Maternal Exposure to Chemicals Linked to Autistic-Like Behaviors in Children

A novel study found correlations between increased expressions of autistic-like behaviors in pre-school aged children to gestational exposure to selected environmental toxicants, including metals, pesticides, polychlorinated biphenyls (PCBs), phthalates, and bisphenol-A (BPA).

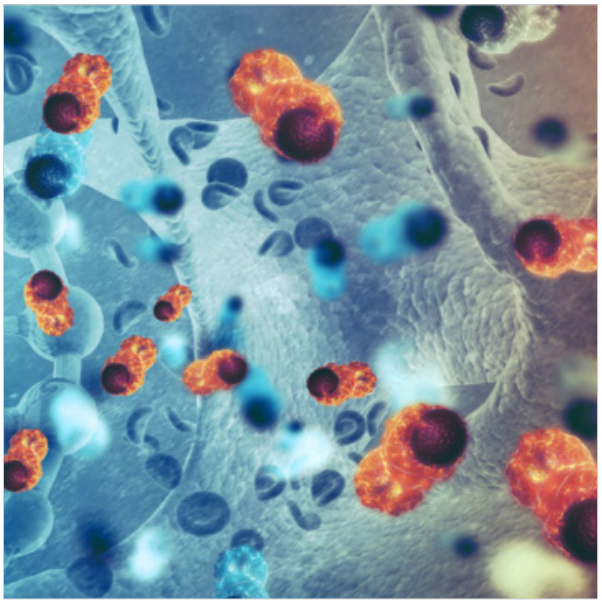
The study led by Simon Fraser University's Faculty of Health Sciences researchers, Canada, was published in the *American Journal of Epidemiology.*

The researchers found that higher maternal concentrations of cadmium, lead, and some phthalates in blood or urine samples was associated with increased Social Responsiveness Scale (SRS) scores, and these associations were particularly strong among children with a higher degree of autistic-like behaviors. Interestingly, the study also noted that increased maternal concentrations of manganese, trans-Nonachlor, many organophosphate pesticide metabolites, and monoethyl phthalate (MEP) were most strongly associated with lower SRS scores.

Dual Drug Approach to Treat Deadly Melanoma

Research from the Centenary Institute, Australia, has found that a new dual drug approach could offer up a highly effective treatment strategy for melanoma, the most serious form of skin cancer.

Reported in the *Journal of Investigative Dermatology* the findings have the potential to benefit melanoma patients who do not respond favorably to current therapeutic treatments.



In the study, the research team found that the combined use of inhibitors targeting two specific proteins markedly reduced the growth of melanoma both in cellular experiments as well in models with mice. The two proteins targeted were the bromodomain and extra-terminal domain (BET) family of proteins and cyclin-dependent kinase 9 (CDK9).

High expression of BET and CDK9 proteins are associated with an adverse prognosis in melanoma patients and also regulate melanoma cellular activity.

According to Dr. Abdullah Al Emran, researcher in the Melanoma Oncology and Immunology Program at the Centenary Institute and lead author of the study, a key finding from the study was that the combination BET and CDK9 inhibitor treatment demonstrated significantly increased melanoma killing benefits when compared to use of the same inhibitor drugs when tested alone.

Progestogens could Reduce the Risk of Preterm Birth

Taking progestogens, steroid hormones, during pregnancy could reduce the risk of preterm birth in high-risk single baby pregnancies, according to a latest study published in the *Lancet*.

Although these compounds have been in use for some time, results of individual clinical trials investigating their effectiveness in preventing preterm birth have been conflicting, and so further evaluation of the research evidence was needed.

University of York, UK, researchers led the Evaluating Progestogens for Prevention of Preterm Birth International Collaborative (EPPPIC) project, a systematic review which brought together and re-analyzed datasets from 31 clinical trials of progestogens, including more than 11,000 women and 16,000 babies worldwide.

Both vaginal progesterone and 17-OHPC reduced the risk of preterm birth before 34 weeks for high-risk single baby pregnancies, mostly for women who had experienced a previous preterm birth or had a short cervix in their current pregnancy.

There was a consistent benefit for other outcomes including fetal and baby deaths and serious neonatal complications, including infection and lung and eye problems.

Certain High BP Medications may Alter Heart Risk in People with HIV: Study

Intake of certain medications that can lower blood pressure in people with human immunodeficiency virus (HIV), can also increase long-term risk of heart disease, stroke and heart failure, according to new research.

