuclei.

It has also been observed during the growth period of the oöcytes of many animals that at a period when the chromosomes and the nuclear framework have become completely oxyphilic, the nucleoli are often basophilic. This suggests that the nucleoli may in such cases be storehouses of nucleic acid to be drawn upon at a later period when the chromosomes are resuming their basophilic character. This view is advanced by JORGENSSEN but so far it is purely hypothetical.

Observations have now begun to accumulate in favour of the conclusion that the true nucleoli may be concerned in the secretory processes of the cell. HIRSCHLER, HOGBEN ('20) and others have observed that such nucleolar material may give rise to various kinds of secretory products or storage-bodies, and they offer as examples the formation of yolk-spheres in oögenesis. In tissue-cells, MONTGOMERY and WALKER have described the extrusion of nucleolar fragments, which according to them are the origin of various formed bodies in the cytoplasm, such as fat-drops, albuminous granules and other products. So far there is no evidence that investigations have been made to see whether the nucleolus may not play a ~~most~~ more important and active part in cell-metabolism than hitherto assumed.

"Where a cell exists, there must have been a pre-existing" "ing cell, just as the animal arises from an animal and the" "plant only from a plant. The principle is thus established", "even though the strict proof has not yet been produced for" "every detail, that throughout the whole series of living" "forms, whether entire animal or plant organisms, or their" "component parts, there rules an eternal law of **CONTINUOUS**" "**DEVELOPMENT**" (1) (Virchow.)

It is now over seventy years since Virchow first adequately stated the principle of genetic continuity of cells by division, which was destined to form the starting point for all future conceptions of heredity and development. Only a very small portion of the vast field of cellular-study and embryology had been examined, and consequently Virchow's aphorism "omnis cellula e cellula" was too far in advance of his time to appear in its true proportions. As years passed, it gradually became evident, that this compact phase embodies one of the most important generalisations of modern science. The advance of cytological research still continues, day by day, to add fresh evidence to the demonstration that cells have no other mode of origin, than by the division of pre-existing cells.

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(1) Cellular **Pathologie**. p.25. 1858.

Retracing our steps in order to consider earlier investigations, we find that the problem of development and heredity became gradually clearer during the first two decades after SCHLEIDEN and SCHWANN. Several earlier observers have observed the origin of the cells dy the division of pre-existing cells, especially the botanists BROGNIART (1827) MEYEN (1830), MIRBEL, VON MOHL (35) and this mode of cell-formation was also recognised by the authors of the cell-theory, though only with considerable hesitation. But priority should be given to PREVOST and DUMAS (1824), who had noticed this cell-division during the segmentation of the animal ovum.

Its significance, however, was obscured for a time by the erroneous conclusion of SCHLEIDEN and SCHWANN, that cells most commonly arise "de novo" by a process of "free cell-formation" - the new cells making their appearance by crystalising, as it were, out of a continuous and formless matrix or "cytoblastema". SCHWANN speaking of the origin of cells remarks "we have in the first instance," a structureless sub-"stance, which, according to the chemical qualities and the "grade of its vitality, possesses" a greater or less capacity of "effecting the development of cells".

SCHWANN was of the opinion that the extracellular formation of cells, that is, their development in free blastema, was the most frequent mode of their production in animals.

The problems thus raised, engaged the efforts of investigators more and more seriously, and from 1840 to 1860, under the leadership of VON MOHL and Nägeli on the botanical side, and of KÖLLIKER, REMAK, and VIRCHOW, on the zoological, the theory of free-cell-formation was overthrown, and that of cell-division established.

STRICKER pays the highest tribute for defending cell-genesis by division, to REMAK who maintained with great steadiness, that in the early stages of the development of the embryo-"no other mode of cell-development occurrs".

