This Week's Citation Classic®

CC/NUMBER 29
JULY 20, 1987

Comings D E. The structure and function of chromatin.
Advan. Hum. Genet. 3:237-431, 1972.
[Department of Medical Genetics, City of Hope National Medical Center, Duarte, CA]

The paper is an extensive review of many aspects of chromatin, including histone and nonhistone proteins, hnRNA, gene regulation, DNA replication, repetitious DNA, the genetic and functional aspects of heterochromatin and its relevance to chromosome banding, and the strandedness of chromosomes. [The *SCI*® indicates that this paper has been cited in over 185 publications, making it the most-cited paper for this journal.]

David E. Comings
Department of Medical Genetics
City of Hope National Medical Center
Duarte, CA 91010

April 25, 1987

In the late 1950s the development of the technique of phytohemagglutinin stimulation of lymphocytes and hypotonic treatment of metaphase cells caused the field of human cytogenetics to explode like a Chinese rocket. Within a few years all the major human chromosome abnormalities had been discovered. This, along with the cracking of the genetic code and the work of F. Jacob and J. Monod,[1,2] stimulated many young scientists, including me, to enter the field of human genetics.

However, by the late 1960s human cytogenetics needed another shot in the arm. This came in the form of an initially obscure paper by T. Caspersson and coauthors[3] that showed that by staining plant chromosomes with quinicrine mustard, multiple bands were present along the arms. When this technique was applied to human chromosomes, miracle of miracles, all the chromosomes could be distinguished from each other.[4] Within a few years the techniques of C-, G-, and R-banding were added to the cytogeneticist's repertoire, and human genetics had its shot in the arm. Once a single chromosome could be identified, spectacular things could be done, such as gene mapping by somatic cell genetics.

The concept of heterochromatin as cytogenetically visible, genetically inactive chromatin material had been well established in *Drosophila* genetics. It became of interest to the human cytogeneticist with the discovery of the Barr body[5] and the demonstration by Mary Lyon[6] that it represented a genetically inactive X chromosome in female cells. The development of C-banding, detecting constitutive heterochromatin at the centromeres, and the demonstration that Q- and G-bands coincided with late-replicating DNA in the chromosome arms heightened the fascination with heterochromatin.

When Henry Harris and Kurt Hirschhorn asked me to write a chapter on chromatin for the *Advances in Human Genetics* series, the time was ripe for an extensive review of heterochromatin and chromosome structure in general. During this time, many individuals were still convinced that chromosomes were binemic. I felt that all the evidence for this was severely flawed and only uninemy made sense.

The article has probably been popular because the lack of restraints on its length allowed a thorough exploration of subjects that were fascinating to many people.

The whole concept of chromosome banding continued to intrigue me, and by 1980 the explanation of the different bands could still be best formulated by a model in which euchromatin and intercalary heterochromatin, containing different types of DNA, were distributed as units along the chromosome arms.[7] This concept, and its evolutionary implications, has recently been nicely expanded by Gerry Holmquist,[8] a former postdoctoral fellow in my laboratory.

1. Jacob F & Monod J. Genetic regulatory mechanisms in the synthesis of proteins. *J. Mol. Biol.* 3:318-56, 1961. (Cited 2,890 times.)
2. Monod J, Changeux J-P & Jacob F. Allosteric proteins and cellular control systems. *J. Mol. Biol.* 6:306-29, 1963. (Cited 1,100 times.)
3. Caspersson T, Zech L, Modest E J, Foley G E, Wagh U & Simonsson E. Chemical differentiation along metaphase chromosomes. *Exp. Cell Res.* 49:219-22, 1968. (Cited 350 times.)
4. Caspersson T, Zech L, Johansson C & Modest E J. Identification of human chromosomes by DNA-binding fluorescent agents. *Chromosoma* 30:215-27, 1970. (Cited 915 times.)
5. Barr M L & Bertram E G. A morphological distinction between neurons of the male and female and the behavior of the nucleolar satellite during accelerated nucleoprotein synthesis. *Nature* 163:676, 1949. (Cited 570 times since 1955.)
6. Lyon M. Gene action in the X-chromosome of the mouse (*Mus musculus*). *Nature* 190:372-3, 1961. (Cited 1,135 times.)
7. Comings D E. Mechanisms of chromosome banding and implications for chromosome structure. *Annu. Rev. Genet.* 12:25-46, 1980.
8. Holmquist G. Role of replication time in the control of tissue-specific gene expression. *Amer. J. Hum. Genet.* (In press.)

CC/LS 1A-14