EDITORIAL

At the Level of Ten Angstroms

THE ELECTRON MICROSCOPE is being used more and more as a research tool. Its greatest contribution in the past ten years has been to demonstrate most of the known viruses. With the perfection of the ultrathin sectioning method, it is now possible to examine cells and tissues in greatest detail and to cut a leukocyte into 800 sections! This new technic has inaugurated an infinite number of new types of research. Most important, it has brought about a whole new concept of cellular structure both from the histologic and pathologic standpoints.

It has been found, for example, that "protoplasmic jelly," which appeared quite homogenous under optical microscopes, is actually composed of extremely complex structures. At a resolving power of 10 angströms (which closely approaches the limit of the resolving power of electron microscopes), other structures can be found. Almost all of the organic molecules now become visible; an even greater resolving power than this would be advantageous, not so much from the biologic standpoint, as from the chemical. In brief, electron microscopy has established a link between morphology and biochemistry which until now has been missing. At the 10-angström level, morphology, biochemistry, and physiology meet on common ground.

It must be admitted that it has not as yet been possible to identify all the molecules which should be seen at this level of resolution, although it cannot be doubted that continued improvements in technic will undoubtedly contribute to eventual identification. It now appears certain, for example, that in the course of time the present technic consisting of simple impregnation with osmic acid will be improved. This will make certain molecules readily identifiable. As yet, this is possible in only a few special instances. These cases nevertheless constitute a significant contribution to hematology, and several are discussed below.

The appearance of most blood cells is already well known. We now know the "submicroscopic" aspects of the nucleus, the nucleoli, the leukocytic granules, and the protoplasm.[1] This exploration has helped to explain the function of many cells. As an example, one may cite the presence of an endoplasmic reticulum (ergastoplasm) which is well developed in plasma cells[2] and which characterizes secretory cells.

The extraordinary complexity of the centrosomic zone in white cells also may be mentioned. Here, the electron microscope shows countless tubules belonging to the Golgi body and one or two centrioles, whereas none of these are visible under an optical microscope. The centrioles are themselves made up of nine tubules, lined up beside a cylinder.[3] Because of their extreme delicacy, the walls in these small bags or tubes cannot be made up of more than a very small number of molecules. The details of these structures are too complex to describe here, and their three-dimensional representation has not yet been achieved. However, visual substantiation of their existence under the electron microscope raises new questions and provides some tangible clues for their solution.

This type of purely morphologic exploration (which, although only just begun, is progressing rapidly) is necessary before a study of physiology or physiopathology can be undertaken. The time when description of the ultrastructure of the blood cells will be completed may be close at hand, and depends only on an increase in the number of laboratories equipped with the electron microscope.

Another phenomenon made visible by the electron microscope, and of particular interest to the physiologist, is that of the iron cycle in the organism. In bone marrow sections, one can easily follow first the phagocytosis of red cells by reticulum cells and then their digestion. During digestion, small granules—about 50 angströms in diameter—are seen which strongly diffract the electrons and thus appear opaque. While the digestion is in progress, these granules increase in number and scatter in the cytoplasm of the reticulum cell. In some other areas of the preparation one can see more reticulum cells, full of these ferruginous granules, and which become surrounded by young erythroblasts. Through a mechanism similar to pinocytosis, the ferruginous granules go from the reticulum cell into the young erythroblasts.[4] From these cells they enter into the mitochondrias.[5] The high resolving power of the electron microscope has allowed us to characterize these ferruginous granules as molecules of ferritin.

A few years ago Farrant,[6] having prepared by chemical process some horse ferritin, saw that under the electron microscope the molecules present a characteristic appearance: four black granules of about 15 angströms in diameter displayed in the four corners of a square the same granulations described above, examined under a magnification of 500,000 times.[7] It is thus evident that one of the mechanisms by which erythroblasts incorporate iron is the absorption of the ferritin molecules. But there is still another phase of the process. Once in the mitochondrias, the ferritin molecules may be seen to disperse and change into much finer ferruginous granules. At this point, the mitochondrias burst, and the granules scatter in the protoplasm where they take part in the synthesis of hemoglobin.

Two conclusions may be drawn from these pictures. Of particular interest to the biochemist, who will find here a new field of exploration, is the part played by mitochondrias in the biosynthesis of hemoglobin. Of special significance for the pathologist is the importance of ferritin as precursor of iron. In certain illnesses, such as Cooley's anemia, hypochromic red cells are present which nevertheless appear full of ferruginous granules. Iron enters the red cell but is unable to participate in the synthesis of hemoglobin.[4] This finds a quantitative expression in the level of nonhemoglobin iron in the red cells of these patients, which is much increased.[8,9]

Thus, thanks to a fortunate natural peculiarity of iron (which is opaque to electrons), it has been possible to perform cytochemical studies at the molecular level, since ferritin contains much iron. It is hoped that this will not prove to be a unique instance. The ferritin molecule measures 50 angströms, and most molecules contained in the plasma have similar dimensions, some of them being even larger. Without verging on the field of science fiction, one can envisage a day when it will be possible to dif-

ferentiate between most molecules in plasma. At that time, one will be able to repeat for these substances the experiments of Leeuwenhoek and his successors when they discovered for the first time the different species of blood cells. Surely, the day is fast approaching when morphologist, chemist, and physicist will meet on common ground. At the level of 10 angströms, chemistry can be morphology, and morphology physics! Thus complexities become simplified, and the simple becomes ever more complex.

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