

March 2016 - Issue #93



Prostate Cancer Canada Network

Montreal West Island

EVERYONE IS INVITED TO ATTEND OUR MEETINGS

We meet every fourth Thursday of each month except July, August and December

MEETING LOCATION

Sarto Desnoyers Community Centre
1335 Lakeshore Drive, DORVAL

OUR NEXT MEETING



On **March 24, 2016**, Dr. Samuel Aronson, Assistant Professor in the Department of Surgery, McGill University, will present an educational session on *“PSA to Prostate MRI—Accurate Diagnosis and Treatment of*

Prostate Cancer”. Come and bring your questions with you, this will be a highly interactive session designed to answer all your concerns on the subject.

On April 28, 2016, we will hold our **Annual General Meeting**, as well as present our **Annual Outstanding Contribution Award** to this year’s candidate—Dr. Serge Carrier’

Dr. Serge Carrier to receive the 2016 Outstanding Contribution Award from the Prostate Cancer Canada Network – Montreal West Island

NEWSRELEASE



Serge Carrier, M.D., FRCS(C), MMgmt



Make an In Memoriam Donation

Consider making a gift in memory of a loved one who has died of prostate cancer. While flowers are beautiful, many people today prefer to make memorial contributions in honour of a loved one’s memory. A tax receipt will be issued upon receipt of a donation.

**Support your local prostate cancer support group
PCCN - Montreal West Island
Get Involved!**



PCCN - The Montreal West Island Prostate Cancer Support Group

Our Website

Be sure to check out our website. Our internet address is <http://mtlwiprostcansupportgrp.ca/> The website provides information about our group, links to PCCN and Procure and gives access to current and past issues of our newsletter as well as up-to-date information about our meetings and other items of interest. Check it out and give us your feedback. Our Director Monty Newborn is the creator and manager of the site and our WEBMASTER.

This Newsletter is available at our website:

<http://mtlwiprostcansupportgrp.ca/>, as well as at www.pccn.org

Newsrelease (con't from p 1)

At its upcoming Annual General Meeting on April 28, 2016, Dr. Serge Carrier will be presented the Prostate Cancer Canada Network – Montreal West Island Support Group's 2016 Outstanding Contribution Award. He is receiving the award "in appreciation of his distinguished career dedicated to the treatment of so many of us in the Montreal area so afflicted."

Dr. Serge Carrier is currently an Associate Professor in the Department of Surgery, Division of Urology at McGill University, Montreal, Canada. He is an urologist at the McGill University Health Centre, Lachine Hospital and Royal Victoria Hospital. He is the surgical site director of the Lachine Hospital, MUHC. Dr. Carrier is renowned internationally for his work on men's health, erectile dysfunction and Peyronie's disease, and is well respected among his colleagues.

Dr. Carrier obtained his medical and urology diploma from the Laval University. He went on to complete his training as a post-doctoral fellow in andrology, sexual medicine and neurourology at the University of California, San Francisco working with Dr. Tom F. Lue and Dr. Emile Tanagho.

His major academic focus and areas of research include: Men's Health, Reproduction and Hypogonadism, Peyronie's disease, Sexual and Bladder Dysfunction, Prostate Health and Benign Prostatic Hyperplasia. He has published over 60 papers. He was awarded the Lapidus prize for his work on the regeneration of the penile nerve after resection. Over the years, he has helped (and continues to help) thousand of men suffering from erectile dysfunction after prostate cancer treatment.

Dr. Carrier served as president of the Quebec Urological Association from 2013-2015. He currently serves on the board of the Sexual Medicine Society of North America, the most important North American association of sexual medicine, as the Treasurer. He has been the president of the Société Francophone de Médecine Sexuelle as well as of the Canadian Male Sexual Health Council. He is a peer reviewer for many journals including the Journal of Sexual Medicine, the Journal of Urology and Urology.

He is happily married and a proud father of three sons. In his spare time, he enjoys coaching hockey.

The ceremony will take place in the Sarto Desnoyers Community Center in Dorval at 7:30PM on April 28, 2016. The public is welcome to attend. There is no admission charge and parking is available and free. For further information, contact Monty Newborn at 514-487-7544 (or preferably by email at newborn@cs.mcgill.ca)

Promising Prostate Cancer-Sniffing Device Passes Important Test Milestone

A team of British researchers from the University of Liverpool and the University of the West of England (UWE Bristol) have passed an important milestone in their quest to develop a urine test for diagnosing prostate cancer. Such a test could mean that invasive prostatic diagnostic procedures that men are currently obliged to undergo will eventually be replaced by faster, simpler, non-invasive techniques that don't require urinalysis.

