MY MISSED TALK FOR THE PLANNED FESTIVE SCIENTIFIC MEETING SCHEDULED FOR MY 90TH BIRTHDAY

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I was born on May 25, 1930, but the Festive Scientific Meeting scheduled for my 90th birthday was announced for June 3 by the Uzsoki Hospital and the Hungarian Nephrological Society. My wife paid for a Mediterranean round trip as a birthday present, so the Festive Scientific Meeting had to be postponed. Covid 19 left it all behind. (If this Festive Session will ever be reorganized lies in the future)

I compiled my festive presentation in early February 2020, when there was no immediate domestic epidemic threat. Now I am trying to convert it to an article in an edited form. I originally planned a reflection on the “beauties of old age” wrapped in personal success and professionalism, but my acquaintanceship vehemently protested against it, saying who cares about the “beauty” of old age. In addition, the olden “bon mot” of the famous compere, Dezső Kellér came into my mind on the beauties of old age: "tell me just one." What was actually originally motivated me was the lecture by Canadian psychiatrist Professor Lehmann (1): “What is wrong with getting old?” Thus, although I abandoned my original plan, it affected me in that I do not present my entire oeuvre in a linear way (since I had already done so at the Festive Scientific Meeting held in honour of my 80th birthday at Uzsoki Hospital), but after a few highlights I will deal with my scientific work done at my old age namely over the last 5 years (even more 2 years), which were partly published on the website of the American International Network for the History of Neuropsychopharmacology (INHN) (Ban 2) and on the website of the Hungarian Commission for the History of Nephrology.

Some summary statistics for my oeuvre (3) are shown in Table 1.

Number of papers

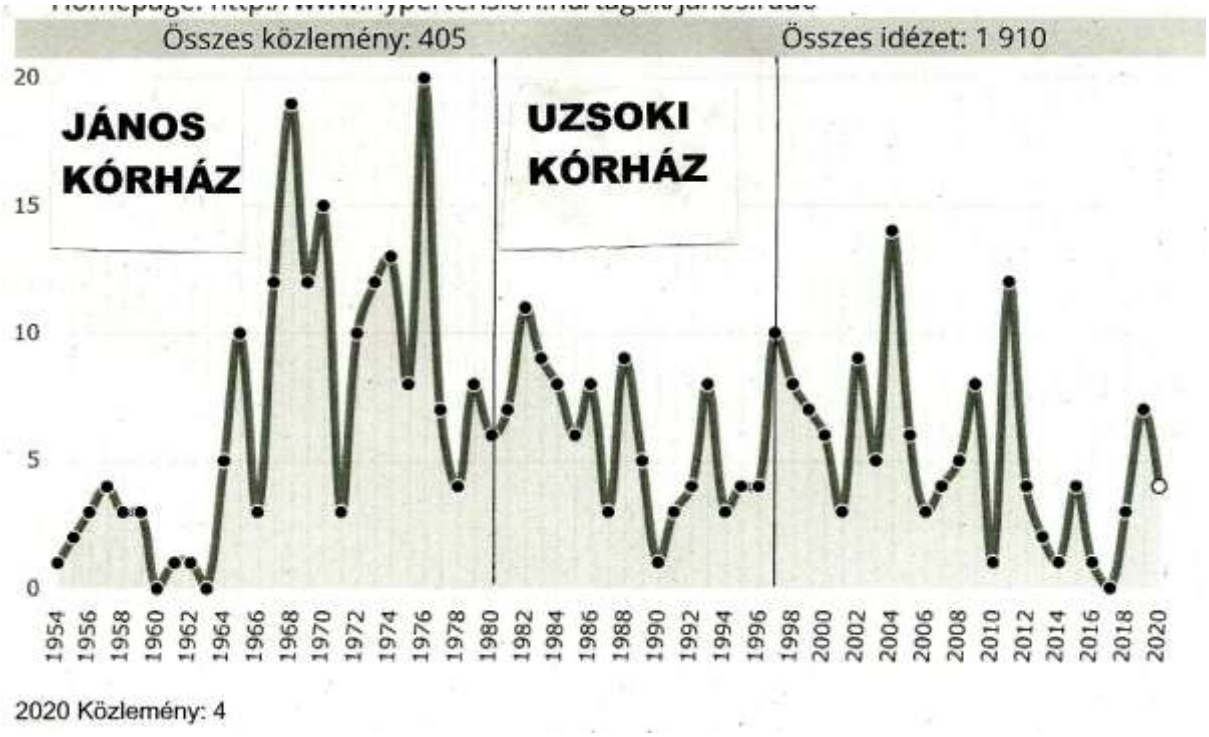
A total of 406 in 66 years,

from this

127 papers, 4.8/year in János Hospital (1954-1980)
99 papers, 6.0/year in Uzsoki Hospital (1980-1996)
180 papers 7.8/year after retirement (1997-2020)