The same author [STRICKER] states - "to Remak also the merit is due of having established the same law in respect to the pathological developments of cells. There is", he states, "at the same time no doubt that Virchow played an important "part in the extension of our knowledge in this direction, and" "that his well-grounded statement, made in 1855 (1) really con-" "stitutes the basis of our present cell theory". Heidenhain on the other hand, states that the credit is due to KÖLLIKER whose classical work on Cephalopods (1844) was considered then to be the standard, but history teaches us that this observer (Kölliker), at a somewhat later period, admitted also the occurrence of free-cell-formation, so that echoes of this old theory were still heard.

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(1) ~~Ovene~~ Omnis Cellula e cellula.

According to BRUCKE and PASTEUR the researchers of this period, distinguished three forms of cells multiplication, one by fission, one by gemmation, and lastly an endogeneous mode. Brucke states that the latter "differs from the two "former in the circumstance that the cells originate like "embryoes in the interior of the parent cell, and gradually "increase in size. Whilst in the other cases, the substance of "the mother cell breaks up into fragments, which constitute "the second generation."

These investigators had also observed, that in the multiplication of nucleated cells by division, like nucleus first "divides, "becoming elongated and finally constricted into two" "portions, which recede from one another. The fission of the " "nucleus is not always followed by division of the cell, though" "it is usually associated with the process of cell multiplicat-" "ion". They also advanced that a "formation of fresh nuclei " "occurred within the cells, not only from fission of old nuclei," "but from the growth of entirely new ones".

In both plants and animals, many cases were found, prior to the seventies, in which the nucleus was lost to view at the onset of cell-division, while at the same time "Star-like "radiations" (Asters) were observed in the protoplasm by REMAK, + VIRCHOW, but these were not carefully studied until

1873 - 1874 when FOL and AUERBACH discovered them in the ova of medusae and nematodes. It was these observations that led to the conclusion, that the nucleus disappears by a process, which AUERBACH called "Karyolysis", to be subsequently formed "de novo" in the daughter-cells; and this was for a short time considered as correct. In the end it became evident that the nuclear division is of two widely different types which, FLEMMING ('79) termed direct and indirect. In the direct type the nucleus, like the cell body, undergoes a simple mass-division into two parts. In the indirect and more complex type, the nucleus is not destroyed, but is spun out into long threads which split lengthwise, so that every portion is exactly divided between the daughter-nuclei. WALDEYER observed that, before the separation of their longitudinal halves, these threads shorten and thicken to form more condensed bodies, which he called chromosomes because of their intense staining-capacity. The products of their fission (daughter-nuclei) separate, and pass to opposite poles, and from the two groups of daughter-chromosomes, are re-built two corresponding daughter-nuclei, which by reason of the preceding processes, are exact duplicates of each other and of the mother-nucleus. In this process we to-day, recognise one of the most fundamental mechanisms of heredity.

SCHLEICHER (1878) had observed the process and called it "Karyokinesis", FLEMMING (1882) proposed another term "mitosis", alluding to the characteristic thread-formation, while the direct mode of division he termed "amitosis". Many other names were introduced, but these gradually became firmly established; But, strictly speaking, all these terms refer to the division of the nucleus only; later however, by an extension of meaning, they became applicable to cell-division as a whole.

In 1887 WHITMAN suggested the term "Cytokinesis" to designate the associated changes taking place in the cytoplasmic cell-body, though, in practice, it is often difficult to draw distinction between the nuclear and cytoplasmic activities, e.g. in the formation of the spindle. From these theories, we may therefore conveniently classify cell-division thus :-

I. Mitosis (indirect division)

(a) Karyokinesis (the nuclear changes)

(b) Cytokinesis (the cytoplasmic changes) which includes (1) Division of the cytosome and (2) Meristic Division or chondriokinesis (chondriosomes) & dictyokinesis [Golgi-apparatus.]

II. Amitosis (Fragmentation)

Amitotic division was regarded by REMAK and his immediate followers, as the typical mode. Modern re-search, however, demonstrated that it is a relatively rare and secondary process, often unaccompanied by division of the cell-body, and especially frequent in highly specialised cells; for instance, in glandular epithelia, and in early stages of degeneration. In any case, it is a known fact to-day that in all the higher forms of life, mitosis is the usual and typical mode, and we may therefore regard it as the basic phenomenon that underlies VIRCHOW's "eternal law of continuous "development", and as a primary factor IN every form of reproduction.