The scientists working on the project describe their objective of creating a diagnostic test procedure that can "smell" cancer in a man's urine in a paper published in the *Journal of Breath Research* titled "[The use of a gas chromatography \(GC\)-sensor system combined with advanced statistical methods towards the diagnosis of urological malignancies.](#)" The paper is co-authored by Raphael B.M. Aggio, Ben de Lacy Costello, Paul White, Tanzeela Khalid, Norman M. Ratcliffe, Raj Persad, and Chris S.J. Probert of various departments and institutes at the University of Liverpool, the University of the West of England at Bristol, Imperial College London, and the Bristol Urological Institute.

Observing that prostate cancer is one of the most common cancers, and that serum prostate-specific antigen (PSA) is currently the gold standard used to select men to be referred for biopsies, they note that PSA use remains controversial as a diagnostic.

As an alternative, the investigators propose a GC-sensor algorithm system that would classify urine samples from patients with urological symptoms. Working in collaboration with the Bristol Urological Institute team at Southmead Hospital and Bristol Royal Infirmary, the pilot study included 155 men presenting to urology clinics, 58 of whom were diagnosed with prostate cancer, 24 with bladder cancer, and 73 with haematuria or poor stream, but cancer-free, and indicate that it is able to successfully identify different patterns of volatile compounds that allow classification of urine samples from patients with urological cancers.

The researchers found significant separation between men with prostate cancer and control samples, as well as between bladder cancer patients and controls and between

bladder and prostate cancer samples. For prostate cancer diagnosis, the GC-sensor algorithm system/support vector machine (SVM) system proved able to categorize samples with 95 percent sensitivity and 96 percent specificity, while in bladder cancer diagnosis, the SVM reported 96 percent sensitivity and 100 percent specificity after leave-one-out cross-validation (LOOCV), while repeated double cross-validation (DoubleCV) reported 87 percent sensitivity and 99 percent specificity, with SVM showing 78 percent and 98 percent sensitivity between prostate and bladder cancer samples.

The scientists report results of their pilot study presented in the Journal of Breath Research paper indicate that the GC system is capable of successfully identifying patterns that allow classification of urine samples from patients with urological cancers, and that the availability of accurate diagnostics based on urine samples would reduce the number of negative prostate biopsies performed, and the frequency of surveillance cystoscopy for bladder cancer patients. They say larger cohort studies are planned to investigate their prototype system's potential, and project that future work may lead to non-invasive breath analyses for diagnosing urological conditions.



Prof. Chris Probert from the University of Liverpool's Institute of Translational Medicine began work on this project with UWE Bristol where he was previously Professor of Gastroenterology and has held a consultancy post for 12 years with clinical and research interest in inflammatory bowel disease. Probert is also chair of the IBD

Section Committee for BSG and vice chair of the Medical Advisory Committee for NACC (CCUK).

The investigative team used a gas chromatography sensor system called 'Odoreader' that was developed by a team led by Probert and Prof. Norman Ratcliffe at UWE Bristol. The test procedure is to insert urine samples into the Odoreader, which then measures them using algorithms developed by the University of Liverpool and UWE Bristol research team.

"There is an urgent need to identify these cancers at an earlier stage when they are more treatable as the earlier a person is diagnosed the better," Probert said in a University of Liverpool release. "After further sample testing the next step is to take this technology and put it into a user-friendly format. With help from industry partners we will be able to further develop the Odoreader, which will enable it to be used where it is needed most: at a patient's bedside, in a doctor's surgery, in a clinic or Walk In Centre, providing fast, inexpensive, accurate results."

"Like An Electronic Nose"

"There is currently no accurate test for prostate cancer; the vagaries of the PSA test indicators can sometimes result in unnecessary biopsies, resulting in psychological toll, risk of infection from the procedure, and even sometimes missing cancer cases,"



Ratcliffe said in the release. "Our aim is to create a test that avoids this procedure at initial diagnosis by detecting cancer in a non-invasive way by smelling the disease in mens' urine. A few years ago we did similar work to detect bladder cancer following a discovery that dogs could sniff out cancer. We have been using the Odoreader, which is like an electronic nose to sense the cancer."



