

János Radó: 90th Year Birthday

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 Dezsó Kellér came to my mind on the beauties of old age: "tell me just one." What actually originally motivated me was the lecture by Canadian psychiatrist Professor Lehmann (2020), “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 honor 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 five years (even more two years), which were partly published on the website of the American International Network for the History of Neuropsychopharmacology (INHN) (Ban 2017) and on the website of the Hungarian Commission for the History of Nephrology.

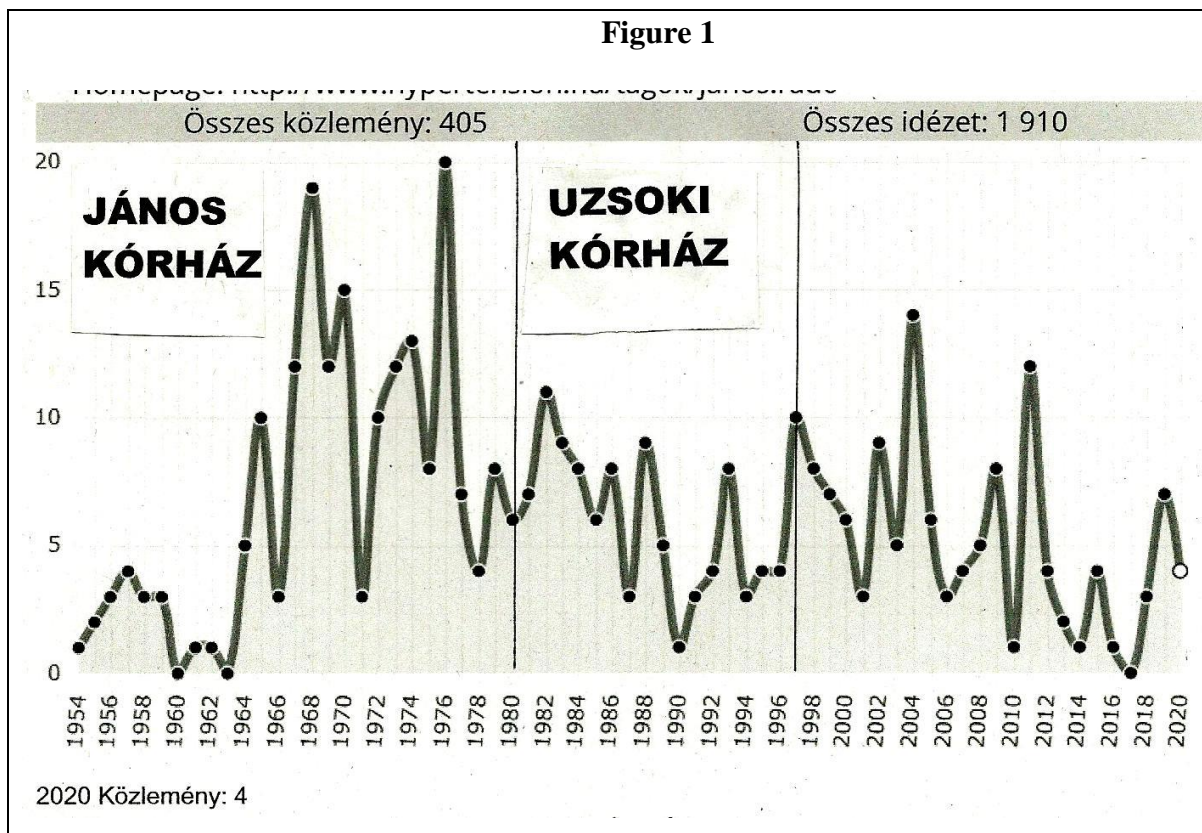
I was born on May 25, 1930 but the Festive Scientific Meeting scheduled for my 90th birthday was announced for June 3 by the Uzsoki Hospital and the Hungarian Nephrological Society. My wife paid for a Mediterranean round trip as a birthday present, so the Festive Scientific Meeting had to be postponed.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

Some summary statistics for my oeuvre (Radó 2018) are shown in Table 1.

No. of Papers	Per Year	Where	When	Total
127	4.8	János Hospital	1954-1980	
99	6.0	Uzsoki Hospital	1980-1996	
180	7.8	after retirement	1997-2020	
				406

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: 407 instead of 405; all citations, 1938 instead of 1910; 10 papers instead of four in 2020.



