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Memories and after-effects of a year (1958-59) as student and resident at Istituto di Fisiologia in Pisa

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ABSTRACT

In the1950s, the Institute of Anatomy in Oslo and of Physiology in Pisa were in close contact and exchanged visitors. I was a medical student at the time, and on Professor Alf Brodal's recommendation Professor Giuseppe Moruzzi welcomed me to Pisa to do research and even offered me a room in the Institute to live in. The year was 1958-1959, which for me it turned out very rewarding and decisive for my later choice of career. In this paper I describe some of my memories from that time and, briefly, some of my pursuits in science after that time.

Key words

Memories from Pisa 1958-59 • Discovery of long-term potentiation (LTP)• Neural control of skeletal muscles

From Oslo to Pisa

More than half way through my medical studies in 1958 I felt I needed a break, go abroad for a year, and do research if possible. I contacted professor Alf Brodal in Oslo, who suggested the Institute of Physiology, directed by professor Guiseppe Moruzzi. Brodal and Moruzzi were in close contact in those days. They were both studying the reticular formation of the brain stem, Brodal using neuroanatomical techniques, Moruzzi using electrophysiological ones to study mechanisms of sleep and wakefullness in particular. Brodal's approach was to cut axons by making small lesions in the spinal cord (and elsewhere in the CNS) and then determine their cells of origin by identifying swollen cell bodies undergoing retrograde chromatolysis (tigrolysis) in sections of the brain stem. Using young kittens (his modified Van Guddens technique) such cells would stand out clearly from intact neurons in the region and thus allow him to trace in some detail their axonal projections. Ottavio Pompeiano and Gian Franco Rossi had both come up from Pisa to work with Brodal around that time.

I had a reason for contacting Brodal. In 1955, in one of his early lectures as our professor of neuroanatomy, Brodal invited students to form a study group of six which would come to his office once a week for discussions about research. I joined that group and found it very much to my taste. We did not do any research ourselves but were introduced to relevant literature and offered his own experimental material to look at. We then discussed the work, including their functional implications. I ended up presented our group's experiences to the rest of the class and that appeared to be the end of it. As it turned out, however, it probably had a decisive influence on my later choice of what to do in life. It caused me to turn to Brodal two years later, which in turn led me to Pisa and a whole year of doing real research. It was also, I think, a fine and relatively rare example for its time of a professor making an effort to introduce and recruit young students to research.

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Brodal wrote to Moruzzi who welcomed me to Pisa. With a fellowship from the Italian State I left Oslo by train one Wednesday evening in August 1958 and arrived in Pisa on Friday afternoon nearly two days later. At the station in Pisa I was met by Arnaldo Arduini. He took me to a nice hotel along the river Arno, where the institute had booked a room for me. He asked me to come to the institute on Monday morning, which suited me fine. The hotel room turned out to be on the top floor, where I quickly stepped into the bathtub to take a shower, looking more like a chimney sweeper after two days on the train and many hours of leaning out of the train window to take in the Italian scene. Then with thick foams of blackened soap all over my body, the water suddenly disappeared and did not come back that day. A trivial event that nevertheless impressed me so that I still can see that room in my mind, its layout, the bath tub and myself scraping off the foam before I went out to have my first Italian meal in a nearby Trattoria with wine and all good things, feeling great but also wondering what the next year would bring.

On Monday, I was shown a little corner room on the 2nd floor, which was to be my home for the next year. To reach it I had to pass through a student laboratory where I later would assist Amilcare Mollica in demonstrating the vagus effect on the heart of anaesthetized rabbits for the medical students. Moruzzi was in Moscow at an international conference on brain research and when he returned to Pisa, he arranged for me to work with Mollica, who had a large laboratory with high windows facing Via S. Zeno and a large Faraday cage in the middle. In a similar, neighbouring room worked among others, Ron Melzack, who with Patrick Wall, would later publish the classic gate control theory of pain. At the time, the Institute in Pisa was an international centre for brain research, attracting researchers from across the world, and over it all presided Moruzzi, *Il Professore*, in somewhat splendid isolation it seemed to me.

I was well accepted at the institute. Although it was customary at the time for some visitors to be living in the institute, I thought it very generous to be offered a room there at no cost to me. Surely, the Pisa-Oslo connection helped in setting up this arrangement, particularly since I was only a medical student with no experience of doing research. I still remember Mollica's surprise when I told him that.

