HETEROCHROMATIN AND NUCLEIC ACID.

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The complexity of the concept heterochromatin may in part be regarded as a matter of controversial definition. In part the actual phenomena to which this term has been applied are so variable — often certainly unrelated — that it is impossible to give a simple definition of the term which would comprise even the most important kinds of heterochromatin. Though a very great number of observations concerning the heterochromatin in various organisms has been made over a long period, it is only the work done during the last decade that has created a common basis for the understanding of these phenomena. In addition to the work done on *Drosophila* we are indebted for this chiefly to two sources: DARLINGTON and his collaborators and CASPERSSON and his coworkers. These studies have had the important result of bringing to light the decisive role played by nucleic acids in the organization of the chromosomes as well as in the whole cell metabolism.

The chromosomes have been found to be built up of certain proteins in combination with thymonucleic acid. Thymonucleic acid occurs as macromolecular fibres, the molecular weight of which varies between 500.000 and 1.000.000. These are made up of smaller units, mononucleotides, in which the central position is occupied by a pentose sugar, desoxyribose. To each pentose molecule a purine or pyrimidine base is attached. The sugar molecules are connected to eachother through orthoshosphoric acid molecules (cf. e.g. GULICK 16). The well-known Feulgen staining, which, properly used, is specific for thymonucleic acid, is carried out in two phases. First the preparation is subjected to hydrolysis in N-hydrochloric acid which breaks the bonds between the purine bases and desoxyribose. Then fuchsin sulphurous acid reacts with the liberated aldehyde groups of the sugar molecules, forming a violet dye, which can thus be used as an indicator for the presence of thymonucleic acid.

Ribose nucleic acids, which are characteristic for the other cell constituents, differ from thymonucleic acid as well as in regard to their smaller molecule size, especially in that the central sugar molecule in this case is ribose.

In addition to the differentiation of the chromosomes into chromomeres and fibrils, which is best seen at pachytene in meiosis and in the salivary gland chromosomes, a number of other regions may be distinguished in the longitudinal structure of the chromosomes. Of these the most important are the primary constriction, where the centromere is situated, and the secondary or SAT-constrictions together with the terminal satellites or trabants.

One category of differing chromosomes or chromosome parts is furnished by the so-called heteropycnotic chromosomes, the term implying a differential condensation, or in other words a differential thymonucleic acid charge and spiralization, of the chromosomes concerned. Heteropycnotic chromosomes may be more or less condensed than the rest of the chromosomes. To both these alternatives the terms positive and negative heteropycnosis have been applied. To use a definition by WHITE (25, p. 68): »A negatively heteropycnotic chromosome is one which thickens more slowly or to a lesser extent than the others during prophase or which undergoes de-condensation more rapidly during anaphase. Conversely, a positively heteropycnotic chromosome is one which thickens faster, earlier or to a greater extent than the rest of the chromosome set, or which remains thickened when the others are undergoing de-condensation at telophase.» To this may be added that the same chromosome or part of it may show negative heteropycnosis at one stage of its cycle and positive at another. Heteropycnosis is characteristic of the sex chromosomes in most animal groups, but other chromosomes too may have this property (cf. WHITE 26). An instructive example of heteropycnotic chromosomes and their behaviour is furnished by the order *Orthoptera* where in some families the sex chromosomes are positively, and in others negatively heteropycnotic (WHITE 25).