To present my oeuvre (Radó 2018), I selected six items from the 78 significant new results I have published so far; these are included in Table 2. Of these, I would like to discuss only the last two items listed in more detail (i.e., Herpes Zoster Virus Epidemic Study and Desmopressin Pharmacology).

Table 2		
Paper	Import	Reference
Diuretic Renography	World's first description	Radó, Banos and Tako 1967
Hyperkalemic Paralysis Due to Spironolactone	first case	Herman and Radó 1966

Water Intoxication Caused by Carbamazepine	first case	Radó 1973
Increase in Diuresis Due to Glibenclamide in Diabetes Insipidus	first description	Radó and Borbely 1971
Herpes Zoster Virus Epidemic Study	U.S. NASA publication	Radó, Tako, Geder and Jeney 1965; Mehta, Cohrs, Forghani et al. 2003
Desmopressin Pharmacology	U.S. Navy publication	Radó JP, Marosi J, Fischer et al. 1975; Doubt and Thorp 1992

Herpes zoster virus epidemic study

Pediatrician von 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 (Radó, Marosi, Fischer et al. 1975). We 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 (Radó, Marosi, Fischer et al. 1975).

The VZ “domestic epidemic” we observed was praised in an editorial in 1967 in the *Schweizerische Medizinische Wochenschrift* (Schwarz 1967); in 1969 in the *Quarterly Journal of Medicine* (Ashton 1969); in 1972 in the *British Medical Journal* (Editorial 1972); and in 1985 in the *Lancet* (Steele 1985).

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* on Nov. 17, 2004, “Stress-induced subclinical reactivation of varicella zoster virus in astronauts” (Mehta, Cohrs, Forghani et al. 2004). A main author of the manuscript is Duane L. Pierson from the group of the NASA Johnson Space Center (JSC). Pierson is the director of NASA’s Microbiology Laboratory and a professor at Baylor College of Medicine and the University of Texas Medical Branch. Another 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 four papers (Gilden, Dueland, Cohrs et al. 1991; Gilden, Mahalingam, Dueland and Cohrs 1992; Gilden, Kleinschmidt-DeMasters, LaGuardia et al. 2000; Nagel and Gilden 2016) 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 (Takó and Radó 1965).

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 two days before the launch. Therefore, eight astronauts were tested for VZ virus in saliva. Thirty per cent 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 (Radó, Tako, Geder and Jeney 1965). 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 (Radó, Marosi, Fischer et al.

1975) 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 (Doubt and Thorp 1992). *In this paper, they described our DDAVP dose-response relationship.*

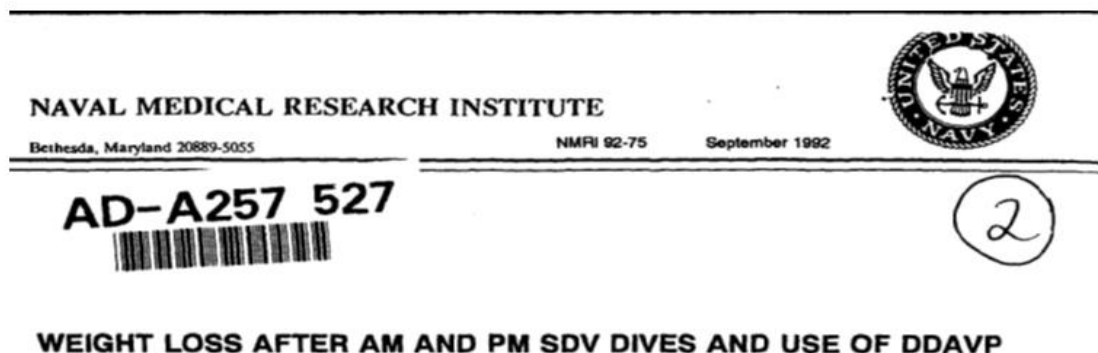
The cover page of the American article (Doubt and Thorp 1992) (Figure 2).

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 mcg) was too low to have a pronounced effect on hydration during water dives. Radó, Marosi, Fischer et al. (1975) found that 10 and 20 mcg intranasal doses of DDAV were nearly equivalent in inhibiting water-loaded diuresis. However, a distinct antidiuretic effect was observed at higher doses (40–320 mcg) (Doubt and Thorp 1992).