Research in Pisa

Moruzzi wanted Mollica to study sleep mechanisms. I remember Moruzzi telling us about a presentation at the meeting in Moscow claiming that it was possible to induce sleep in humans by letting them rest in a bed that was rocked back and forth at a certain frequency. On his suggestion, we therefore had a cage made that swung to and fro at a similar frequency while suspended from the ceiling of the Faraday cage. Inside we placed a rabbit with screws in the skull for EEG recordings. The problem was that we could never make these rabbits sleep. The EEG was more or less continuously desynchronized and if hopeful signs of synchronization should appear, sudden loud noises from Via S. Zeno would put an end to it, as when the local rag-and-bone man made his rounds shouting out his goods.

We gave up the project, which Mollica from the beginning did not believe in anyway, and went on to a more conventional approach to sleep research based on the *encephale isolé* preparation. Mollica was not interested in this approach either and was happy to leave the surgery to me, first on rabbits and, when that turned out difficult, on cats, the more common preparation. I don't remember the purpose of the effort and before long this project also was abandoned. Occasionally, Moruzzi would come down from above to ask how we were doing. As progress was zero, he eventually gave up making suggestions and left Mollica to his own devices.

We then turned to what I suspect Mollica had wanted to do all along, namely recording from single units in the cortex of awake rabbits, using electrolytically sharpened, insulated tungsten electrodes, the technique for which David Hubel had recently published in Science (Hubel, 1957). I don't remember Moruzzi taking any interest in this project but when we told him about it, he suggested that I went to Rome at the Institute's expense to see G. M. Ricci who had recently returned from Herbert Jasper's lab in Montreal and was setting up his own lab to do similar single unit recordings. I was well received by Ricci, saw Rome for the first time, and enjoyed a very interesting couple of days there.

But well before this, when Mollica and I were at our most frustrated, Ron Melzack, perhaps concerned that I was having a difficult time, suggested that I could join his group, to which also C.J. Smith, and

F. Magni belonged with Moruzzi every now and then coming down from his office on the 3rd floor to participate in the experiments. However, Mollica and I got along very well together and I was happy to work with him. It is true, that at times of frustration, we would distract ourselves by shooting down flies from the high ceiling by squirting ether on them from syringes. With every hit, the fly would drop to the floor and then quickly recover from the anesthesia, which allowed the game to continue. It is also true that Mollica was very upset after visits by Moruzzi, not because Moruzzi, as far as I could see or now remember, was unkind or unreasonable, but rather because hierarchic traditions and Mollica's character were such that when facing Moruzzi and even strongly disagreeing with Moruzzi's proposals, he was unable to express his own. Perhaps Mollica took as orders what Moruzzi meant as suggestions and generally answered Moruzzi with "Sì Professore" in his presence, while resorting to fits of temper as soon as Moruzzi had left the room.

By New Year 1959 Mollica and I were on our own. We designed a microdrive and asked a machine shop in Piacenza to make it. The shop, which specialized in high precision tools, belonged to the father of an engineering student in Pisa who had become a close friend of mine. We attached the drive to the skulls of rabbits under anesthesia and later recorded from single units in the visual cortex with the rabbit, now awake, loosely attached with a strap to a wooden cage open at both ends, head and chest sticking out at one end, tail at the other. I made the electrodes according to Hubel's description, realizing soon that this was not always straight forward. Despite efforts to standardize the procedure, particularly the coating of the electrodes with insulating material, the electrodes varied enormously in quality for reasons I never understood. Perhaps variations in ambient temperature and humidity, for which we did not control, adversely affected the insulation of the electrodes. Nevertheless, over the ensuing months we were able to record many units with high signal to noise ratios over periods of up to several hours. We exposed rabbits to light, sound, odors, pinpricks and squeezes of the tail, described the firing patterns of responding neurons and the modulating effects of different sensory inputs on the visual responses, as wells as effects of barbiturates and local applications of strychnine to the cortical surface.