The time distribution of the publications can be seen in Figure 1 on the website of the Hungarian Academy of Sciences.

The figure shows the situation before the date of this publication. Today's situation: 406 instead of 405; all citations 1934 instead of 1910; 8 papers instead of 4 in 2020.



To present my "Oeuvre" (3), I selected 6 items from the 78 significant new results I have published so far; this is included in *Table 2*. Thereof, I would like to discuss only the last two items in more detail (HERPES ZOSTER VIRUS EPIDEMIC STUDY; and DESMOPRESSIN PHARMACOLOGY).

1. DIURETIC RENOGRAPHY

World's first description (Lancet 1967 DECEMBER 30) (4)

2. HYPERKALEMIC PARALYSIS DUE TO SPIRONOLACTON (Arch Neurol (Chicago) 1966) first case (5)

3. WATER INTOXATION CAUSED BY CARBAMAZEPINE (British J Med 1973) first case (6)

4. INCREASE IN DIURESIS DUE TO GLIBENCLAMIDE IN DIABETES INSIPIDUS (Lancet 1971) first description (7)

5. HERPES ZOSTER VIRUS EPIDEMIC STUDY (Arch Int Med (Chicago) 1965 (8) [see U.S. NASA publication] (9)

6. DESMOPRESSIN PHARMACOLOGY (INHN.org 2019) (10) [see U.S. Pat. NAVY publication] (11)

Herpes zoster virus epidemic study

Pediatrician Bókay was the first to find that varicella in children and herpes zoster, which mostly occurs in the elderly, are essentially the same disease (VZ). The VZ virus lurks in the human nervous system (ganglia) after the disease (mostly varicella) has taken place. However, it can reactivate in a variety of conditions when cell-mediated immunity declines, causing mostly herpes zoster, in elderly individuals, cancer patients, in those with autoimmune diseases and AIDS (10). We ourselves noticed in the early 1960s that a "home" epidemic of herpes zoster had developed in our hospital ward, but only patients *treated with steroids* became infected. *It was impossible not to think that zoster and varicella diseases developed in steroid-treated patients as a consequence of the reactivation of the latently present VZ virus.* László Géder, viral researcher trained in the laboratory of Professor Sabin, confirmed the origin of VZ virus in steroid-treated zoster varicella patients by means of virus cultures and serological tests. (10)

The VZ "domestic epidemic" we observed was praised in an editorial in 1967 in the Schweizerische Medizinische Wochenschrift (12), in 1969 in the Quarterly Journal of Medicine (14), in 1972 in the British Medical Journal (13), and in 1985 in the Lancet (15).
The VZ home epidemic has been included in the literature citations of a manuscript from the National Aeronautics and Space Administration (NASA), Lyndon B. Johnson Space Center, Houston, Texas, labelled as "Source of Acquisition NASA Johnson Space Center" handled as NASA internal material).

This manuscript was later published in the *Journal of Medical Virology online* on 11/17/2003. "*Stress-induced subclinical reactivation of varicella zoster virus in astronauts*". (11)
The main author of the manuscript is Pierson DL from the group of NASA Johnson Space Center (JSC). Pierson DL is the director of NASA's Microbiology Laboratory and a professor at Baylor College of Medicine and the University of Texas Medical Branch. The other outstanding author in terms of scientific merit is Donald H. Gilden, a professor in the Department of Neurology and Microbiology at the University of Colorado. In his 4 papers (16-19) he also referred to one of our patients with generalized herpes zoster (varicella) treated with a steroid (not belonging to the epidemic group), who also had zoster meningoencephalitis. (20).

