

with the end result that only a very small amount of glue remains on the tip of the cantilever (see Fig. 3). One advantage of pressing the cantilever against the surface is that one can easily check to see if the cantilever is good or broken. Replace the cantilever if it is broken.

- (6) Lift the probe and move it to locate spheres on the same glass slide, position the tip of the cantilever on the top of a sphere (see Fig. 4), lower vertically and allow the cantilever's tip to touch a sphere and then quickly lift up. If positioned well, the sphere is attached to the foreside of the pyramid-shaped tip (see Fig. 1 and Fig. 5). Note that when a sphere fails to be glued to the cantilever, one should leave this sphere and try another one, since the just-touched sphere may roll along the glass slide and very probably get coated with glue if it is touched repeatedly with the cantilever.
- (7) Release the probe from the clip and keep it in a clean place for the glue to cure before beginning force measurements.
- Our experience established that this technique is much more efficient than the routine "two wires" method we can produce five colloidal probes tips in about 20 minutes.

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Nissl: The Man, The Stain and The Substance

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Nissl staining of nervous tissue is widely practised to show the distributions of layers and groups (nuclei) of neurons. Commonly, the staining is carried out to provide an anatomical framework for immunohistochemical and electrophysiological studies. Since the early days of histochemistry and electron microscopy, it has been known that the basophilic granules or stripes in the cytoplasm of a neuronal cell body are composed of granular endoplasmic reticulum, with the staining properties being attributable to ribosomal RNA. How did these stainable organelles come to be called the Nissl substance?

Franz Nissl (1860-1919) was a German neuropsychiatrist, a physician who took on the whole gamut of diseases affecting

the nervous system and also carried out histopathological studies of his deceased patients. He developed his staining technique in 1884, while he was a medical student in Munich. He wrote an essay on the pathology of the cells of the cerebral cortex, entered it in a competition, and won the prize. The formal publication of the staining method and description of the revealed intracellular details appeared ten years later as a series of papers in Volume 13 of the journal *Neurologisches Centralblatt*.

After obtaining his doctorate in 1885, Nissl became an assistant to Johan Bernhard Aloys von Gudden (1824-1886), a prominent neuropsychiatrist now remembered especially for his contributions to neuroanatomy. In 1886, von Gudden was probably murdered by an ungrateful patient, King Ludwig II of Bavaria. von Gudden and two other distinguished neuropsychiatrists had recently examined Ludwig, who had brought his country close to bankruptcy by building fairytale castles and palaces. They made a diagnosis that we would now call paranoid schizophrenia. The king was relieved of all official responsibilities and taken by von Gudden to Schloss Berg. On the evening of June 12th 1886, the two men went for an evening walk by the nearby Lake Starnberg. Their bodies were found at the water's edge later that night. It is widely believed that the mad king killed his physician and then committed suicide by drowning, but it is also possible that both men were murdered as part of a conspiracy (Kleinert, 2001).

In the decade following, now in Frankfurt, Nissl worked alongside Ludwig Edinger (1855-1919), Carl Weigert (1845-1904) and Alois Alzheimer (1864-1915), whose names have long been household words in the world of neuroscience. In 1895 Nissl moved to the University of Heidelberg, invited by the great psychiatrist Emil Kraepelin, whom he succeeded as professor in 1901. In 1918 Kraepelin moved back to Munich and collaborated for a year with Korbinian Brodmann (1868-1918), whose numbering system for cortical areas, based on the structure revealed in Nissl-stained sections, is in widespread use to this day.

Nissl called the basophilic objects in neurons granules; the terms Nissl granules, Nissl bodies, Nissl substance and tigroid bodies are all synonymous. They stain with cationic dyes - Nissl used methylene blue - on account of their high content of RNA. The first high quality electron micrographs of neurons (Dawson et al. 1955; Palay & Palade, 1955) revealed that the Nissl substance was rough endoplasmic reticulum: parallel membranes associated with granules that were later called ribosomes. George Emil Palade (born 1912) shared the Nobel Prize in Physiology or Medicine in 1974 for describing the structures and functions of organelles in cells. The other recipients were Albert Claude (1898-1983) for isolation and biochemical study of organelles, and Christian Rene de Duve (born 1917) for the discovery of lysosomes.