People with HIV are able to live longer with the anti-retroviral therapy (ART). However, the medication likely elevates blood pressure (hypertension) and hypertension-related heart problems in the HIV group than among people without the virus.

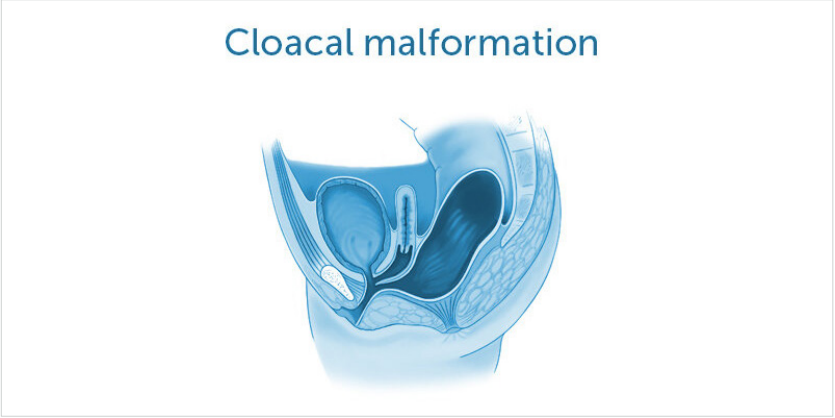
"We suspected there could be differences in risk based on which medication providers select to treat hypertension among people with HIV due to potential interactions between blood pressure medications and some therapies used to treat the virus," said Jordana B Cohen, Assistant Professor at the University of Pennsylvania in Philadelphia, US. "Additionally, factors such as how the body handles salt, inflammation and the accelerated ageing of blood vessels may affect the risk of cardiac events in people with HIV differently than people who do not have HIV, which could be influenced by which blood pressure medication is used," Cohen added.

According to the findings published by the researchers in journal *Hypertension*, 25 per cent people experienced a cardiovascular event. The risk of developing heart disease, heart failure or stroke for the first time was 90% higher among those taking beta-blockers compared to those who were taking ACEi/ARBs, the most frequently prescribed type of high blood pressure medication.

Cohen said the results also highlight that there is possible harm from beta-blockers as first-line treatment for hypertension whether a person has HIV or not.

Laparoscopic Approach to Cloacal Malformation Repair

A minimally invasive surgical approach called laparoscopic rectal mobilization and urogenital separation appears to be a safe alternative to open surgery in eligible patients with cloacal malformations. That's the conclusion of a recent study by the team in the Colorectal and Pelvic Malformation Center at Boston Children's Hospital, US.



While laparoscopy has been used for rectal dissection, it had not previously been used for management of the urogenital structures. The center's director, Belinda Dickie, MD, Ph.D., and associate director, Erin McNamara, MD, MPH, and their colleagues recently adopted a laparoscopic approach to rectal mobilization and urogenital separation.

This minimally invasive approach provides surgeons with a magnified view of the child's anatomy. Because it requires smaller incisions, it also has the potential to result in faster recoveries, shorter hospital stays, and less pain medication.

"This minimally invasive approach allows us to visualize all structures in the abdomen and pelvis and separate them safely, offering the benefits of laparoscopic surgery," says McNamara. "We will continue to follow these patients to see if there is improvement in other outcomes, such as continence."

Facts Related to Antihistamines

Among the millions of people worldwide suffering from allergies, antihistamine pills are commonly used to ward off hives, sneezing and watery eyes.

But people may be taking their medications incorrectly, says Derek Chu, a McMaster University, Canada, allergy expert and clinical scholar.

This team's study is published in the *Canadian Medical Association Journal (CMAJ)*.They list five facts as follows:

1. Antihistamines are among the most commonly and incorrectly used medicines worldwide. Antihistamines are best used to relieve symptoms of hay fever and outbreaks of hives, but not for asthma, eczema, coughs or insomnia.
2. First-generation antihistamines are associated with substantial and sometimes fatal side effects. Antihistamines with diphenhydramine, chlorpheniramine or hydroxyzine are first-generation antihistamines that can cause drowsiness and affect cognitive functions such as school performance. Overdosing can cause death and they are potentially dangerous for both young and older people.
3. Newer antihistamines are safer, as affordable and as effective as first-generation antihistamines. Later-generation antihistamines are proven to be more effective and last longer with less side-effects like drowsiness.
4. Antihistamines should not be used instead of epinephrine to treat anaphylaxis. Oral drugs can be used together with epinephrine injections to treat anaphylactic reactions, but they are not a substitute.
5. Most antihistamines are safe to use during pregnancy and breastfeeding. Medical research has shown that antihistamines at standard doses do not harm fetuses during pregnancy and may be used during breastfeeding. They are also safe for children to use.