Growth and cell-division constitute the central phenomena in every process of reproduction, and upon them, depend the genetic continuity of living organisms, and the phenomena of heredity. In higher animals generally, the individual life runs its allotted course somewhat automatically, and given the normal conditions, every individual displays a succession of youth, maturity, old age and death as progressive phases of a process that goes forward, without pause, from the moment that the germ-cell begins its development.

In lower organisms, many cases are known in which the life-cycle of the species, as shown by the alternation of generations, is dependent upon changes of the eternal environment. In the highest animals, however, the life-cycle is a strictly sexual one, which so far as the race is concerned, may be said to begin and end in the egg or sperm - that is, as stated by HUXLEY. "The egg is the" "mid-passage or transition stage between parents and off-" "spring, between those who are, or were, and those who are" "about to be". But it must not be overlooked that in many lower animals and very generally in plants, the life-history is complicated by the occurrence of various forms of a-sexual reproduction, so that we may distinguish asexual as well as sexual cycles. And again at the opposite extreme, we find, among the simplest forms of life, some cases in which no sexual cycle is yet definitely known.

There are several problems involved in the sexual reproduction of higher organisms, such as syngamy, senescence and rejuvenescence. Morphologically the most important effect of syngamy, to-gether with the accompanying processes of maturation, is to bring about a periodic reorganisation of the nucleus, but such reorganisation is also possible in parthenogenesis. Physiologically, we may recognise four distinct effects of syngamy. In higher animals the most conspicuous of these is the imitation of the development in the egg, thus inaugurating a new cycle of activity. CALKINS ('19) held that an analogous effect is produced by the conjugation of unicellular organisms, but this is disputed by more recent writers.

Another effect of syngamy, is to bring into close association, two previously separate lines of heredity which WEISMANN calls "amphimixis". And a third effect, somewhat less obvious than the foregoing, is an increase of external diversity in the offspring.

That sexual reproduction often yields a more varied progeny than asexual, was generally accepted, and out of this grew the conclusion, that syngamy is a source of variation - a view which was later developed by DARWIN, SPENCER, BROOKS ('83) and WEISMANN ('91). But JENNINGS, having in mind the Mendelian theory states that diversity arising from syngamy is due to "the separation and re-union in new groupings of definite "heredity factors that have previously been separated in diff- "erent individuals or races". "What is new in such cases, is "not the genes or factors concerned, but only their particular" modes of combination".

It has, therefore, become a debatable question, whether syngamy can produce new variations in the sense that this word was used by WEISMANN.

Lastly, turning to the cytological aspects of syngamy and its associated phenomena, we appear to be treading on a much firmer ground. The most definite knowledge we have in this field is concerned with the history of the nuclei and the cycle of the chromosomes, which will now be considered.

Concerning the history of chromosomes, we are to-day in a position to state three principal conclusions, each of fundamental importance for the problems of heredity :-

(a) In the course of syngamy, the two gamete-nuclei unite or become closely associated (Karyogamy), each giving rise to a single or haploid group of chromosomes, the number of which, according to Beneden, is half the typical somatic number of the species. The two groups thus associated in the Zygote, respectively of maternal and paternal origin, are nearly identical. The double or diploid group thus produced, is perpetuated throughout the life of the resulting individual, being handed on by progressive division to all the nuclei of the body without change in its essential character.

(b) At a certain period during the life-cycle the number of chromosomes is again reduced to one-half i.e. the diploid chromosomes are reduced to single or haploid groups, so that the numbers and other characteristics of the chromosomes, are thus held constant from generation to generation.

This process is known as "meiosis" or "reduction".

The period at which meiosis takes place varies widely in different cases. In animals generally it constitutes one of the steps in the formation of the gametes themselves.