During spaceflight, huge gravitational changes occur abruptly during launch and landing. The NASA team was particularly inspired by their finding that in a 47-year-old astronaut, out of 81

physically fit healthy individuals, chest herpes zoster developed 2 days before the launch. Therefore, eight astronauts were tested for VZ virus in saliva. Thirty % of the saliva samples became VZ virus positive during and after spaceflight. The anti-VZ virus IgG levels were found to increase 2-3-fold after spaceflight.

Subclinical reactivation of the VZ virus was observed in astronauts during space flight stress. Later, the effect of spaceflight on ACTH and cortisol levels was also investigated, and based on the observed increase, it was hypothesized that subclinical reactivation of the VZ virus was due to this. Previous clinical experience has also suggested that steroid activity may lead to VZ virus reactivation, as described by Radó et al. in their publication in the Archives of Internal Medicine in 1965 (8). So perhaps it can be stated that our work could even be considered an intellectual forerunner by this NASA task force.

Desmopressin pharmacology

I have been dealing with the pharmacology of Desmopressin (DDAVP) almost continuously for nearly 50 years. One of our communications (10) caught the attention of researchers at the U.S. Navy (NAVY) Research Institute and they used our data to evaluate the results of their own experiments (11). *In this paper, they described our DDAVP dose-response relationship.*

*The cover page of the American article (11) (***Figure 2***).*

The title of the American article was written in Navy jargon. SDV = seal dive vehicle = submarine carrying commandos on the high seas. AM and PM refers to a day and night dive respectively.

Practical (free) translation of the title of their paper (more precisely, their 45-page monograph): *Weight loss of commandos during day and night SDV dives and the application of DDAVP*.

The problem for the Navy was the weight loss of the commandos due to the loss of water in their naval (submarine) vehicles due to high temperatures. Therefore, they resorted to using DDAVP during their day and night dives, in the hope that it would prevent weight loss. However, their hypothesis did not work because DDAVP did not prevent weight loss. *Analyzing the cause of their failure, they checked our dose-response relationship study and concluded that they did not use a sufficient dose of DDAVP*. They wrote, “It is possible that the DDAVP dose (20 pg) was too low to have a pronounced effect on hydration during water dives. Radó et al. found that 10 and 20 pg intranasal doses of DDAV were nearly equivalent in inhibiting water-loaded diuresis; however, a distinct antidiuretic effect was observed at higher doses (40–320 pg) (11).

NAVAL MEDICAL RESEARCH INSTITUTE

Bethesda, Maryland 20889-5055 NMRI 92-75 September 1992

(2)