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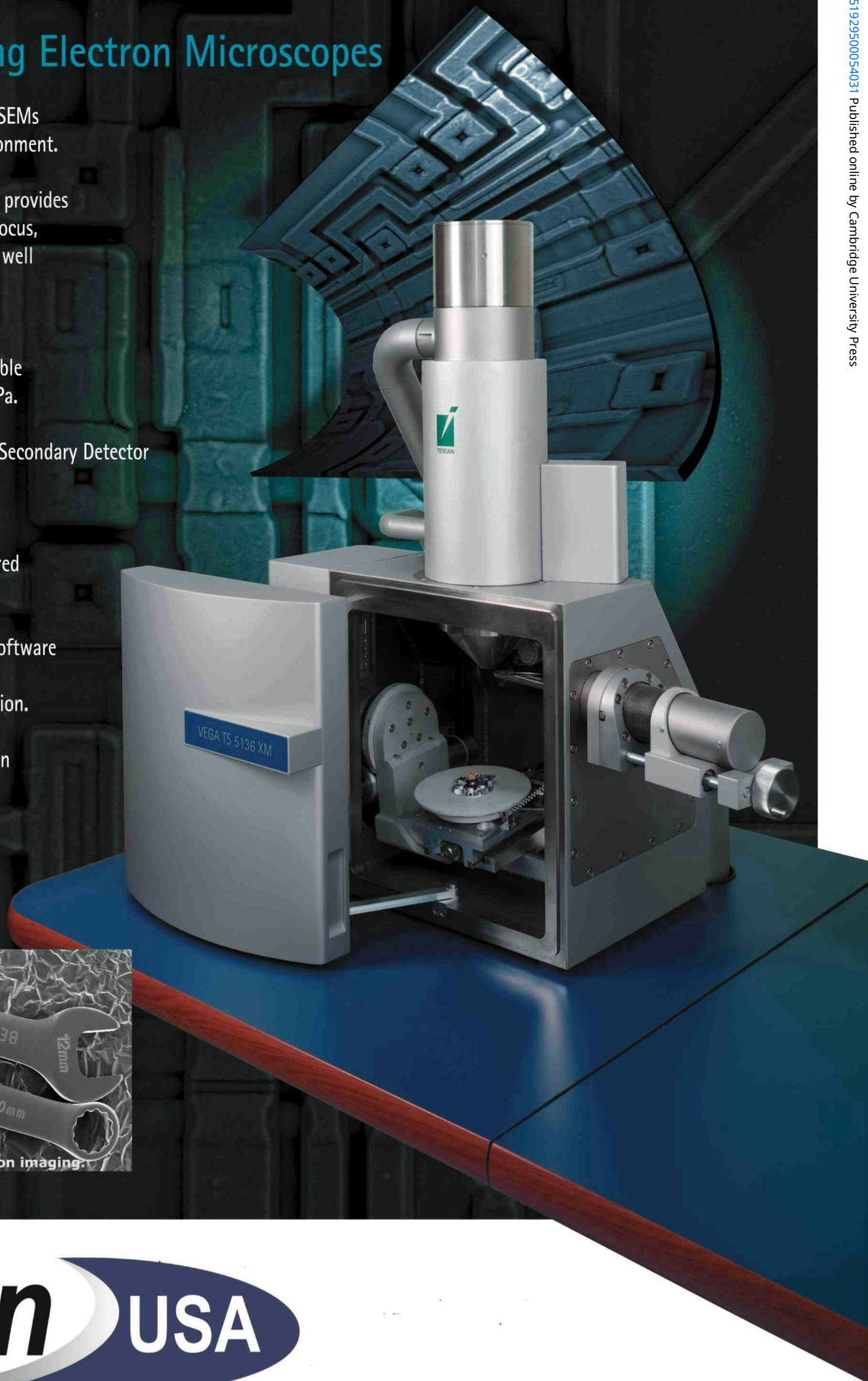
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