The third conclusion is the regrouping of the chromosomes - Segregation. This is brought about, by a modified form of mitosis in which the chromosomes undergo segregation, the diploid group separating into two haploid groups, without undergoing division in the usual sense. In this meiosis, we therefore see the force of WEISMANN'S remarks in 1887 - "There "must be yet another kind of karyokinesis IN which the primary "equatorial loops are not split longitudinally, but are separ- "ated without division into two groups."

In order to understand the relation between cell-division and genetic continuity, a brief review of the changes which occur in the nucleus, will suffice. In the course of mitotic division the nucleus usually disappears from view as an individualised body, while in its place appears a complicated structure known as the mitotic or karyokinetic figure. This structure is differentiated into a "chromatic" and an "achromatic" figure, of which, the former is derived solely from the nucleus, the latter, often from both nucleus and cytoplasm. The chromatic figure consists of the chromosomes, which are most often rod-shaped or V-shaped bodies, originally threads formed by a transformation of the net-work of the nucleus. The most constant feature of the achromatic figure as seen in sections, is a fibriller "spindle" around, or, in, which lie the chromosomes, while in many cases near each of its poles, is a central body or centriole, often doubled, surrounded by a star-shaped body called the aster. The chromosomes undergo their final division at the equator of the spindle, the daughter-chromosomes then, separating and proceeding along the spindles to the opposite poles. While this process is going on, the cell divides through the equatorial plane of the spindle, so that each daughter-cell contains a daughter-nucleus. STRASBURGER (1884) observed that this process displays a typical sucession of general phases to which he accordingly designated names as follows :-

1) Prophases- in which the mitotic figure is formed, and the chromosomes become divided longtitudinally.

2) Metaphase - in which the longtitudinally split chromosomes take up a position in the equatorial plane.

3) Anaphases - in which the daughter-halves of each, split chromosome separate, thus giving rise to two sister-groups which pass to opposite poles.

To these, Heidenhain added a fourth, the Teleophases, in which the daughter-nuclei are reconstructed from the two groups of daughter-chromosomes, and as a rule, a division of the cell-body follows. The process of Karyokinesis also passes through the same phases, with the ultimate production of chromosomes.

The theory that hereditary characters are transmitted by the nucleus, as advanced by HERTWIG and STRASBURGER was based originally, on the history of the gamete-nuclei in fertilisation and on the "idioplasm" idea of "NAGELI". The latter did not localise the idioplasm or germ-plasm in the cell, but emphasized the equal parts played by the gametes in heredity - HERTWIG and STRASBURGER applied this argument to the nucleus. Additional weight was brought to bear upon this consideration by the wide contrast between the nucleus and cytosome during mitotic division. This nuclear theory of heredity was generally accepted, but its complete demonstration only came with a closer study of the chromosomes which followed the re-discovery of Mendelian theory by CORRENS & DE VRIES, in 1900.

With this re-discovery, it became evident that the Mendelian phenomena run parallel with the history of the chromosomes, out of which grew the chromosome-theory of heredity, the whole of which may be summed up in the following manner :-

(1) The somatic or diploid-chromosomes are made up of two equivalent chromosome-groups, one of maternal derivation and one of paternal.

(2) The chromosomes retain their morphological individuality and are genetically continuous throughout the life-cycle (Beneden and Boveri).

(3) The process of synopsis consists in the union or conjugation of corresponding or homologous maternal and paternal chromosomes which in reduction-division become disconnected and pass to the opposite poles of the spindle, and thus always into different germ-cells (Montgomery and Sutton).

(4) Each chromosome plays a definite part in the determination of development.(Boveri).

The tendency of modern investigations, however, is to consider that the egg is a reaction-system (1) and "that the whole germinal complex is directly involved in the production of every character", and Genetic research is constantly bringing to light new cases of the co-operation of several factors in the production of single characters.