The Odoreader, which has been under development for seven years, can also be used to rapidly diagnose bladder cancer, and to sniff out gastrointestinal pathogens like *Clostridium difficile*, by 'reading' the odor of stool samples. It has a 30 meter column that enables the compounds in urine samples to travel through at different rates, thus breaking them into a readable format. These data are then translated into an algorithm enabling detection of cancer by reading patterns presented. The positioning of the prostate gland very close to the bladder gives the urine profile a different algorithm if the person undergoing the test has cancer.

"If this test succeeds at full medical trial it will revolutionize diagnostics," Raj Prasad, consultant urologist at Southmead Hospital, North Bristol NHS Trust, said in the release. "Even with detailed template biopsies there is a risk that we may fail to detect prostate cancer in some cases. Currently indicators such as diagnosed prostatomegaly



[enlarged prostate] and unusually high PSA levels can lead to recommendations for biopsy if there is a concern that cancer may be prevalent. An accurate urine test would mean that many men who currently undergo prostate biopsy may not need to do so."

The pilot trial was supported by the Rotary Club in Bristol, which raised funds by holding annual Run for the Future events in Bristol. The research team is now seeking funding for a full clinical trial. A video featuring Professor Probert speaking about the research paper and explaining how the Odoreader works can be found here:

<https://stream.liv.ac.uk/7zr3akrx> The full Journal of Breath Research study can be found here:

<http://iopscience.iop.org/article/10.1088/1752-7155/10/1/017106>

Prostate Cancer Risk Lower in Type 2 Diabetics



In contrast, type 2 diabetes is associated with increased risks of bladder, kidney, liver, and other malignancies.

Individuals with type 2 diabetes mellitus (T2DM) are at increased risk for a number of cancers, but older men with T2DM have a reduced risk of prostate cancer (PCa), according to a retrospective, population-based cohort study.

At least 3 years after a T2DM diagnosis, men aged 65–74 years had a 27% decreased risk of PCa compared with non-diabetic men, researchers led by Diego Serraino, MD, of the Epidemiology and Biostatistics Unit, IRCCS CRO National Cancer Institute, Aviano, Italy, reported in *Cancer Epidemiology* (2016;41:80-87). The reason for this inverse relationship may be the reduced androgen levels among diabetics, the researchers said. They pointed out, however, that the mechanisms underlying this association remain unclear.

In contrast, among individuals with T2DM for 3 or more years, the risk of colorectal, lung, pancreatic, kidney, and bladder cancer was 56%, 37%, 55%, 43%, and 30% higher, respectively, compared with non-diabetic subjects. The risk of liver cancer was 2.6 times higher. Women with T2DM had a 24% increased risk of breast cancer.

The study included 32,247 T2DM patients (17,827 men, 14,420 women) and 1,018,518 people without

diabetes in northeastern Italy. Serraino's group obtained data from administrative health-related databases covering the entire population living in the Friuli Venezia Giulia region in northeastern Italy. The median duration of follow-up was 3.65 years. The investigators documented 2,069 cancer cases (6.4%) among the 32,247 T2DM patients during the study period.

For the T2DM group overall (regardless of the time elapsed since T2DM diagnosis), the risk of cancer at any site was 28% higher and the risks of bladder and kidney cancer were 36% and 47% higher, respectively, compared with individuals who did not have T2DM. The risk of pancreatic cancer was 2.6 times higher.

The investigators noted that previous studies support a relationship between diabetes and the risk of kidney and bladder cancer, “making our results comparable with existing epidemiological evidence.”

The study found sex differences in the risk of various cancers. For example, among patients with T2DM for 3 years or more, men had a 47% increased risk of bladder cancer whereas women had a 31% decreased risk. In the T2DM group overall, the risk of pancreatic cancer was 3-fold higher among women versus 2-fold higher among men.

Among the T2DM patients, the overall probability of surviving 5 years after diagnosis of T2DM was 88.7%. With respect to the impact of T2DM on cancer survival, the researchers observed no differences in survival probabilities for prostate, colorectal, liver, pancreatic, and bladder cancers.