Before I returned to Norway in July 1959, Mollica had started writing the paper that described our results. The paper appeared in 1962 in Archives Italiennes De Biologie (Lømo and Mollica, 1962). There, we acknowledge that the research was carried out with funds from the United States Air Force and the Rockefeller Foundation. This was a time when the United States was still very active in rebuilding and supporting Europe after the war with direct donations in the best traditions of American philanthropy.

Mollica wrote the paper in Italian, and T.D.M. Roberts and J.D. Christie translated it into English, an unusual practice today. Roberts visited Pisa when I was there. We went out together with my Italian friend who spoke no English. Roberts was walking with notebook and pencil in hand asking for the Italian words of just about everything that caught his eye. I was impressed and had I done likewise, my Italian would have been much less mediocre than it is. I cannot remember that I took any direct part in writing the paper. Perhaps it wasn't even considered that I might be of use, being a student with no previous research experience and without English as my native language. As it was, it suited me fine. Back in Norway I was busy taking up my medical studies again and would have found it very difficult to enter into the mind set and vocabulary needed to describe and discuss the complex issues addressed by the work.

I don't know that our paper has ever been referred to. It is not listed under PubMed. Those were early days for recording from single cortical neurons in awake animals and yet the paper became one of many to disappear without leaving a trace, except, I suppose, in CVs for job applications. And yet, for me the year in Pisa was not only very enjoyable, satisfying, and educational but also decisive for my later choice in life.

I was probably the last person to collaborate with Mollica and our paper together was probably his last. Later, I heard that Mollica had had a serious mental breakdown and that he never returned to science. I found this very sad. Our relation and collaboration had been very good. Mollica was interested in many things, which we frequently discussed. He had top grades from medical school. I found him very clever, even brilliant, in many ways. But, as far as I could tell, he had little or no social life outside work.

He lived alone with his mother. After work he would take his bicycle and apparently go straight home. Outside work, we never met and I never saw him with others. When difficulties arose and he stopped working, Moruzzi, I believe, tried to help him. It is one of my many regrets in life that after I returned to Norway and the correspondence relating to the paper came to an end, I failed to keep in touch with him.

Life in the Institute

I liked living in the institute and having my own private room there. Seeing it again last summer for the first time in more than 50 years filled with outdated instruments and computer ware, I was amazed at how small it was, room for a bed, a wash basin, and a writing desk in front of the window and little more. I don't remember having any problems with that or with the walks down to the common restroom and shower on the first floor.

Coming from the north to the sunny Mediterranean of my imagination I had not expected some of the winter days to be so cold but with an electric stove installed, my room was fine. In the mornings I went straight to lab without breakfast of any kind, which was contrary to everything that had been drilled into me for as long as I could remember, namely the absolute necessity of a regular, substantial, and healthy breakfast. But again, no adverse effects came to pass. Only a healthy appetite building up before lunch at a little eating place for regulars simple, cheap, but always well tasting meals. Where I grew up on the west cost of Norway the nearest place to buy anything alcholic was "Vinmonopolet", the Norwegian State's monopoly shop in Bergen nearly a day and night away by coastal steamer. I immediately took advantage of this state of affairs and started having wine for lunch. But this had to stop if I were to get anything done in the lab in the afternoon.

In my experience there was little social interaction between the people working in the institute, no common room where one could go for a cup of coffee or tea, or to talk about science, ongoing work, or whatever, no seminars that I can remember. Had I known better, I think I would have missed it. But I may also have missed much of what was going on in the institute since I was away most of the time outside working hours. By some happy coincidence I had met an Italian engineering student as I stepped out of the train that brought me to Pisa. He became an almost daily companion during my year in Pisa and a life-long friend. He introduced me to many of his friends and made my days in Pisa far from lonely.

Leopoldo Nicotra, the recently arrived electronic engineer, was exceptional. Soon after I arrived in Pisa, he invited me to go with him to Siena where he would help Alberto Zanchetti with some equipment in Zanchetti's new laboratory there. I enjoyed the drive in Leopoldo's Topolino and the friendly reception in Siena and I remember well entering the centuries old hospital in the centre of Siena through an old narrow door to find Zanchetti's small but completely refurbished modern laboratory next to a large medieval hall decorated with large murals and with many patients in their beds. On other occasions, Leopoldo would take me and others to trattorias in the neighbourhoods of Pisa. When my parents visited in the spring, Leopoldo and his wife Kirsti invited them and people from the institute to excellent food and drinks in their home. In later years I visited Pisa several times to collaborate with Alberto Cangiano. On such occasions I would stay with Leopoldo or Alberto. In particular, I remember one summer when my wife and I and our three sons spent a week on a farm in the hills outside Pisa which Leopoldo and Kirsti had newly bought. There, Leopoldo had already installed a beautiful modern toilet with nicely decorated tiles. But the roof was still missing so at night we would watch the stars from there and contemplate the world outside.