The union and close association of the two corresponding groups of chromosomes derived from the two respective pronuclei discussed above, leads us to consider the problem of fertilisation in relation to cell-division. Superficially regarded, these two functions seem to be opposites; for fertilisation involves the fusion of two cells into one, while mitosis results in the division of one cell into two.

Fundamentally, however, the same cytological elements are involved in both, and the same end-result sooner or later follows, namely the formation of mitotic figure and the resulting process of cleavage. Possibly, this will become clearer if we regard parenthenogenesis, or the activation of the egg, by some agency other than the sperm, a process which is connected with true fertilisation by intermediate gradations.

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1) Loeb describes the cell as Chemical machine; oxidation and destructive chemical processes of metabolism.

Both processes are analogous, in that they set in motion the mechanism, not only of cell-division, but also of development. Boveri was the first to show the necessity of making a distinction "between how egg and spermatozoon produce a cell capable of division, and the question how these cells come to be capably of reproducing the qualities of the parent in the offspring". The latter problem has been considered under the chromosome theory of heredity, but the specific problem of fertilisation is included in Boveri's question concerning the union of gametes to form a Zygote. His own theory of fertilisation 1887 was - "The ripe egg possesses all the organs and qualities "necessary for division excepting the ~~chromosome~~ centrosome, by which "division is initiated. The spermatozoon, on the other hand, is "provided with a centrosome, but lacks the substance in which "this organ of division may exert its activity. Through the "union of the two cells in fertilisation, all of the essential "organs necessary for division are brought to-gether; the egg "now contains a centrosome which by its own division leads the "way in the embryonic development". (1)

This theory does not take into account the problem of the union of the gametes, nor of their specific behaviour.

Researchers in experimental parenthogenesis have sought

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1) Lille's Problems of Fertilisation.

to find some common factor responsible for the imitation of development. By some it is held that the common effect of parthenogenetic agents is that of superficial cytolysis; by others increased permeability; others again, increased viscosity.

LOEB holds that the essential feature in the activation of the egg, whether by fertilisation or by parthenogenesis, "is the change underlying membrane-formation", which he believes to be cytolysis of the superficial layer of the egg.

LILLE advances the ~~fertilising~~ FERTILIZIN- theory, which postulates that a substance borne by the cortex of the egg (fertilizin) exerts two kinds of actions (1) an agglutinating action on the spermatozoon, and (2) an activating effect on the egg. The Spermatozoon is conceived by means of a substance which it bears - "sperm-receptors", and which enters into union with the "fertilizin" of the egg, to set free the latter's powers and thus initiate development within the egg.

All living systems, including single cells, as well as complete organisms of all kinds, react to changes occurring in their immediate environment, or to changes in their relations to the environment, by exhibiting characteristic alterations in their own special activity. This power of "responses" is the fundamental physiological property, to which modern scientists have applied the term "reactivity" instead of the more familiar term "irritability". They state that an isolated nerve is "irritable", but does not "react" in the sense of acting upon and changing the conditions in the surroundings. Hence their reason for adopting the new term.

We observe that almost any kind of environmental change, if its degree is sufficient, may act as a stimulus to the living cell or cell-system, and calls forth a reaction or response. Mechanical influences, gravity, changes of temperatures, light and electrical conditions, may all be considered as stimuli. On the other hand, changes in the relation of the organism to the environment, although the latter remains unchanged, may also furnish the conditions for stimulation and response. From this we may deduce that living system and environment are always in contact with each other, so that, broadly speaking, organism and environment form parts of a single system, exhibiting a complex type of equilibrium, characterised by a continual interchange of materials and energy. Under normal conditions, this interchange is of such a kind that the organism maintains itself - lives, grows, and eventually reproduces itself - in its environment. In order to accomphish this successfully, its own activities must be "adjusted" accordingly. The precise character of the response varies from cell to cell and depends in each case upon special inherited features of structure and organisation. For example, the unfertilised egg - cell, responds to the contact of the spermatozoon, by beginning its cycle of cell-division and development; similarly a stimulated gland cell secretes, and muscle cell contracts - ; and the nature of the response is not changed by changing the nature of the stimulus, that is, the response is both qualitatively and quantitatively constant; either the cell does not respond, or it responds with full force, "all or none" type, as shown by the cardiac and voluntary muscle cells. According to LOEB and MARSHALL the response appears to be, an expression of the fundamental, physical and chemical changes, which occur in the living-substance. Variation of electrical potential, changes of permeability, increase in oxygen, consumption and carbon-dioxide output and a temporary loss of irritability (refractory period) are the chief. Normally, these changes occur almost simultaneously, which indicate that the chemical and physical changes are interdependent.