A phenomenon corresponding to heteropycnosis was discovered in plants by HEITZ (17) in the sex chromosomes and certain autosomes of the liverworts. He proposed the term heterochromatin for these heteropycnotic chromosome regions as opposed to euchromatin of the main chromosome body. Later HEITZ (18, 19) found, in Phanerogams too, chromosomes in which the heterochromatic part remained condensed and visible in the resting stage. Such condensed chromosomes have been called chromocentres. HEITZ especially pointed out that the terms euchromatin and heterochromatin were used by him exclusively in a morphological sense. The term heterochromatin has, however, later been extended from indicating merely cytological differentiations in the chromosomes to comprise chromosome parts which differ from the other euchromatic chromosome segments either in their chemical and physiological or genetic properties. Heterochromatin may for the present perhaps most adequately be defined as a purely cytological concepts in the sense that all chromosome regions which at any stage of their cycle differ from the main part of the chromosomes in regard to their thymonucleic acid content are regarded as positively or negatively heterochromatic. According to this definition negatively heterochromatic chromosome parts would include too secondary constrictions which at most stages seem to contain less thymonucleic acid than other chromosome parts.

Attempts to analyze the nuclei of different organisms chemically have not

been wanting. For this purpose various methods have been employed. In regard to the extensive literature we may refer in this connection to the excellent reviews of CASPERSSON and SANTESSON (6), DARLINGTON (8, 9), GULICK (16), and MIRSKY (23), considering these questions from different viewpoints. A usual macrochemical analysis is here confronted by great difficulties, depending on the small size of the structures to be studied and the impossibility of freeing the nuclei completely from other cell components. The first attempts of this kind were made by MIESCHER 1870 (cf. GULICK 16) when he digested away the plasm of pus cells with pepsin- hydrochloric acid. From the remaining nuclei he isolated a phosphorus-containing compound which later has been identified as nucleoprotein. Related methods have been applied also to the investigation of fish sperm. KOSSEL (cf. GULICK 16) could thus state that during spermatogenesis higher proteins were replaced by simpler histones and protamines. The latter are comparatively simple compounds made up of 15—30 amino acid radicals which form a polypeptide chain. Of these amino-acids the most important are arginine, histidine and lysine, which all contain six carbon atoms, and are relatively strongly basic, which renders the proteins made up by them basic too. Histones resemble the protamines in many respects, having, however, a larger molecule and containing a greater variety of amino-acids. In the nucleoproteins the strongly acidic thymonucleic acid apparently forms a salt-like compound with these basic proteins.

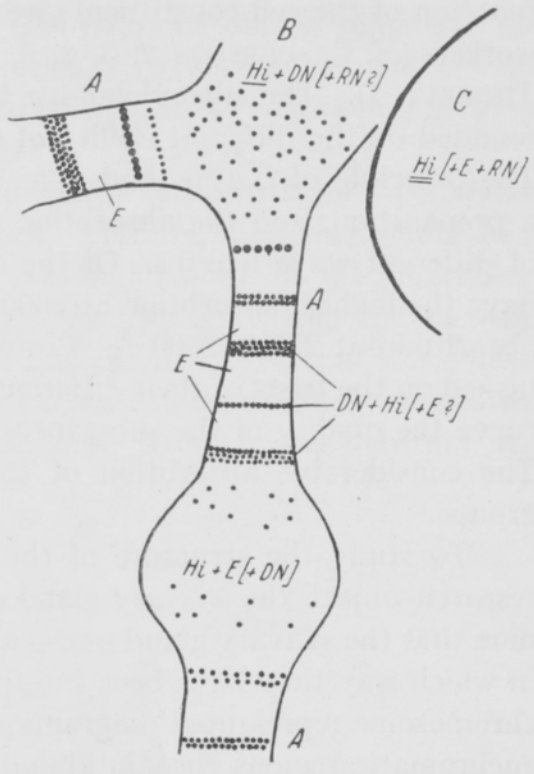

Fig. 1. Scheme of the structure of the salivary gland nucleus. A euchromatin B heterochromatin, C nucleolus, DN ribodesose nucleotides, RN ribose nucleotides, E protein of the globulin type, Hi protein rich in hexone bases. Underlining indicates large quantities, parenthesis small quantities. (CASPERSSON *and* SANTESSON 6).