Figure 2



T. J. Doubt
J. W. Thorp



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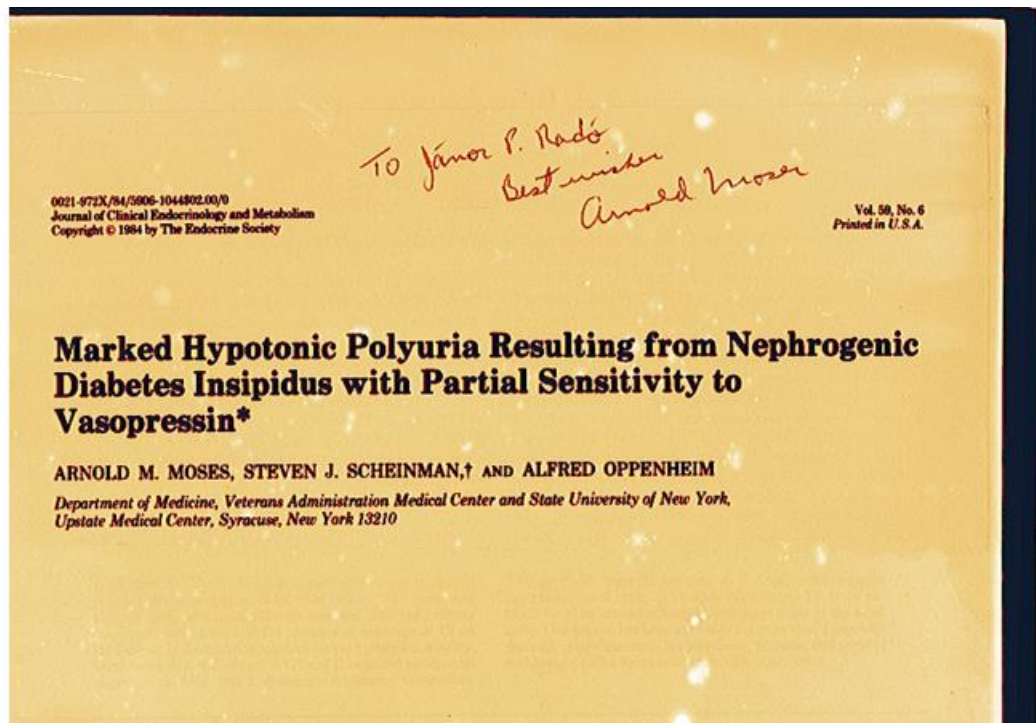
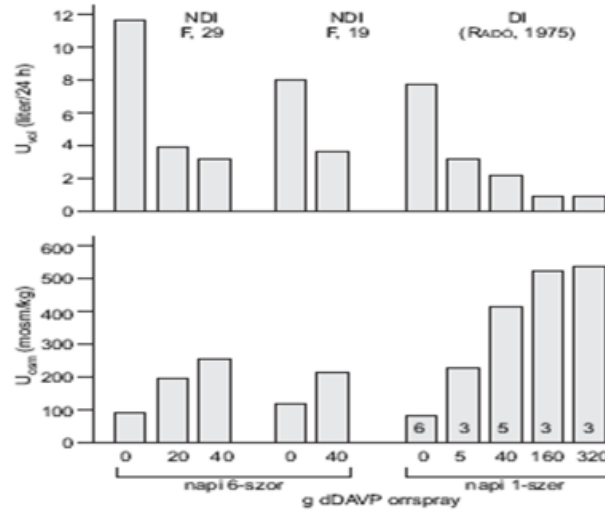


I should mention here that at New York University, Moses et al. made a similar comparison between the data from our dose-response relationship study and the dose-response of DDAVP when applied to their own patients (Moses, Scheinman and Oppenheim 1984).

In their Figure, (Figure 3) of our dose-response study is labelled as “DI Radó, 1975” (Translation of the Hungarian title: Comparison of the effectiveness of dDAVP in nephrogenic diabetes insipidus (NDI) and central diabetes insipidus (DI).