One feature of normal stimulation which should be noted as of fundamental, bio-chemical and physiological significance, is their reversibility. Stimulation alters the chemical and physical state of the irritable protoplasm; evidence of this is seen in the fact that immediately after stimulation there is always a period, varying in length in different organisms, during which irritability is lost, or greatly decreased. This period of insensitivity is known as the "absolute refractory period"; (1) it is succeeded by a somewhat longer period, "the relative refractory period", during which the properties of the system return by degrees to normal. Stimulation can then be repeated with the same result as before. The first or "absolute" part of the period, corresponds to the time during which the chemical and structural conditions, necessary for stimulation are absent, apparently as a result of structural and chemical breakdown accompanying stimulation; these conditions are then restored (during the relative period) by some process of chemical repair. During this period processes are active, which are apparently of the reverse kind to those associated with the excitation stage, so that evidently the return to the resting state, is an active process in which there is a removal or reversal of the conditions in which the system

1) Tait and Lucas.

finds itself as a result of stimulation. This reversal automatically follows excitation effect, and both must therefore be regarded as forming part of a single cycle, consisting of alternate destructive and constructive stages.(1)

A beating heart affords an excellent example of this. Processes of chemical breakdown and production of energy occupy the first or contractile phase of the cycle, and ths system shows almost complete non-excitability during this period; during the second or relaxation phase, irritability returns progressively to normal; this phase represents the period of reversal, consisting essentially in reconstructive processes. The process of reversal is evidently complete, as is shown by the fact, that the system repeats the same cycle regularly for years. Claude Bernard and Hering called attention to this conception; the latter conceived that every stimulation caused a chemical breakdown [katabolic change] - which is succeeded by a reconstructive process - [anabolic change.] Recent studies of the refractory period (ADRIAN 1911) show that a higher co-efficient of temperature is registered during this period, than during the excitation process and according to LILLE the former period, is differently affected by lack of oxygen, and various other elements. Also electrical sensitivity (2)

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1) Lecons sur les phenomenes de la vie Vol.1 - Claude Bernard.

2) WALLER'S Expts. 1903.

seems to be a universal property of the cell. The sensitivity of nerve, muscle and other highly protoplasmic systems to the electric current, has been known since ~~all~~ GALVANI'S time. Lund in 1921, observed the directive influence of electric currents on growth- also according to Lille, growth, the fundamental vital process, may be promoted or inhibited - that is, its rate altered in either direction by electrical current. It is also known that variations of bioelectrical potential accompany all cases of stimulation - that is, the living system in its own activity gives rise to electric currents which traverse the protoplasm and the surroundings. And according to a fore-mentioned investigator, these various facts, favour the general hypothesis that in all cases of stimulation and transmission, the electrical factor seems to be the controlling power. Protoplasm and the cell media, contain salts, and are therefore good electrolytic conductors; the characteristic structure, the thin semi-permeable membranes furnish the essential conditions for differences of potential, and hence for the production of electric currents.

In a system of this nature, both physical and chemical effects may be produced by passing a current, since polarisation effects if any, may furnish the conditions for chemical changes which consequently may cause structural changes.