WEIGHT LOSS AFTER AM AND PM SDV DIVES AND USE OF DDAVP

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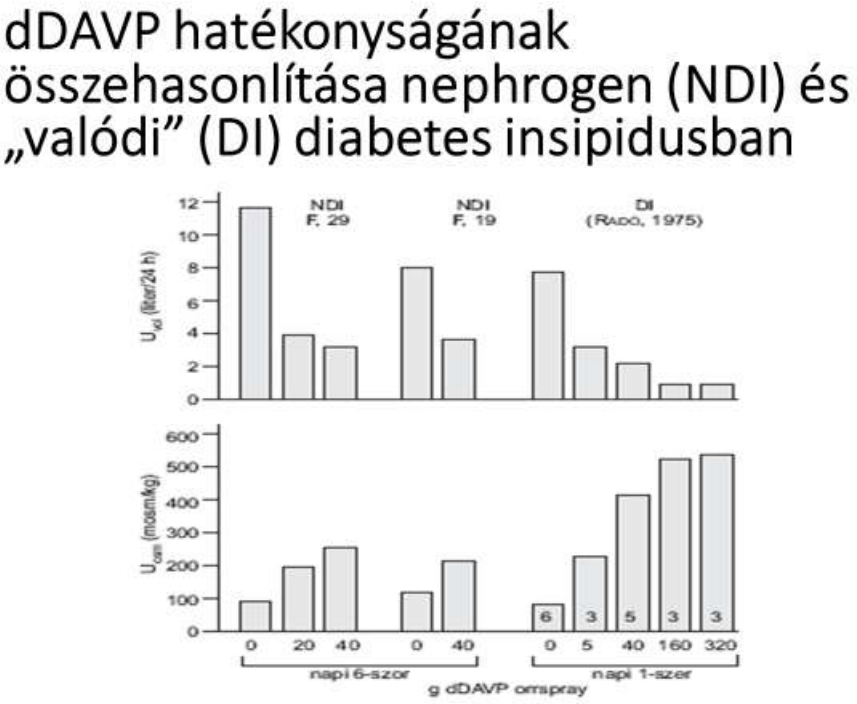
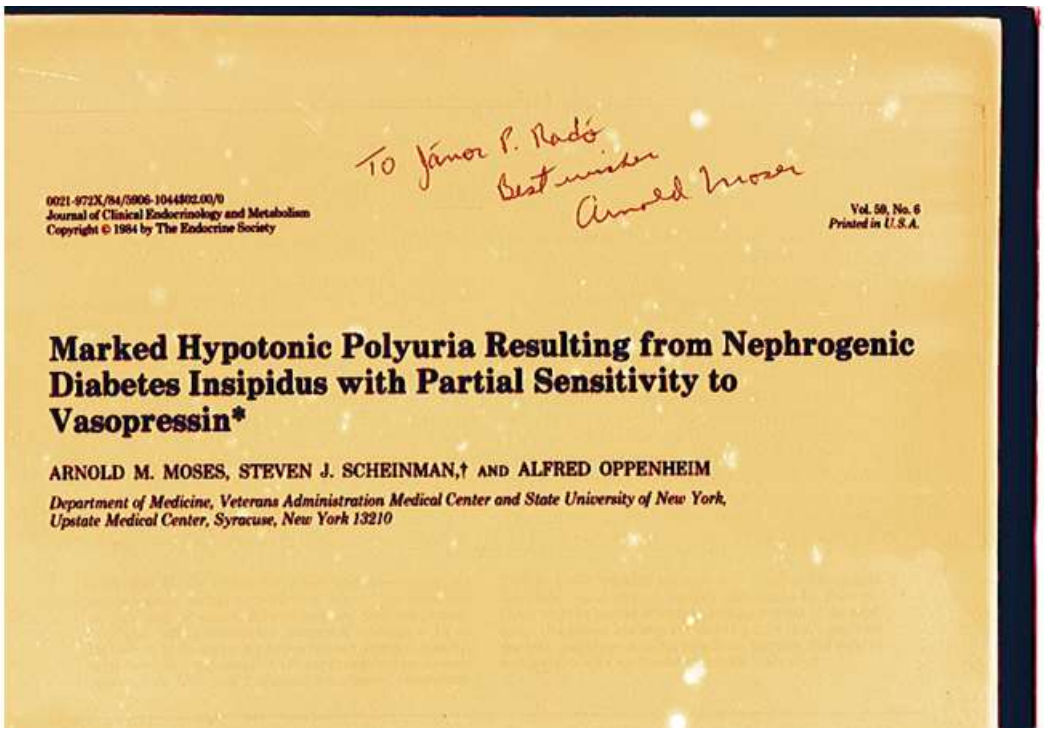
I should mention here that at New York University, Moses et al. made a similar comparison between the data from our dose-response relationship study and the dose-response of DDAVP when applied to their own patients (21).

In their Figure, Figures 3-4 of our dose-response study is labelled as "DI Radó, 1975".





To János P. Radó
Best wishes
Arnold Moses

0021-972X/84/5906-1044$02.00/0
Journal of Clinical Endocrinology and Metabolism

Vol. 59, No. 6
Printed in U.S.A.

Marked Hypotonic Polyuria Resulting from Nephrogenic Diabetes Insipidus with Partial Sensitivity to Vasopressin*