Figure 2

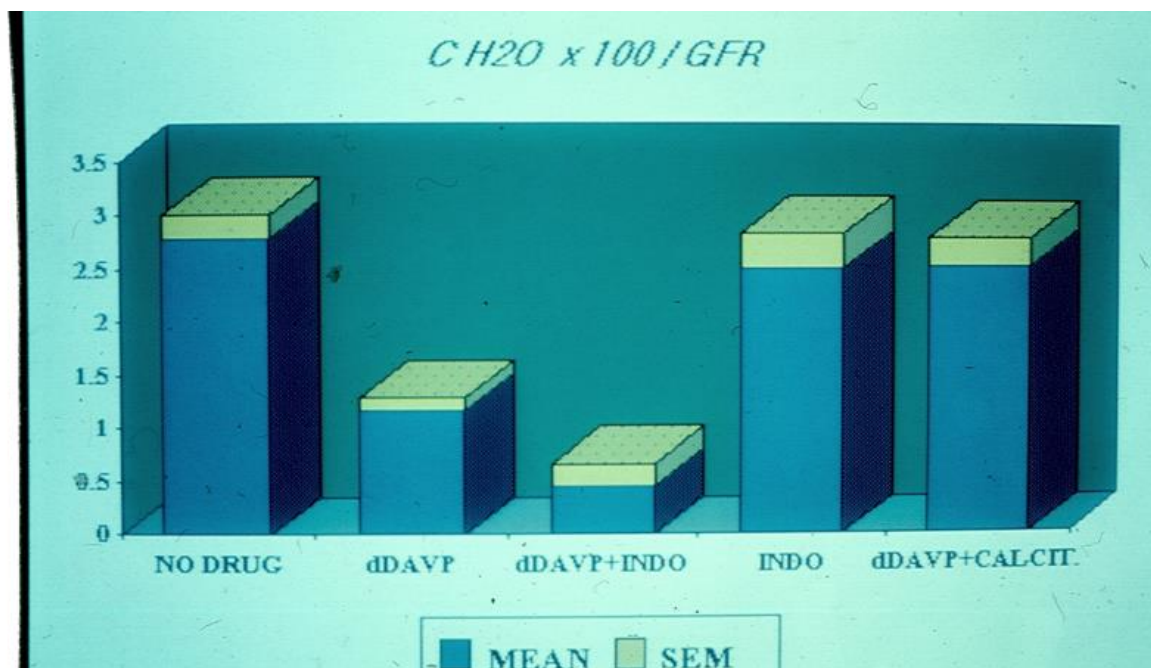
dDAVP hatékonyságának összehasonlítása nephrogen (NDI) és „valódi” (DI) diabetes insipidusban



Our DDAVP dose-response relationship studies were conducted in the 1970s. Perhaps it is remarkable that Oiso, Robertson, Nørgaard and Juul in 2013, Garrahy and Thompson in 2020; Gasthuys, Dossche, Michelet et al. in 2020; and da Silva Jr., Barros, Daher and Veronese in 2020 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 (Radó and Zdravkova 1991). **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 by Radó and Zdravkova at the 1993 International Congress of Nephrology in Jerusalem.

Figure 5



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 (Radó 2018). In a later post, Barry Blackwell noted that lithium “this simple ion remains the best, safest, and least expensive treatment to prevent recurrent episodes of bipolar disorder” (Blackwell 2018). Blackwell also wrote that if Cade (1912-1980 - the discoverer of lithium treatment) and Mogens Schou (1918-2005 - the greatest clinical pharmacologist of the treatment) 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 September 13, 2018 on the INHN website (Radó 2018). The website editors then asked me to write about the renal toxicity of lithium, which was published on May 2, 2019 (Radó 2019a). In these three publications I dealt so much with the effects of DDAVP that it seemed worthwhile to provide a literature review on the issue that DDAVP can counteract lithium polyuria. This paper was published on June 27, 2019 (Radó 2019b). 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 (Radó 2019c). Finally these five papers (Radó 2018a,b; Radó 2019a,b,c) were published together in an E-Book in Canada and partly in the columns of this Journal (Radó in press).

Figure 6

Thomas A. Ban: Neuropsychopharmacology in Historical Perspective (Collated 38)

Lithium E-BOOK Chapter 6. Safety

Janos Radó

Mechanism of Lithium Induced Polyuria

Use of Modern Antidiuretic Agents in the Treatment of Lithium Induced Permanent
Nephrogenic Diabetes Insipidus

Calcitonin in Lithium-Induced Nephrogenic Diabetes Insipidus

Desmopressin May Counteract Polyuria in Lithium Induced Nephrogenic Diabetes Insipidus

Renal Toxicity of Lithium in Historical Perspective with Special Reference to Lithium Induced
Nephrogenic Diabetes Insipidus

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 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, Emeritus Professor of Psychiatry at Vanderbilt University in 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 and 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 and Szdreska Zdravkova). It is a pity that although many more colleagues deserve it, 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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