The close relation which exists between the living-substance and electricity - the fact that every atom is a system of electrons, probably lead MATHEWS to describe the human body as a battery and that the biochemist has been transformed into an electrical engineer, in embryo, however, for he is not yet able to understand completely the battery which is placed under his care; he cannot yet construct the simplest of these - he cannot set one battery and the motor attached to it, running, or even stop one already running, in a manner that he can set it going again. He can slow it almost to a standstill, and increase the speed again; he can replenish the supplies necessary for its maintainance - water and the proper chemicals - he is in reality more of repairer than an engineer. RIGNANO has likened the storage of momories, to the storage of potential electricity in a storage battery, and CRILE (1923) has likened the brain, to a self changing condensor.

"The morphologist, on the one hand, strives to elucidate "the structure of protoplasm down to its finest details; the "biochemist, on the other hand, with his apparently ruder, yet "still more searching method, seeks to determine the chemical "functions of the same protoplasm, broadly speaking, they are only dealing with two different sides of the same thing." - HOFMEISTER.

Modern physiologists generally accept the fundamental conclusion, that all vital energies are traceable to the chemical energy of food stuffs, that have been incorporated into the cell and are there set free by oxidation and reduction, processes of metabolism- i.e. it is an "apparatus" for the transformation and application of chemical energy.

Within limits the activities of every cell are of specific type - the muscle-cell, the nerve-cell or the gland-cell displays its own characteristic performance, and we assume the specific property depends essentially upon what is known as organisation i.e. upon "the construction" of the cell-machine, in some sense or other - morphological, physical, or chemical. The chemical conditions existing in living cells are somewhat imperfectly known and generally speaking our statements concerning these conditions are limited to inferences, based upon the chemical behaviour of dead cells or their components. It is supposed that neither the protoplasm nor the nucleus consists of a single substance of fixed composition, both being made up of a great number of different chemidal components, which are themselves often highly complex, and in a continual flux of chemical transformation.

Only in a very restricted degree has it been possible to isolate these components for chemical analysis; and our "micro-chemistry" - ie. observation by the microscope of the effect of treatment with dyes, and other reagents - is probably still too rudimentary to give us more than a few rough indications of the contents. Very little is known for example, of the chemical differences between different chromosomes of the same group; yet the experimental evidence clearly shows us that such differences exist.

Regarded from a purely chemical point of view, the cell-substance is a complex mixture of substances, of which a large percentage (60 to 70%) consists of water, while one per cent or less is formed by various inorganic salts. Among the latter, the compounds of sodium potassium, calcium and magnesium preponderate; small quantities of iron are probably also always present and sometimes, manganese, silicon. It is an interesting fact, that the chief inorganic constituents of the living body, as indicated by the salt compositions of blood, are the same as those of the sea-water; and this has been ingenuously conjectured by Macallum 1904, and others, to indicate that living matter first appeared in the sea, and has thus from the first maintained an adjustment or colloidal equilibrium with its characteristic salts.

The organic constituents of the cell are for the most part, compounds of carbon with oxygen, nitrogen and other elements, the whole have been generally classified into carbohydrates, fats, proteins and Lipins.

More recent researchers, however, have endeavoured to approach this problem from an entirely different view, taking as their basis the idea that "all atoms, and consequently all molecules, can exist in more than one form, differing in energy content". The work of Bohr permits, according to them, that the atom (Hydrogen in this case) can exist in various states containing different amounts of energy, the most stable being the commonest form of Hydrogen. In accordance with this idea, the form possessing the most energy is called "anakinetomere"; and that with the least - katakinatomere, the former they consider the living, the latter the dead form.

Irvine (1923) also has been able to discover instances of this kind in sugars. The gamma γ- sugars differ from the alpha and beta forms in their stability. It is not yet known what these gamna sugars are, but they esterify at ordinary temperature, they decompose readily to the unreactive forms - They will oxidise readily and will reduce Fefling's solution rapidly without application of heat - in view of all these facts, Irving has suggested that the sugar in the living plant in this gamna form and is hence capable of the great reactivity which sugar shows in plant.