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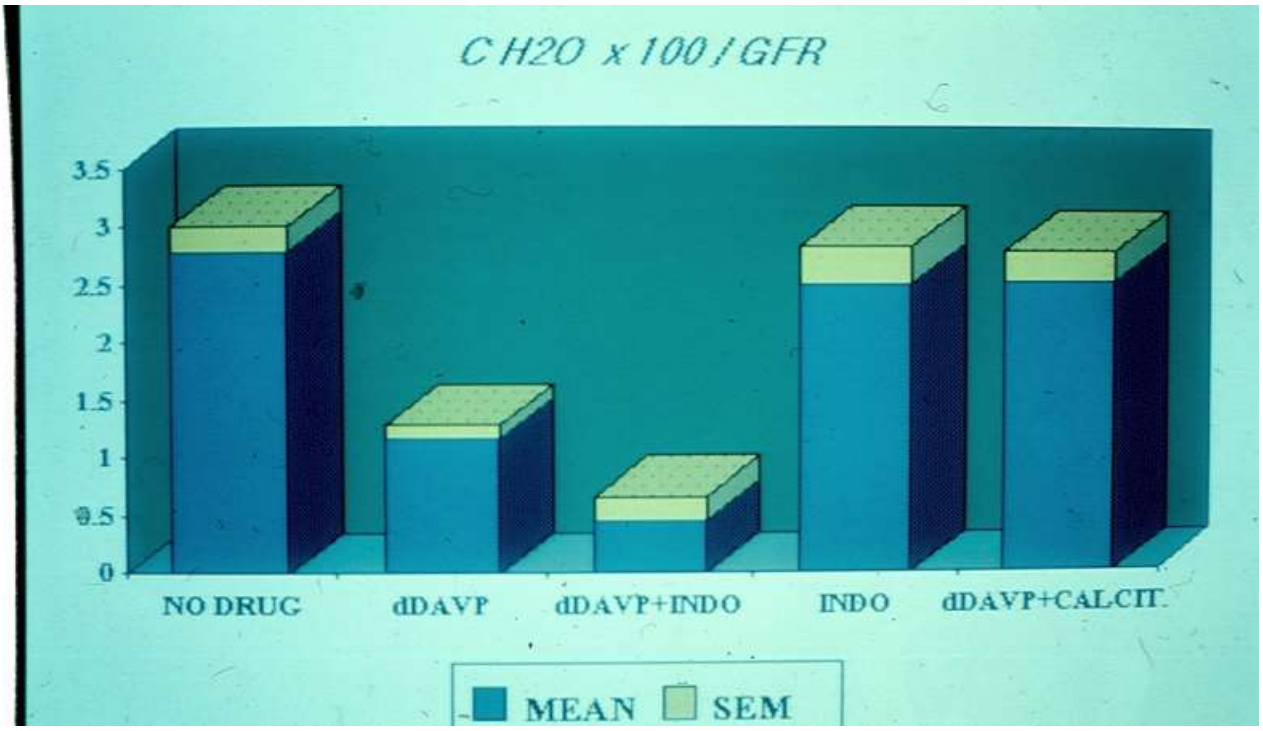
Our DDAVP dose-response relationship studies were conducted in the 1970s. Perhaps it is remarkable that Oiso et al. in 2013, Garrahy and Thompson in 2020 (23), Gasthuys et al. in 2020 (24), and da Silva Jr. et al. in 2020 (25) referred to these papers.

After so much experience with DDAVP, we developed a new treatment method, a combination of indomethacin and an excessive dose of DDAVP, for a patient with permanent lithium-induced nephrogenic diabetes insipidus, who was enrolled in 1989 at the 3rd Department of Nephrology and Hypertension of Uzsoki Hospital. He was also treated with calcitonin due to joint and bone pain (26). **Our results are shown in Figure 5.** We selected free water clearance expressed as a percentage of glomerular filtration as the most sensitive parameter to study the antidiuretic effect. *It can be seen that although DDAVP is effective, indomethacin significantly increases its effect.* Indomethacin alone is hardly effective. Our surprising discovery was that calcitonin suspended the effect of DDAVP, which was presented at the 1993 International Congress of Nephrology in Jerusalem (27).