Gene Discovery Suggests new Treatment Approach for Liver Cancer

In a comprehensive analysis of human gene activation data, researchers from the Centenary Institute, Australia, have discovered that the dipeptidyl peptidase-4 (DPP4) gene family is strongly implicated in the development of human hepatocellular carcinoma (HCC), the most common type of primary liver cancer.

Reported in the journal Cancers, the research suggests that the DPP4 gene family and the four enzymes that it contains should be further studied to support potential new therapeutic approaches to fighting tumors found in the liver.

"In this study we interrogated a number of publicly accessible human gene databases including the Cancer Genome Atlas to identify cancers associated with the DPP4 gene family," said Dr. Hui Emma Zhang, researcher in the Centenary Institute's Liver Enzymes in Metabolism and Inflammation Program and co-senior author on the paper.

"Our analysis indicates that high levels of all enzymes of the DPP4 family occur in liver cancers, which encourages us to target these enzymes as a possible new therapeutic approach to tackling the disease," said Dr. Zhang.

Metabolic, Cardiovascular Side Effects of Second-Generation Antipsychotics

A recent meta-analysis done by Carla Rognoni, Centre for Research on Health and Social Care Management (CERGAS), SDA Bocconi School of Management, Bocconi University, Italy, provided an insight on variations in metabolic and cardiovascular side effect profiles of oral second-generation antipsychotics.

First-line antipsychotic therapy used to treat schizophrenia may contribute to the development of metabolic abnormalities and weight gain. A systematic review examined the metabolic and cardiovascular adverse effects of commonly prescribed second-generation antipsychotics.

Results showed that patients who took olanzapine and risperidone reported the greatest weight gain. Olanzapine was also associated with the largest body mass index (BMI) increaseand significantly increased triglycerides and fasting glucose. Paliperidone treatment was reported to increase total cholesterol, but also led to an increase in HDL cholesterol. Aripiprazole also showed a large increase in triglyceride level.

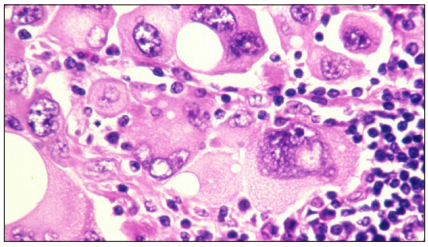
The highest increase in systolic and diastolic blood pressure was reported with quetiapine. Treatment with this agent also led to the greatest decrease in fasting glucose. Conversely, lurasidone was associated with the lowest increase in body weight, a reduction in BMI, and a decrease in total cholesterol and triglycerides. However, it resulted in the highest decrease in HDL cholesterol.

An Amyloid Link Between Parkinson's Disease and Melanoma

Scientists report a molecular link between the two diseases in the form of protein aggregates known as amyloids.

In Parkinson's disease, α-synuclein forms amyloid deposits that are thought to kill dopamine-producing neurons in the brain, causing symptoms such as tremor, slow movements and dementia. Jennifer Lee, Ph.D., Dean's postdoctoral advisor at NHLBI, part of the National Institutes of Health, US, had previously studied another amyloid-forming protein called premelanosomal protein (Pmel).

To investigate whether α-synuclein and Pmel could interact, the researchers used microscopy and western blotting to show that the two proteins both



resided in the melanosomes of human melanoma cells. When Dean added preformed α-synuclein amyloid to a test tube containing the amyloid-forming region of Pmel (known as the repeat, or RPT, domain), the α-synuclein fibrils stimulated Pmel to aggregate and form a twisted fibril structure that the protein does not normally adopt on its own.

"We now have preliminary data that suggest an amyloid from one protein can 'seed' or template amyloid from another, and in the soluble form, α-synuclein prevents Pmel aggregation." Lee says. Loss of skin pigmentation could contribute to the increased melanoma risk in Parkinson's disease patients, the researchers say.