BALY, HEILBRON and BARKER have also shown similar instance with formaldehydes. On the other hand an e-xamination of starch, fats and protein has not yet definitely revealed the presence of those two forms.

From these observations these investigators maintain that the living protoplasm has a relatively large number of molecules in a reactive, anakinetomeric form, so that at every response to a stimulus, part of the protoplasm dies and becomes irresponsive; the recovery being due to the conversion of the Kata- to the anakinetomeric form, which occurs during the refractory period.

The synthetic powers of protoplasm has also been observed. The simplest of the complex substances which are formed, are the carbohydrates e.g. Glucose. This can be synthetised by animals out of lactic acid glycerine, aldehyde, and various amino-acids.

This in reality is a dehydration synthesis, and is more or less the bases of cell-life. Without going into the chemical details, we may here assume that the hydrolytic decompositions which occur in cells, is of extreme importance in medicine. It is known that water is an essential part of protoplasm, but its conditions within the cell and the rôle it plays are somewhat obscure. DUBAIS and RIGGS state that it is held their in peculiar condition; that the molecules are hydrated so that there is both, bound and free water. It is a well-known fact that a frog's nerves may be stimulated by depriving them of water, and it often makes one wonder why this does occur, and, so far, no definite explanation has been given and no doubt the problem of oedema is bound up in hydrolysis. Similarly the question of the penetrating power of various substances that is, cell permeability which was so extensively studied by OVERTON 1895 - 6-9 etc., is now receiving great attention and will no doubt help us to discover many hitherto, unknown facts regarding protoplasm.

Lastly, a brief review of cellular differentiation. All differentiation is transformation from a more general and homogeneous to a more special and heterogeneous condition. There are many differentiations which are purely temporary, others are more permanent, but, in general, protoplasm is not constant or static with respect to differentiation, but oscillates between different phases. These oscillations may be short, as in the process of assimilation and dis-assimilation, contraction and expansion, mitosis etc.; or they may be long as in life - cycles of individuals, in which differentiation may be more or less permanent. These life-cycles differentiations are generally known as "development", which may be defined as progressive differentiation, co-ordinated as to time and place. Differentiation seems always to be associated with integration; specialisation with co-ordination and co-operation. These two are correlative processes,-two aspects of one thing,- namely organisation. Differentiation has always been defined as "physiological division of labour" but, it is also a "morphological division of substance", for these are merely two aspects of one and the same thing, and in life they are inseperable.

Protoplasm exists only in the form of cells, and all cells have certain fundamental differentiations. As already stated some of these differentiations of the cell are temporary and appear, and then disappear with certain phases of cell-activity. For example, the chromosomes, asters and spindles differentiate during mitosis and again dedifferentiate during intermitosis. Chromosomes give rise to chromosomial vesicles and vesicular nuclei, and these in turn give rise to chromosomes.

Many experiments indicate that the life and activity of the cell is associated with interchange between the nucleus and cytoplasm. Processes of oxidation, assimilation, are known to be dependent upon this interchange, and the same is true of differentiation. One of the simplest cases of differentiation is found in the formation of secretion products within the cells, such as yolk and oil; which appear first as minute granules that gradually grow to fill the cell.

According to GOLDSCHMIDT (1910) the yolk and Zymogen begin to form in the vicinity of the nucleus out of the granular mass, which is either chromidia, mitochondria or the granular substance surrounding the centrosomes & known as sphere-substance which probably gives rise to the "yolk-nucleus". This same author states that intracellular fibrils, such as skeletal muscle and nerve fibrillae are derived from chromidia and hence are formed in the greater part by substances derived from the nucleus. MEVES (1910) and DUASBERG, maintain that such are derived from mitochondria which are purely cytoplasmic.

As a result of all these observations it is impossible to avoid the conclusion that the nucleus is intimately concerned with differentiations, and the mechanism of the "nuclear control" of the cell is at least suggested by the escape of the chromatin and other nuclear substances into the cytoplasm, and the formation there of various differentiation products.

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