Of the staining methods the most important is the Feulgen technique mentioned above. Other staining methods are less useful since they are not specific like the Feulgen method. In general the differential staining of the various parts of the cell depends on their basic or acidic reaction. Thymonucleic acid and accordingly the chromosomes stain with basic dyes. Histones again, having a basic character, react with acidic dyes which causes the nucleoli to be stained by the latter. The possibilities of the different staining methods may further be increased by using various mordants. The digestion of the cell constituents with enzymes which are specific for some compound has also proved a valuable tool in the study of the chemical structure of the cell.

For the most important results in the elucidation of the chemical structure and

function of the cell constituents we have, however, to thank CASPERSSON and co-workers (cf. CASPERSSON 2, 3, 4, 5, CASPERSSON and SANTESSON 6, CASPERSSON and THORELL 7). The ultraviolet-spectroscopic method developed by CASPERSSON is founded on the different ability of different compounds to absorb ultraviolet light. The principle of the method is as follows. The tissue to be studied is made into a preparation, and the absorbtion of the preparation is determined using a series of different wave lengths. Of the compounds present in the nucleus nucleic acids have the highest absorbtion at 2600 Å, while the proteins show a considerable lower absorbtion at 2750—2900 Å. Proteins of globulin or histone types may be distinguished on the basis of their different absorbtions. From the shape of the absorbtion curve the quality of the substances may be inferred, from its height their amount. The considerable absorbtion of the nucleic acids is caused by their pyrimidine groups.

To study the structure of the interphase nucleus CASPERSSON has used as a research object the salivary gland chromosomes of *Diptera*. For he holds the opinion that the salivary gland nuclei are permanent interphases rather than prophases, in which way they have been interpreted earlier. In Fig. 1 we see a salivary gland chromosome represented diagrammatically. The chromomere bands situated in the euchromatic regions contain abundantly thymonucleic acid together with histones and a small amount of higher proteins. In the fibrils thymonucleic acid is wholly lacking and the proteins are of a higher globulin type. Heterochromatic regions have fused and form a chromocentre. They contain histones combined with thymonucleic acid and possibly a small amount of ribose nucleic acid. The nucleolus is chemically related to heterochromatin in that its proteins are histones; in addition a certain amount of higher proteins and ribose nucleic acid have been found to be present.

Metaphase chromosomes which have been studied by CASPERSSON using chiefly grasshopper chromosomes differ from the interphase chromosomes in that the higher proteins have broken down. Consequently the chromosomes consist of approximately equal amounts of histones and thymonucleic acid.

Fig. 2 shows which chemical changes according to CASPERSSON accompany the different nuclear phases. A metaphase chromosome, the one end of which is heterochromatic, the other euchromatic, is compactly spiralized and contains, as mentioned above, thymonucleic acid and histones. During telophase the spirals uncoil and thymonucleic acid disappears from the euchromatic chromosome parts, whereas a certain amount of it is retained by the heterochromatic parts. During this stage and the following interphase the euchromatic regions produce highly specific proteins of high molecular weight which surround the genes. During these phases heterochromatic parts again produce histones of which a part forms the nucleolus. During prophase the process is reversed in that the higher proteins and the nucleolus break down and the chromosomes are recharged with thymonucleic acid. At the same time the chromosomes spiralize into compact metaphase chromosomes. We may summarize the abovesaid as follows. The cycle of thymonucleic acid is co-ordinated with the nuclear cycle in that the acid is synthesized

during prophase; in metaphase its amount is highest, and during telophase the acid breaks down until it is almost completely absent in the resting nuclei. The protein content seems to vary inversely with thymonucleic acid, being greatest in the resting nuclei and smallest at metaphase.