“Considering the high prevalence of T2DM in Italy, even a small increase in cancer risk could have severe consequences at a population level,” the authors concluded. “Therefore, specific primary and secondary cancer prevention programs are a priority among T2DM patients.”

Strengths of the study include its large study population and the use of a database covering the entire population in their region of interest, thus eliminating selection bias, the researchers noted.

The authors also acknowledged study limitations, including a lack of information on potentially confounding variables such as body mass index, obesity status, and smoking, as well as clinical information.

[From the March 2016 Issue of Renal And Urology News »](#)

Testosterone-lowering therapy for prostate cancer may increase Alzheimer's risk

Date:

December 7, 2015

Source:

Perelman School of Medicine at the University of Pennsylvania

Summary:

Men taking androgen deprivation therapy (ADT) for prostate cancer were almost twice as likely to be diagnosed with Alzheimer's disease in the years that followed than those who didn't undergo the therapy, an analysis of medical records from two large hospital systems has shown.

Men taking androgen deprivation therapy (ADT) for prostate cancer were almost twice as likely to be diagnosed with Alzheimer's disease in the years that followed than those who didn't undergo the therapy, an analysis of medical records from two large hospital systems by Penn Medicine and Stanford University researchers has shown. Men with the longest durations of ADT were even more likely to be diagnosed with Alzheimer's disease.

The findings, published in the December 7 issue of the *Journal of Clinical Oncology*, do not prove that ADT increases the risk of Alzheimer's disease. But the authors say they clearly point to that possibility, and are consistent with other evidence that low levels of testosterone may weaken the aging brain's resistance to Alzheimer's.

"We wanted to contribute to the discussion regarding the relative risks and benefits of ADT, and no one had yet looked at the association between ADT and Alzheimer's disease," said lead author Kevin T. Nead, MD, MPhil, a resident in the department of Radiation Oncology at the Perelman School of Medicine at the University of Pennsylvania, and a fellow at Penn's Leonard Davis Institute of Health Economics. "Based on the results of our study, an increased risk of Alzheimer's disease is a potential adverse effect of ADT, but further research is needed before considering changes to clinical practice."

Nigam Shah, MBBS, PhD, associate professor of biomedical informatics research at Stanford, served as senior author. Samuel Swisher-McClure, MD, MSHP, an assistant professor of Radiation Oncology at Penn Medicine, served as a co-author.

Androgens (male hormones) normally play a key role

in stimulating prostate cell growth. Thus, therapies that suppress androgen production or activity are often used in treating prostate tumors. In the U.S. alone, about half a million men are taking ADT at any given time.

Drastically reducing androgen activity can have adverse side-effects, however. Studies have found associations between low androgen levels (chiefly low testosterone levels) and impotence, obesity, diabetes, high blood pressure, heart disease, and depression. Research in recent years also has linked low testosterone to cognitive deficits, and has shown that men with Alzheimer's tend to have lower testosterone levels, compared to men of the same age who don't have the disease.

For the study, Nead, Swisher-McClure and their colleagues at Stanford's School of Medicine evaluated two large sets of medical records, one from the Stanford health system and the other from Mt. Sinai Hospital in New York City. Together the records covered about five million patients, of whom 16,888 received a diagnosis of prostate cancer and met all the other criteria for the study.

Of the 16,888 prostate cancer patients, about 2,400 had received ADT and had the necessary follow-up records. Nead and his colleagues compared these ADT patients with a control group of non-ADT prostate cancer patients, matched according to age and other factors.

Using two different methods of statistical analysis, the team showed that the ADT group, compared to the control group, had significantly more Alzheimer's diagnoses in the years following the initiation of androgen-lowering therapy. By the most sophisticated measure, members of the ADT group were about 88 percent more likely to get Alzheimer's during the follow-up period.

The analyses also suggested a "dose-response effect." The longer individuals underwent ADT the greater their risk of Alzheimer's disease, they found. The longer-duration ADT patients also had more than double the Alzheimer's risk of non-ADT controls.

The findings held up when the patient groups from the two hospital systems were considered separately.

"It's hard to determine the precise amount of increased risk in just one study and important to note that this study does not prove causation," Nead said. "But considering the already-high prevalence of Alzheimer's disease in older men, any increased risk would have

significant public health implications."