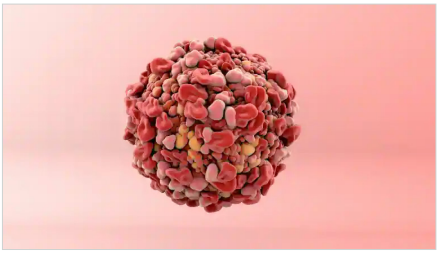
Scientists Discover Drug that can Stop Tumors From Growing

Cancer doctors may soon have a new tool for treating melanoma and other types of cancer, thanks to work being done by researchers at the University of Colorado Cancer Center, US, who claimed to have found a drug that can reduce inflammation and the resultant tumor expansion.

In a paper published in the journal *PNAS*, scientists from the University of Colorado Anschutz Medical Campus detailed their work on NLRP3, an intracellular complex that has been found to participate in melanoma-mediated inflammation, leading to tumor growth and progression. By inhibiting NLRP3, the researchers found, they can reduce inflammation and the resultant tumor expansion.

Specifically, NLRP3 promotes inflammation by inducing the maturation and release of interleukin-1-beta, a cytokine that causes inflammation as part of the normal immune response to infection. In cancer, however, inflammation can cause tumors to grow and spread.

With the hypothesis that an NLRP3 inhibitor is one of the therapies, CU Cancer Center researchers are studying the drug's effects on melanoma, as well as breast cancer and pancreatic cancer. In addition to improving the immune



response, the NLRP3 inhibitor can also help reduce the side effects of checkpoint inhibitors.

Carlo Marchetti, Assistant research professor, University of Colorado Cancer Center, says this research can make a big difference for melanoma patients who don't respond to checkpoint inhibitors alone.

Naloxone Use Linked to Acute Pulmonary Edema

A recent report published in the American Journal of Case Reports describes the cases of 2 young patients who developed non-cardiogenic pulmonary edema (NCPE) and required ventilator support following the administration of several doses of naloxone for the treatment of opioid overdose.

Naloxone is the mainstay therapy for reversing the effects of opioid overdose. At normal doses, the drug's adverse effects are minimal, with the majority being attributed to acute withdrawal effects. However, adverse events such as acute pulmonary edema, ventricular arrhythmias, and cardiac arrest have been previously reported when larger naloxone doses are used or when the drug is infused rapidly.

In this series, the authors presented the cases of 2 young patients who developed NCPE and required ventilator support after being administered several doses of naloxone following opioid overdose. "Both

our patients required frequent dosing due to insufficient response or owing to the washout of the naloxone effect shortly after, given its short half-life," the authors explained.

"Although the administered doses were different, both patients developed the adverse effect of NCPE and required ventilator support," the authors noted, adding that the findings suggest a dose-dependent relationship.

Aspirin to Prevent Colon Cancer

Long-term use of low-dose aspirin may reduce the risk of death from colon and rectal cancers, according to new research,

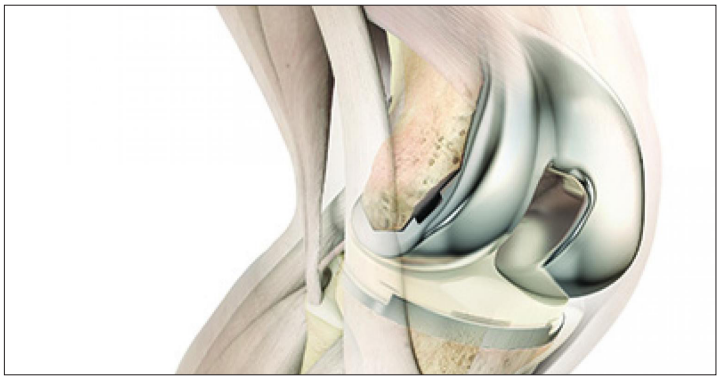
Researchers found that aspirin prevents blood cells called platelets from producing an enzyme that allows them to clump together. Tumor cells can attach to these clumps and spread (metastasize) throughout the body.

"Aspirin inhibits platelet activation, which also could inhibit metastases," said lead author Jane Figueiredo, director of Community and Population Health Research at the Samuel Oschin Cancer Institute at Cedars-Sinai Medical Center in Los Angeles. The use of non-aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, acetaminophen and naproxen were not associated with better outcomes.

Patients who began taking aspirin after their cancer diagnosis had better outcomes than those who didn't take aspirin, the difference was not significant, the study found. The findings were recently published in the *Journal of the National Cancer Institute.*

"These findings may provide an inexpensive lifestyle option to people seeking to prevent colorectal cancer, or to improve their prognoses if they are diagnosed," Figueiredo said.