It is not known for certain which compounds in the cell constitute the material for the nucleic acid synthesis. The old hypothesis that the nucleolus would be a source of reserve material, which is used for the building up of »chromatin» at prophase, has been revived by CASPERSSON (3). According to him the histones would be most likely to form the material for nucleic acid synthesis, since their hexone bases, i.e. the amino acids containing six carbon atoms, would be best suited to form the pyrimidines characteristic of nucleic acid. This view is born out also

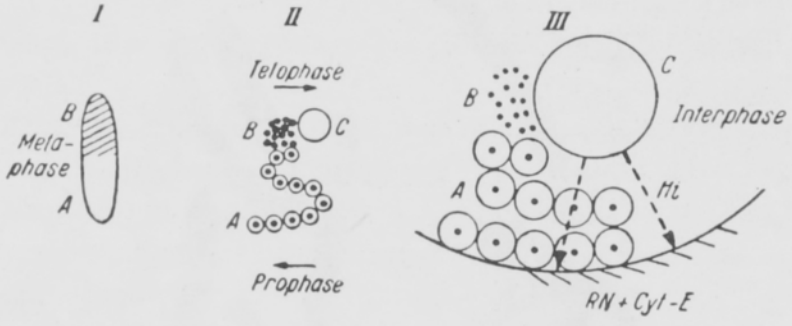

Fig. 2. Schematic presentation of the protein changes during mitosis. I a metaphase chromosome. II the same chromosome in the beginning of the telophase and late in the prophase, III in the telophase or interphase. Terminology as in Fig. 1.
(CASPERSSON *and* SANTESSON 6).

by the fact that the histone-rich nucleoli disappear just when the thymonucleic acid is built up, to reappear again when it is broken down.

Investigations carried out on different organisms and tissues have made evident the decisive role played by nucleic acids in the metabolism of all cells. Nucleic acids seem to be specifically concerned with protein synthesis, thymonucleic acid being connected with the production of the highly specific gene proteins and ribose nucleic acids with the less differentiated proteins of the other cell constituents. CASPERSSON and his coworkers have been able to show that always when protein synthesis takes place nucleic acids are also present. It has been mentioned above that thymonucleic acid is localized on the gene-carrying parts of the chromosomes, whereas ribose nucleic acids are an important constituent in plasm, plastids, bacteriophages and many viruses. In addition it has been observed that the more intensive the growth of a tissue or a cell is the higher is its nucleic acid content. They have been found to occur especially abundantly in egg cells, in growth tissues of plants, in embryonic tissues of animals, and in dividing yeast.

CASPERSSON's views on the protein metabolism of the cell are shown diagrammatically in Fig. 2. As was mentioned, heterochromatin produces large amounts of histones during telophase and interphase, of which a part forms the nucleolus. From the heterochromatin and the nucleolus the histones wander towards the

nuclear membrane, where they induce a synthesis of ribose nucleic acids in the surrounding plasm. The ribose nucleic acids in turn seem to be intermediates or at least active factors in the production of the cytoplasmic proteins. Heterochromatin would accordingly have an important function as a regulator of the nucleic acid and protein metabolism of the cell. In addition to the abundant occurrence of nucleic acids in cells in which the protein synthesis is intensive the nucleoli too are