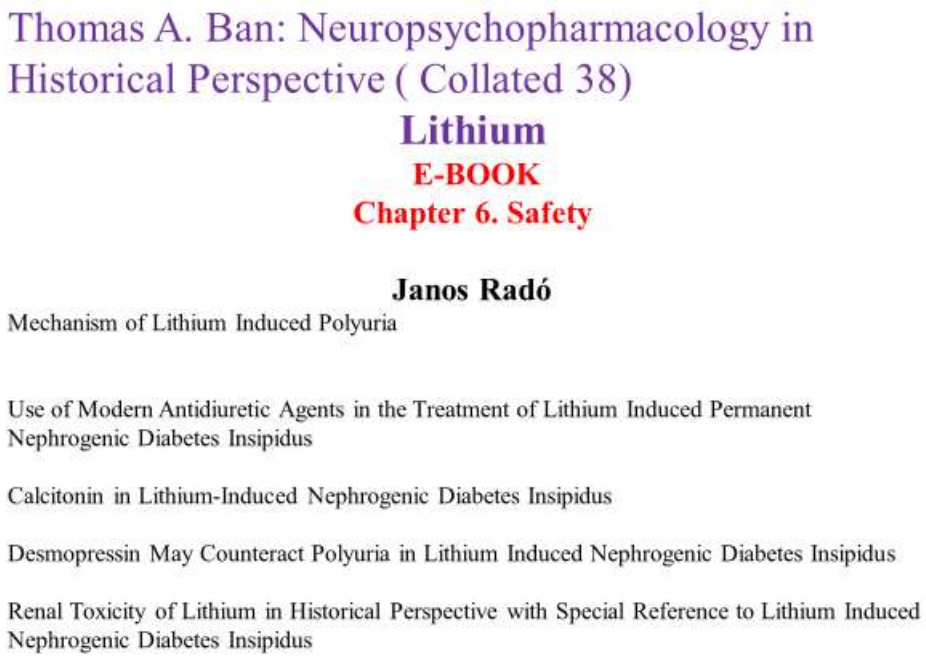


During the period of these studies, between 1989 and 1993, further publication of our detailed data was cancelled. Treatment with lithium was in the descending period when our professional research concept took shape. The elaborate treatment, the need to regularly determine plasma lithium concentrations, the side effects, the frequent urine concentration defect and sometimes the unavoidable end-stage renal disease, as well as the appearance of new molecules replacing lithium have diverted physicians from lithium-treatment. However, when treatment with lithium became popular again in 2017, it seemed worth rethinking the issue and I wrote a paper that INHN published on January 25, 2018 (28). In his post, Barry Blackwell noted that lithium "this simple ion remains the best, safest, and least expensive treatment to prevent recurrent episodes of bipolar disorder" (29). Blackwell also wrote that if Cade (the discoverer of lithium treatment 1912-1980) and Schou (the greatest clinical pharmacologist of the treatment 1918-

2005) could have seen our paper, they "would have been happy". *I could not have received more laudation.*

Thereafter I wrote an additional paper on the possible background of DDAVP and calcitonin antagonism, which was published on 13th September, 2018 on the INHN website (30). The website editors then asked me to write about the renal toxicity of lithium, which was published on 2 May, 2019 (31). In these 3 publications I dealt so much with the effects of DDAVP that it seemed worthwhile to provide a literature review on that *DDAVP can counteract lithium polyuria*. This paper was published on June 27, 2019 (32). While working on this last manuscript, I realized that a genetic discovery potentially points to the use of new drugs against lithium polyuria, as detailed in my fifth work, published on July 4, 2019 (33; 34-36). Finally these 5 papers were published together in an E-Book in Canada and partly in the columns of this Journal (37).

Figure 6.



It made my old age beautiful that I could contribute to the topic of treating "bipolar disorder" depression, a disease that affects millions - and thereby I could approach the theme "beauties of old age" from a positive perspective. It was also a great pleasure for me to be able to participate in the editing of this Journal from 1999 to 2012, so I thank the harmonious collaboration to my fellow editors, Sándor Alföldi and György Reusz. I thank the encouraging help of Thomas Ban, Professor of Psychiatry at the University of Nashville and Editor-in-Chief of INHN.

I take this opportunity to pay tribute to my former colleagues at János Hospital (Csaba Bános, late Lajos Borbély, Éva Juhos, Slava Kalcseva, Judit Marosi, László Szende, József Takó) and in the Uzsoki Street Hospital (József Arányi, Mária Csabuda, late György Gercsák, Ágnes Haris, Anna Hartai, Éva Karácsony, Andrea Kovács, Géza Megyeri, Éva Pató, Andor Tóth,

Szdreska Zdravkova). It is a pity that many more colleagues would deserve it, but they were not added to the lists above. I also think of them with a grateful heart. Last but not least, I would like to thank my wife, Mária Löffler, for not only tolerating my scientific work, but rather for supporting and sometimes participating in it.

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