One event in the institute made a particular impression on me. One day I heard loud noises from the lab next door, went in and saw a cat on the loose knocking down bottles and making a great confusion. I tried to grab it but it turned around in its loose skin, bit and scratched my hand. This caused some concern and I was sent to the hospital with a prescription for immunization against rabies. There, the doctors filled a large syringe with an opaque, whitish fluid that they injected under the skin of my belly. I did not like the sight of the fluid and when they told me to come back for an astonishing number of additional injections, I started thinking about risks, about the likelihoods of rabies in that cat and of immune reactions in my brain in particular. No more injections for me, I quickly concluded, and went back to observe the cat which in the meantime had been caught and brought back to the "stabulario" in the garden. It clearly did not like the sight of me and acted accordingly, but as it continued to do so without any signs of disease, I dropped the matter without at any time having felt really worried. This may have been the first time that I became conscious of an enduring scepticism of doctors for their readiness to overtreat and, in the process, underappreciate risks, sideffects, and complexities. Some times it is better not to treat and give the body time to heal itself.

Mollica and I liked our rabbits, nice docile animals well suited for our single unit studies in awake animals. But then they got myxomatosis, a nasty disease with multiple, large discharging tumours in and around their faces that forced us to make a big pyre in the garden for all our rabbits and after disinfecting the animal house, start all over again.

Memories from Pisa

I had a good year in Pisa. I was on my own, felt free, and was never homesick. I greatly appreciated the room I had at the institute. I loved the trees in the garden, although they probably also contributed to the variety of bugs that ended up in my bed and caused intense itching during the summer season. My stipend and supplements from my father allowed me to buy a wonderful new Vespa, travel, eat, and drink well, see Toscana, walk in the nearby mountains, or go out to the sea.

Every midday I would walk across Piazza dei Cavalieri and Piazza dei Miracoli to a little bar just outside the old city wall, where, in a little room behind the darkness of the bar, the wife of the bar owner served a delicious, simple, low cost lunch for a few regular customers, including myself and one or two friends among the students. This became such a routine that at one point I told my surprised friend that I needed a break and to be more on my own. Before long, however, I fell back into the routine. After Norway, where I was used to partying, drinking, dancing, and the rest from the time of my confirmation, Pisa at the time appeared very provincial. Everybody, it seemed would dress up and walk up and down the streets before disappearing behind gates and shutters for dinner, leaving a good number of male students to wander aimlessly around in the evenings. From what I understood, the church controlled the choice of films shown by most of the cinemas so that was not much fun either. Often I would drive my Vespa down to the railway station to get the latest International Herald Tribune, a favorite newspaper of mine till this day, and then stop at a bar along the way and, with a cup of coffee, enjoy the latest news and comments from around the world.

Return to Norway

I returned to Norway in July 1959. Soon afterwards, I was invited to present the work from Pisa at a meeting of the Neurological Society in Oslo. There I met Per Andersen for the first time. He was enthusiastic about the work but it would take nearly 5 years before we would meet again.

I graduated from the University of Bergen in December 1961 and worked as a doctor, first in northern Norway, then in the Norwegian Navy as part of my military service. In 1964 I went to Oslo to look for a job and accidentally met Per Andersen on the street. Per had just returned from Canberra, Australia, where he had spent two very productive postdoctoral years with John Eccles. Per was setting up his own lab in Oslo and invited me to join him. I had no intention then of returning to neurophysiology but Per's invitation and enthusiasm for research convinced me otherwise. So in August 1964 I began working closely with Per for over a year mainly on synaptic mechanisms in hippocampus, learning the tricks of the trade as we did the experiments together.