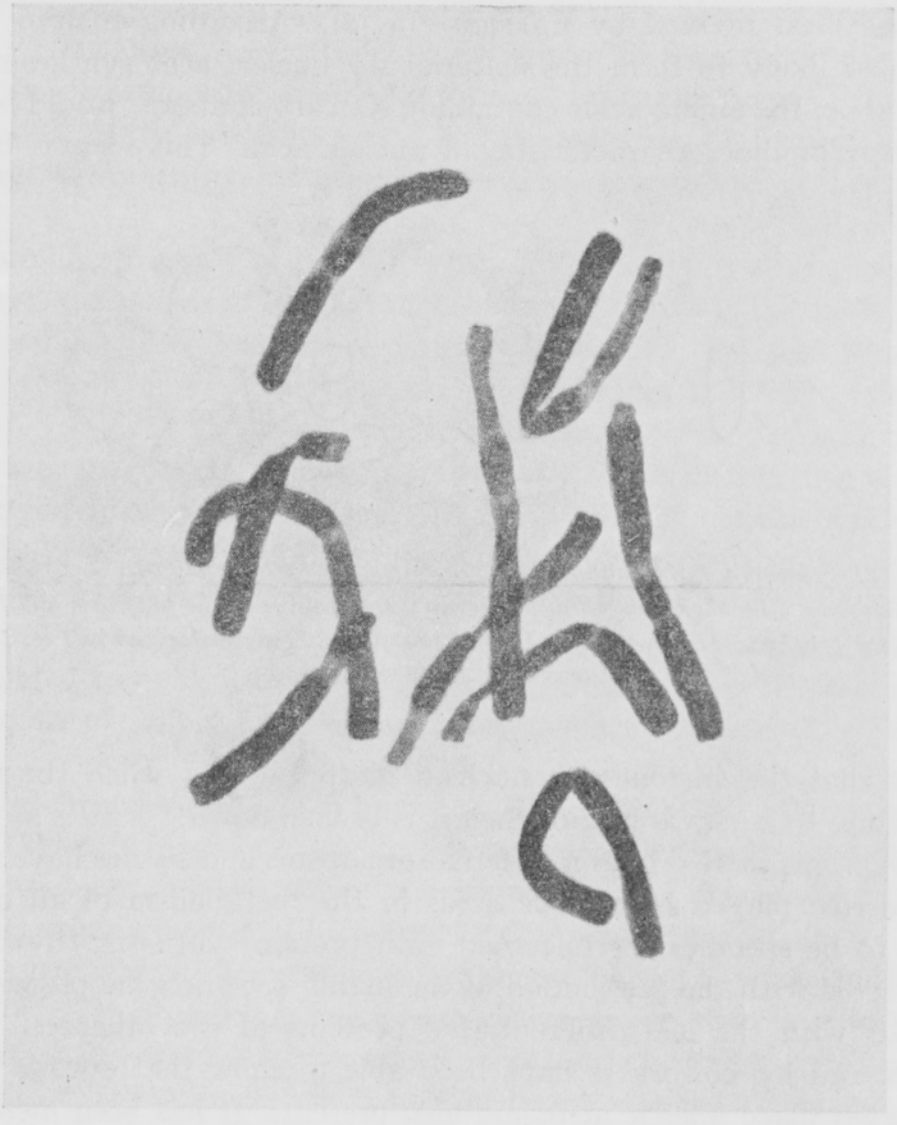

Fig. 3. Microphotograph of a metaphase plate from a root tip cell in Trillium stylosum showing nucleic acid starvation after cold treatment. × 1700. (Darlington *and* La Cour 11).

of larger size in such cells. The increase of the amount of the heterochromatin in the cell seems to give rise to various effects, partly morbid changes in the growth and metabolism of the cell.

It must be noticed, as Caspersson and Santesson (6) have stressed, that heterochromatin defined from a chemico-physiological point of view, is difficult to identify cytologically except in a limited number of cases. Caspersson (5,

p. 143) has therefore later adopted the name nucleolus-associated chromatin »to avoid the name heterochromatin, as the cytological and genetical definition of the latter in ordinary nuclei still seems to be very difficult and to some extent a matter of choice».

A cytologically detectable case of heterochromatin was discovered by DARLINGTON and LA COUR (10) in the somatic chromosomes of *Paris*. When the plants were kept for a few days before fixation in a temperature approaching the freezing point, certain parts of the chromosomes appeared as thinner and less stained differential segments. This depended apparently on the fact that they contained in metaphase and anaphase less thymonucleic acid than other chromosome regions (Fig. 3). Similar heterochromatic segments made visible with cold treatment have later been observed in *Trillium* and *Fritillaria* (DARLINGTON and LA COUR 11), in *Adoxa* (GEITLER 15) and in *Triton* (CALLAN 1) for instance. In the resting nuclei these segments which at other stages are less stained, form condensed and intensively stained chromocentres.