Posterior Cruciate Ligament Substitution vs Retention in Total Knee Arthroplasty



The role of the posterior cruciate ligament (PCL) in total knee arthroplasty (TKA) has been widely discussed in the orthopedic literature. Theoretical and functional arguments and survivorship have all been used to support both its retention and its substitution. Moreover, with the advent of robotics and ever evolving kinematic surgical procedures, the results for the cruciate-retaining arthroplasties are found to be more variable than for the cruciate substituting arthroplasties.

The in vivo studies which have used fluoroscopy to investigate knee kinematics after TKA however, have reported abnormal kinematics when compared with normal knee. The gross differences in the design and the normal knee include, less posterolateral femoral roll- back as the knee movefrom full extension to flexion, abnormal axial rotation between the femur and the tibia throughout the range of movement (ROM), different center of rotation of the knee in the horizontal plane and even the condylar lift-off.

In a recent study conducted by team at Dept. of Orthopaaedics, Government Medical College, Bhavnagar, Gujarat, India, researchers sought to investigate if there was a difference in the clinical outcome as measured by the commonly-used scoring systems which includes (International Knee Society Score, Western Ontario McMasters Osteoarthritis (WOMAC) index and the SF- 36 health survey along with the radiological scores and outcomes of the two procedures in TKA.

The findings of the study are published in Indian *Journal of Orthopaedics Surgery*. They found almost similar results for Cruciate ligament retaining and substituting procedures in long term follow up at 3 months, with slightly better outcomes for Cruciate ligament retaining groups at the earliest phases pre operatively and post operatively.

Virus Therapy Shows Promise Against Inoperable Skin Cancers

Early results show that a new combination drug therapy is safe and effective against advanced skin cancer in patients who were not able to have their tumors surgically removed.

The drug combination is among the first, researchers say, to demonstrate the potential value of a live common cold virus, coxsackievirus, to infect and kill cancer cells.

The Phase I study, led by a researcher at NYU Langone Health and its Perlmutter Cancer Center, US, is also among the first to show how such oncolytic viruses can safely boost the action of widely used cancer therapies that help the body's immune defence system detect and kill cancer cells. Currently, such immunotherapies are only effective in shrinking melanoma tumors in just over a third of patients who receive them.

The new study results showed that injections of experimental coxsackievirus drug V937, along with pembrolizumab, an immunotherapy drug known as

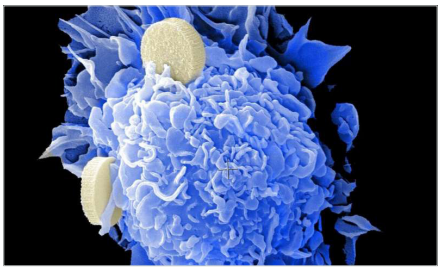
pembro or Keytruda, was well tolerated. Among the study's other findings was that patients least likely to respond to immunotherapy alone were those who responded best to the combined treatment. Patients, for example, who responded best had less of the chemical receptors (PDL1) on the surfaces of cancer cells that are blocked by pembrolizumab than patients who did not respond as well.

New Genetic Drug Target for the Treatment of Resistant Colorectal Cancer

Targeting a specific cancer survival gene in colorectal cancer could lead to new treatment options for advanced disease, new research suggests.

Researchers from the Wellcome Sanger Institute, in collaboration with the Candiolo Cancer Institute in Italy and the Netherlands Cancer Institute, UK, used state-of-the-art patient-derived organoid models to gather information about this genetic dependency, known as Werner Helicase (WRN), in cancers that had become resistant to standard treatment.

The new study, published in *Cancer Discovery*, shows that developing novel drugs to target WRN could lead to new treatment options for those whose cancer no longer responds to other treatments. The study also provides new insight into which tumours display WRN dependency. These results might allow clinicians to identify better those who could benefit from potential targeted drugs.



The results are a consequence of the Cancer Dependency Map-based at the Sanger Institute, which is a major initiative to provide a detailed rulebook of precision cancer treatments to help more patients receive effective therapies. The researchers also discovered that alterations in specific genes involved in mismatch repair were involved in WRN dependency. Understanding more about the genes involved in this pathway could lead to the identification of biomarkers that might determine which cancers would be most sensitive to blocking WRN.