Discovery of Long Term Potentiation (LTP)

Then, in late 1965 or early 1966 I started my own research project for the PhD, in Per's lab but on my own since work for the PhD in those days was supposed to be independent. In agreement with Per, my initial focus was on so-called frequency potentiation in the perforant path from the entorhinal cortex to the dentate granule cells, already described by Per as a dramatic increase in dentate granule cell firing during repetitive stimulation (tetanization) of the perforant path. But soon I also started to look for effects after the tetanization and noticed a dramatic increase in efficiency of transmission at the perforant path-dentate granule cell synapses that lasted for hours after the last brief tetanus, published in abstract form in 1966 (Lømo, 1966).

My thesis, however, which I finished in 1969, did not deal with frequency potentiation or its after effects, now known as LTP. These were complex phenomena and to tackle them I felt I needed to know more about the basic organization of the dentate gyrus, its inputs and outputs, and the generation and spread of excitation and inhibition following single electrical stimuli to the perforant path. Consequently, the focus of my thesis shiftet to these simpler aspects as the work progressed.

At the time I was well aware that the long-lasting increase in synaptic efficiency might be important as a mechanism for learning and memory but neither Per nor I anticipated the enormous interest in LTP seen today and felt no urgency to further explore the phenomenon there and then.

Tim Bliss, on the other hand, started his research career with a particular interest in neural mechanisms for learning and memory. Working in London at the time, he used a neocortical preparation that offered little progress because of its complexity. He then happened to read a paper by Per Andersen on the hippocampus and, after meeting him in London, made arrangements to come to Oslo for a year to work with Per and learn about the hippocampus, which seemed a much simpler and more promising part of the cortex in which to pursue his interest. Arrangements were also made for Tim and me to do experiments together to follow up my earlier preliminary results on LTP.

Our very first experiment in August 1968 was immensely exciting. For each stimulus train in the experimental pathway, the granule cell population spike increased dramatically and remained potentiated, while the control pathway was unaffected. Conversely, when the control pathway was similarly tetanized many hours later, substantial potentiation occurred also there. This experiment and many subsequent ones led to our paper in The Journal of Physiology (Bliss and Lømo, 1973). The paper was reprinted in Journal of NIH Research in 1995 as a landmark paper and commented on by Roger Nicoll as follows. "So, the question is, Why did this paper start this dramatic field? First of all, it describes all of the basic phenomena of the process of long-term potentiation. These include pathway specificity, saturation, and an increase in the coupling of the synaptic potential to the discharge of the granule cells. Second, there's not a single controversial result in that paper – a very remarkable thing in this field".

Bliss and Lømo (1973) appeared 4 years after completion of the experiments. There was less pressure on publishing quickly in those days. With a few exceptions the early papers on LTP (Bliss and Lømo, 1973; Bliss and Gardner-Medwin, 1973) made little impression on the neuroscience field. As late as 1981, LTP was not mentioned in the textbook *Principles of Neuros*cience by Kandel and Schwartz nor in Alf Brodal's influential book Neurological Anatomy in Relation to clinical Neurology. Interest in LTP began in earnest in the first half of the 1980-ties when G.L.Collinridge, P. Ascher, G. Lynch, and others discovered that LTP in the CA1 region of the hippocampus requires both activation of postsynaptic NMDA receptors by glutamate and sufficient postsynaptic depolarization to remove the Mg^{2+} block of NMDA receptors, and that postsynaptic injection of calcium chelators blocks the induction of LTP (for a review see Bliss and Collingridge, 1993).

The discovery that impulse activity controls expression of non-junctional muscle properties

I defended my thesis in October 1969 and soon afterwards went to the Department of Biophysics, University College London for postdoctoral work. There, I teamed up with Jean Rosenthal, a postdoc from Yale University, in a little lab and, on Ricardo Miledi's suggestion, started exploring whether motor neurons control the properties of skeletal muscle fibers through some unidentified, activity-independent trophic factor, which was the prevailing idea at the time.

After much trial and error, the experiments that Jean and I did in London turned out highly successful. It was well known at the time that normal muscle fibres are sensitive to the neurotransmitter acetylcholine (ACh) only immediately underneath the nerve terminal, and that cutting the nerve (denervation) caused acetylcholine receptors (AChRs) to appear along the entire muscle fibre membrane (ACh supersensitivity) together with numerous other changes, including muscle fibre atrophy, fibrillations, and a marked drop in resting membrane potential. It was thought that denervation caused such changes by interrupting the release of putative trophic factors from the motor nerve terminals in the muscle and that these factors acted independently of impulse activity in the nerve. Thus, John Eccles wrote in his book The Physiology of Synapses (1964)): "In summary of the preceding section it can be stated that the evidence for a trophic influence from nerve on to muscle membrane is conclusive…".