At anaphase the heterochromatic segments in the daughter chromatids do not separate clean as other chromosome parts, but remain attached forming long bridges at telophase. DARLINGTON and LA COUR (11) explain that this depends on the fact that thymonucleic acid is necessary for the proper reproduction of the chromosomes, and since the heterochromatic segments are undercharged with nucleic acid, their normal division and consequently their separation are prevented.

The work on the structure and behaviour of heterochromatin has been continued by DARLINGTON and LA COUR (12) in their ingenious study of the effects of x-rays on the chromosomes. These studies have brought to light an important factor influencing chromosome behaviour, viz. the polymerization of nucleic acid. X-rays seem to increase the nucleic acid content of the cell, but at the same time they upset their regular polymerization, which is a necessary condition for normal chromosome structure and behaviour. The unpolymerized nucleic acid makes the chromosome surface fluid, which in turn renders the chromosomes sticky and finally induces them to fuse into a pycnotic mass. Further, the breakage and reunion of chromosomes, when treated with x-rays, seem to be dependant on their thymonucleic acid charge. The chromosomes are not breakable at prophase or metaphase, being then charged with thymonucleic acid. The same is true of the charged heterochromatic segments at resting stage. The fusability of the chromosomes again seems to act in inverse relation to their breakability, the most heavily charged chromosome parts fusing most readily.

There have been different opinions concerning the interrelation between spiralization and thymonucleic acid charge of a chromosome. It seems, however, evident that the former is, to a certain extent, a function of the latter. It may be stated in general that when the thymonucleic acid charge of the chromosomes is at its height the spiralization is also most compact. This is the case both in regard to the different stages of the normal cycle and in the positively heteropycnotic chromosomes during the resting stage. Conversely, it has been observed that when the chromosomes are undercharged as in the negative heterochromites spiralization is weaker

also. In extreme cases such chromosome regions may even remain completely unspiralized (cf. CALLAN 1).

In addition to cold treatment other circumstances too may give rise to thymonucleic acid deficiency in the cell, thus rendering heterochromatin visible as more faintly stained segments. Starving has been found to have an effect of this kind in certain animals. Thus for instance WICKBOM (27) observed heterochromatic chromosome segments in *Triton* individuals which had been kept without food from May to July. The same phenomenon has been observed in *Mecostethus* as well as in the golden hamster, in the latter old age too resulting in a nucleic acid starvation of the heterochromatic segments. Evidently in these cases thymonucleic acid synthesis is already blocked at an early stage through lack of material. The neighbouring cells in the same tissue must compete for the small amount of thymonucleic acid available, which results in the differential behaviour of heterochromatic segments even in adjacent cells (KOLLER 21).

Cold treatment in its turn slows down all the metabolic activities of the cell, thus preventing the conversion of ribose nucleic acid into thymonucleic acid. X-rays seem not to decrease the nucleic acid content of the cell, but on the contrary to increase it. Instead they prevent their regular polymerization, as described above. The excess of nucleic acid is carried away from the cell at higher temperatures, whereas low temperatures greatly slow down this process (DARLINGTON and LA COUR 12).

HEITZ (18) has been the first to present the hypothesis that heterochromatic chromosome regions might be genetically inactive, inert. Later experimental studies especially on *Drosophila* have proved this line of thought to be justified. It has, in fact, turned out that heterochromatic chromosome parts do not contain genes in the usual sense and neither do any detectable mutations take place in them. It does not seem to influence the morphological characters of *Drosophila* whether it has none, one or several Y-chromosomes. A male in which the Y-chromosome is lacking is, however, sterile. Other observations too have shown that although typically heterochromatic regions do not contain real genes, they are by no means without significance. On the contrary, it has become evident that they have functions of essential importance for the cell and thus for the whole organism. MATHER (22) on the basis of his investigations has proposed the term polygene instead of the earlier inert gene. Polygenes are not so highly specialized as other genes, but have small, similar and complementary effects. They are *inter se* more or less similar and the influence exerted by them depends on their number.