How low testosterone would lead to increased Alzheimer's risk isn't precisely known, but there is some evidence that testosterone has a general protective effect on brain cells, so that lowering testosterone would leave the brain less able to resist the processes leading to Alzheimer's dementia. Studies in mice and in humans also have suggested that lower testosterone levels may allow greater production of the Alzheimer's protein amyloid beta. Moreover, low testosterone may increase Alzheimer's risk indirectly, by promoting conditions such as diabetes and atherosclerosis that are known to predispose to Alzheimer's.

Ultimately, further studies will be needed to determine whether ADT does increase Alzheimer's risk. Nead and colleagues are now hoping to examine this association in large cancer registry datasets to see which subgroups of patients might be at greatest risk.

Story Source:

The above post is reprinted from materials provided by **Perelman School of Medicine at the University of Pennsylvania**. Note: Materials may be edited for content and length.

Journal Reference:

Kevin T. Nead, Greg Gaskin, Cariad Chester, Samuel Swisher-McClure, Nicholas J. Leeper, and Nigam H. Shah. **Androgen Deprivation Therapy and Future Alzheimer's Disease Risk**. *Journal of Clinical Oncology*, December 2015 DOI: 10.1200/JCO.2015.63.6266

The Psychological Impact of Prostate Cancer



Patients diagnosed with prostate cancer often struggle with their diagnosis.

It would not be hard to guess the psychological impact on patients the moment a doctor tells them they have cancer. Just hearing that word probably leaves most patients stunned and, in the moments that follow, perhaps only half-listening to whatever else the doctor has to say. To some, cancer

equals death. Cancer may or may not be life ending, but it is almost certainly life changing. The diagnosis may intrude often on patients' thoughts and reshape their vision about the trajectory of their lives. Some may decide to take that cruise around the world they have been dreaming about sooner rather than later. Rare would be the patient who is not at least a little concerned or frightened about the odyssey of tests and treatment they face. As a result of the diagnosis, some patients may experience harmful physiological effects and contemplate suicide. Men with prostate cancer (PCa) are not immune.

The medical literature on the effects of a PCa diagnosis on the mental health of men is growing. For example, this issue of *Renal & Urology News* reports on a study published in the *Journal of the National Comprehensive Cancer Network* showing that elderly men have a significantly higher risk of hospitalizations for non-cancer conditions after receiving a diagnosis of non-metastatic PCa. The authors, led by Amit D. Raval, PhD, of West Virginia University in Morgantown, gave some plausible explanations for the increased risk, citing research showing that a PCa diagnosis "can trigger psychological distress, anxiety, and suicidal ideations. This increase in psychological stress may increase blood levels of epinephrine and norepinephrine, resulting in increased heart rate, blood pressure, and blood sugar levels."

In a previous study published online ahead of print in *BJU International*, Quoc-Dien Trinh, MD, and colleagues at Harvard Medical School in Boston, found that men with PCa are at increased risk of suicide and accidental death within the first year of diagnosis compared with men diagnosed with other solid cancers. The authors concluded that their findings suggest "the need for close monitoring and coordination with mental health professionals in at-risk men with potentially curable disease."

While mental health professionals may have a role, urologists who deliver to men what may be among the most distressing bits of news they will ever hear could have a big positive impact. The vast majority of men diagnosed with PCa have low-risk disease, which has an extremely favorable prognosis. The cancers can be cured with surgery or radiation or managed with active surveillance. Even patients with more advanced disease often have good long-term outcomes. These facts, couched in the right language and delivered with empathy by the urologist, could do much to put patients at ease.

[From the March 2016 Issue of Renal And Urology News »](#)

Vitamin D Deficiency Linked to Adverse Pathology in Prostatectomy

(HealthDay News) -- For men with localized prostate cancer undergoing radical prostatectomy, serum 25-hydroxyvitamin D (25-OH D) insufficiency/deficiency is associated with increased odds of adverse patholo

NOTICE OF THE ANNUAL GENERAL MEETING

APRIL 28th, 2016

In accordance with Article X of the General By-Laws, the Annual General Meeting will be held at the Sarto Desnoyers Community Centre, 1335 Lakeshore Drive, Dorval on Thursday, April 28th, 2016 at 7:30 p.m.

This meeting will take place just prior to the monthly general meeting.