Our experiments turned this view upside down. By cutting the sciatic nerve, we prevented all release of possible trophic factors from motor nerve terminals in the muscles of the leg. We then implanted electrodes on the denervated slow soleus and fast ext. dig. long muscles and found that chronic stimulation restored their sensitivity to ACh to normal. Evidently, evoked muscle impulse activity controlled the expression of AChRs in the muscle fibres. Since then, my lab in Oslo has shown that nerve-evoked muscle impulse activity plays a major role in controlling a host of muscle properties, in fact all the properties that we have looked at. We have recorded the natural firing patterns of single fast and slow motoneurons over 24 hours in rats moving freely in their cages and shown that similar fast and slow stimulus patterns applied through chronically implanted electrodes on denervated slow and fast muscles have the same effects as cross-reinnervation on their contractile speeds. Today, convincing evidence for motoneuronal control of non-junctional muscle properties by trophic substances does not appear to exist and what evidence there was back then, can now be given other explanations. Obtaining such clear evidence against a dogma of the time was as exciting as seeing for the first time the enduring increase in synaptic efficiency after brief episodes of repetitive impulse activity.

Jean Rosenthal and I published our results in Journal of Physiology in 1972 (Lømo and Rosenthal, 1972). In contrast to the results on LTP, their significance was immediately recognized because the issues involved were already of general interest and well known. The trophic hypothesis was an important topic and many neurophysiologists had convinced themselves that it was real. Consequently, numerous papers then appeared that critizised our work and presented further evidence purporting to favour the trophic hypothesis but with no success in the end. Today, all that work seems essentially forgotten. Lømo and Rosenthal (1972) is hardly referred to any longer, although I believe that this work and those made later in Oslo demonstrated perhaps for the first time the essential role of impulse activity and activity patterns in regulating the properties of postsynaptic cells. There were other works demonstrating the effects of electrical stimulation of the nerve on muscle properties. But since the nerve was intact, the problem of separating impulse activity from trophic effects could not be addressed. Moreover, the presence of unknown amounts of endogenous impulse activity made the effects of particular patterns of activity less clear. Today, the importance of impulse activity is taken for granted. How different the recognitions of Lømo & Rosenthal (1972) and Bliss & Lømo (1973), the first immediate but temporary, the last delayed but enduring.

Concluding remarks

After London I was all set to return to LTP but unexpected experimental difficulties along that line (see Terje Lømo, *The History of Neuroscience in Autobiography*, Ed. Larry, R. Squire, Vol. 7, Oxford University Press. 2011) and the success of our work in London made me focus my research on motoneurons, neuromuscular junctions and skeletal muscle properties for the next 30 years.

Today, however, I am back to the hippocampus. After my thesis in 1969 I submitted four papers to Exp. Brain Res. The reviewers suggested some changes, which I made for two of them, published in 1971 (Lømo, 1971a,b). The other two remained in my files until recently when I immersed myself in the literature of the intervening years, wrote a new manuscript based on them, using the same data and figures and saw it published in Hippocampus in 2009 (Lømo, 2009). Today at 76, I am in the lucky position to be able to do experiments as in the good old days, using my own hands, in close collaboration with my younger friend and good colleague, Arild Njå, into whose laboratory my own set up has been incorporated. We are addressing questions relating both to the hippocampus and nerve-muscle intereactions but it is harder today then back then to get up early in the morning and keep at it at the end of the day, so what will become of our efforts remains to be seen.

My year in Pisa more than 50 years ago turned out well for me in many ways. In itself, the year was an inspiring, maturing, and enjoyable experience. Without it, I probably would not have had a career in neuroscience. Nor would I have been able to enjoy such close connections with Italy through collaborations and friendships over many years with Alberto Cangiano, Stefano Schiaffino, Guido Fumagalli, their families, many friends, and coworkers. For all this I consider myself very lucky and grateful.

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