If this genetical concept of polygene is considered in the light of what we know of the chemical properties of heterochromatin we arrive at the following conclusions. When during telophase and interphase the gene-carrying parts produce specialized proteins of high molecular weight, the heterochromatic parts secrete less differentiated histones of smaller molecular size. Heterochromatin regulates the nucleic acid metabolism and through it also the protein metabolism of the cell. The role of heterochromatin in cell metabolism is thus important though less specific than the activity of euchromatin. Consequently its functions are much more difficult to

define and distinguish. We must, however, remember that the differences between euchromatin and heterochromatin are by no means absolute either from a cytological or genetical point of view, and evidently there exist between the two typical extremes all possible intermediates.

Such cases in which the amount of heterochromatin has been increased owing either to natural or experimental disturbances have thrown light on its genetical and physiological activity. In a number of plants as for instance *Sorghum* (DARLINGTON and THOMAS 13), *Zea* (DARLINGTON and UPCOTT 14) and *Anthoxanthum* (ÖSTERGREN 24) certain strains have supernumerary heterochromatic chromosomes, called B-chromosomes. Their activity in *Sorghum* (DARLINGTON and THOMAS l.c.) is to be seen in the pollen grains. In the normal cells the first pollen grain mitosis which results in the formation of the vegetative and generative nucleus is followed by the division of the generative nucleus into two nuclei. In the cells which contain B-chromosomes, however, the generative nucleus divides four to five times, which finally causes the death of the pollen grain. DARLINGTON and THOMAS (13) have concluded from this that even in normal cells the heterochromatic chromosome parts accelerate the division of nuclei and thus also of the cells.

On this question light has been thrown also by studies on the physiology and cytology of malignant tumour cells (CASPERSSON and SANTESSON 6; KOLLER 20). A malignant tumour is characterized by unlimited growth which is founded on intensive protein synthesis. CASPERSSON and SANTESSON (l.c.) have observed that tumour cells contain more nucleic acids than normal cells and also the nucleoli are of bigger size. The excessive nucleic acid gives rise to a number of chromosomal irregularities, as. e.g. stickiness, clumping, non-disjunction, multinucleate and polyploid cells, and spindle abnormalities (KOLLER l.c.). From these data may be inferred that the activity of heterochromatin is abnormally increased in these cells. Evidently the mechanism which in normal cells controls this activity has here ceased to function. Both KOLLER (20) and CASPERSSON and SANTESSON (6) therefore represent the view that the origin of the malignity of the tumour cells is to be sought in an abnormal increase of heterochromatin in one or a few cells, which causes disturbances in the growth and metabolism of the cells concerned. In the following cell generations the disturbances accumulate, resulting finally in the formation of a typical malignant tumour. This explanation would also agree with the fact that the malignity of tumours has been observed to increase gradually.

If we try to summarize the data described above we may say that heterochromatin in the genetical sense comprises all the chromosome parts which earlier were regarded as inert, but which now are thought to contain polygenes. From the chemical and physiological viewpoint those chromosome parts are heterochromatic which during telophase and interphase contain and produce histones, thus controlling the nucleic acid and protein metabolism of the cell. From a purely cytological and morphological point of view heterochromatin seems to be most difficult to define. The most essential feature is evidently expressed if we say that by heterochromatin are meant all those chromosome parts which are allocyclic, in other words in which the thymonucleic acid charge and cycle differ from that in the main part of the

chromosomes. This difference seems often to lie in the divergent timing of the thymonucleic acid cycle of the heterochromatic chromosome segments as compared with the euchromatic chromosome parts. It seems, however, to be evident that the concepts of heterochromatin arrived at from different points of view are not at least for the present identical. Although the structure and activity of heterochromatin have been the subject of intensive research, and a great number of important results have been achieved unsolved questions seem to be abounding. The discovery of the underlying relationships between the results obtained with different methods will be the great task of further work.