AGENDA

- Minutes of Meeting of April 23th , 2015
- President's Report
- Treasurer's Report
- Nomination Committee Report
- New Business
- Adjournment

It should be noted that opinions and questions are welcome from all participants. However, only those who have paid their membership fee are eligible to vote.

Nominations for the position of Officer or Director must be accompanied by the signed approval of the nominee and the signed endorsement of two other members. These are to be submitted to the Secretary.

George Larder
(Acting Secretary)

REPORT OF THE NOMINATION COMMITTEE

The nominees recommended by the committee to be the officers and directors of the board for the year 2016/2017 are as follows, and the specific responsibilities are as listed:

<u>POSITION</u>	<u>NOMINEE</u>	<u>RESPONSIBILITY</u>
President	Ron Sawatzky	Officer
Vice-President	Allen Lehrer	Officer
Secretary	Bob Johansson	Officer
Treasurer	Wayne Hemsworth	Officer
Director	Fred Crombie	e-mail
Director	Ron Sawatzky	Outreach
Director	Open *	Hospitality
Director	Dr. Irwin Kuzmarov	Founding Member
Director	Allan Moore	Library
Director	Jeff Watson	Newsletter Editor
Director	Monty Newborn	Publicity & Website
Director	Ron Sawatzky **	Speakers
Director	George Larder	Membership
Director	Open *	Fundraising
Members at Large	John Bauer and Frank Scully	

* Position urgently to be filled

** Will continue until someone suitable is found.

gy, according to a study published online in the *Journal of Clinical Oncology*.



Insufficiency/deficiency of serum 25-OH D linked to increased odds of adverse pathology.

Yaw A. Nyame, MD, from the Cleveland Clinic, and colleagues conducted a cross-sectional study nested within a large epidemiologic study of 1,760 healthy controls and men undergoing prostate cancer screening. Within the cohort, 190 men underwent radical prostatectomy. The correlation between adverse pathology at the time of radical prostatectomy, defined as presence of primary Gleason 4 or any Gleason 5 disease, or extraprostatic extension, and 25-OH D levels was assessed.

The researchers identified adverse pathology at radical prostatectomy in 45.8% of the cohort. Men with adverse pathology at radical prostatectomy had lower median serum 25-OH D than their counterparts, on univariate analysis (22.7 versus 27.0 ng/mL; $P = 0.007$). Serum 25-OH D <30 ng/mL correlated with increased odds of adverse pathology after adjustment for age, serum prostate-specific antigen, and abnormal digital rectal examination (odds ratio, 2.64; $P = 0.01$).

Newsletter Disclaimer:

All articles appearing in this newsletter are for information purposes only and not intended to be a substitute for the advice of a doctor or healthcare professional or recommendations for any particular treatment plan. It is of utmost importance that you rely on the advice of a doctor or a healthcare professional for your specific condition.

2016

PCCN - WIPCSG - Calendar of Events

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"Serum 25-OH D may serve as a useful biomarker in prostate cancer aggressiveness, which deserves continued study," the authors write.

One author disclosed financial ties to GlaxoSmithKline. One author is co-inventor of a urine assay for prostate-specific antigen enzymatic activity.

Source

Nyame YA, Murphy AB, Bowen DK, et al. Associations Between Serum Vitamin D and Adverse Pathology in Men Undergoing Radical Prostatectomy. *JCO*. doi: 10.1200/JCO.2015.65.1463.

Telephone Helpline (514) 694-6412

IMPORTANT NOTICES:

- ❖ The PCCN—Montreal West Island Prostate Cancer Support Group encourages wives, loved ones and friends to attend all meetings. Please ask basic or personal questions without fear or embarrassment. You need not give your name or other personal information.
- ❖ The PCCN—Montreal West Island Prostate Cancer Support Group does not recommend treatment procedures, medications or physicians. All information is, however, freely shared. Any errors and omissions in this newsletter are the responsibility of the authors.
- ❖ The PCCN—Montreal West Island Prostate Cancer Support Group is a recognized charitable Organization (registration # 87063 2544 RR0001). All donations are acknowledged with receipts suitable for income tax deductions. Your donations and membership fees (voluntary) are a very important source of funds vital to our operations. Together with contributions from several pharmaceutical companies these funds pay the cost of printing and mailing our newsletter, hall rental, phone helpline, equipment, library, etc.

Your support is needed now! Please help us continue helping you!

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