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SELOSTUS.

HETEROKROMATIINI JA NUKLEIINIHAPPO

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Maatalouskoelaitos, Puutarhaosasto, Piikkiö.

Heterokromaattisiksi tämän käsitteen laajimmassa merkityksessä on nimitetty kromosominosia, jotka spiraloitumiseensa ja värjäytyväisyyteensä nähden jossain tuman vaiheessa eroavat muista, eukromaattisista kromosominosista. Heterokromatiini, sen rakenne ja toiminta, ovat erikoisesti viimeisen kymmenen vuoden aikana olleet vilkkaan tutkimuksen kohteena. Näissä tutkimuksissa on käynyt ilmi, että erään tärkeimmistä tekijöistä kromosomien ja solun rakenteessa ja elintoiminnoissa muodostavat nukleiinihapot.

Kromosomit ovat rakentuneet tymonukleiinihaposta sekä valkuaisaineista, joiden määrät vaihtelevat tuman vaiheiden mukana. Metafaasi-kromosomit sisältävät jokseenkin yhtä paljon tymonukleiinihappoa ja histooneja. Telo- ja interfaasin aikana tymonukleiinihappo hajaantuu muista paitsi heterokromaattisista kromosominosista. Näiden vaiheiden aikana eukromaattiset kromosominosat tuottavat erikoistuneita globuliinityyppisiä valkuaisaineita, heterokromaattisten osien tuottaessa pienempimolekyylisiä histooneja. Profaasissa korkeammat valkuaisaineet hajaantuvat ja kromosomit varautuvat jälleen tymonukleiinihapolla.

Osa heterokromatiinin tuottamista histooneista keräytyy telofaasissa tumajyväseksi. Heterokromatiinista ja tumajyväsestä histoonit vaeltavat tumakelmun luo, missä ne aikaansaavat hiivanukleiinihappojen syntymisen ympäröivässä solulimassa. Hiivanukleiinihapot vuorostaan näyttävät olevan tärkeitä tekijöitä, ehkä väliasteita, soluliman valkuaisainesynteesissä. Heterokromatiinilla on tämän käsityskannan mukaan tärkeä tehtävä solun nukleiinihappo- ja valkuaisaine-talouden säätelijänä.

Sytologisessa mielessä heterokromatiini voidaan ehkä parhaiten määritellä siten, että heterokromaattisiksi nimitetään kromosominosia, jotka jossain tuman vaiheessa eroavat muista kromosominosista tymonukleiinihappovaraukseensa nähden. Erikoisen luonteenomaista näille osille on useissa tapauksissa tymonukleiinihapposykluksen käänteisyys verrattuna muihin kromosominosiin, heterokromaattisten osien sisältäessä enimmän nukleiinihappoa lepotumassa ja vähimmän meta- ja anafaasiasteessa.

Heterokromaattisia kromosominosia pidettiin aikaisemmin geneettisesti toimettomina, inertteinä. Nyttemmin on kuitenkin tultu siihen tulokseen, että vaikkeivät ne sisälläkään varsinaisia geenejä, niillä on tärkeä merkitys solulle. Niiden sisältämiä geenejä on nimitetty polygeeneiksi, joilla on todettu olevan keskenään samankaltainen ja vähemmän erikoistunut vaikutus kuin tavallisilla geeneillä.

On huomattava, että heterokromatiinin määritelmät, joihin on tultu eri näkökannoilta lähtien, eivät ainakaan nykyisellään tarkoin vastaa toisiaan. Lisäksi ei pidä unohtaa, että eukromatiini ja heterokromatiini eivät ilmeisesti ole missään mielessä jyrkästi toisistaan erotettavia, vaan niitä yhdistävät lukuisat väliasteet.