## BCG: LUEBECK, NOT HAMBURG

**To the Editor:**

Dr. Weisz, in his article in the September 2012 issue of *IMAJ* [1]. Dr. Weisz, perhaps confused these two major cities of north Germany. A full quotation [2] seems in order:

**"Luebeck disaster**

In 1930, a tragedy focused international attention on the participation of children in research. In Luebeck, Germany, administration of the Calmette (BCG) vaccine against Tuberculosis to 250 children resulted in the death of over 76 infants. The public outcry prompted the German Ministry of the Interior to issue regulations concerning new medical treatments and scientific experiments on man (1931), including special protection for children under the age of 18…."

**M.N. Lowenthal MD**
Bayit BeLev Facility for Complicated Nursing, Kfar Saba, and Division of Medicine, Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer Sheva
[markll@bgu.ac.il]

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## REPRODUCIBILITY OF MICROVOLT T-WAVE ALTERNANS IN PATIENTS WITH ISCHEMIC HEART DISEASE

**To the Editor:**

The report by Fuchs et al. [1] in the June issue of the Journal focuses on the short-term (one week) reproducibility of microvolt T-wave alternans (MTWA) in 40 patients with ischemic heart disease (IHD) participating in a rehabilitation program employing a bicycle exercise test. Overall the authors reported a correlation between the results of the first and the second study in 32 of the 36 patients (89%), with 4 patients excluded after they tested indeterminate in their first test. This confirms results on the "back-to-back" short-term and long-term MTWA reproducibility, obtained previously, with the advantage in the present study, of investigating this issue in a more homogeneous cohort of patients with IHD, at a specific time point of their disease course, and while they were treated with their routine drug regimen. The authors used the spectral method, and the MTWA was reported as positive or negative based on the ≥ 1.9 μV threshold in any of a set of Frank orthogonal of precordial electrocardiogram leads. Speculations have arisen that MTWA in μV may be T-wave amplitude dependent [2], and this issue has not yet been resolved. The authors could provide an answer to this question by examining whether there was any correlation between the actual values of MTWA in μV and the amplitude of the corresponding T-waves (the areas under the J-T would have been ideal) in the different ECG leads used in the bicycle stress test, at the time of MTWA calculation, in each individual patient (intra-test), or whether the change in the magnitude of MTWA in μV in each ECG lead correlated with the change in the amplitude of the corresponding T-waves between the two bicycle stress tests (inter-test) in each individual patient.

**John E. Madias MD FACC FAHA**
Mt. Sinai School of Medicine of New York University, and Division of Cardiology, Elmhurst Hospital Center, Elmhurst, New York, USA
[madiasj@nychhc.org]

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**To the Editor:**

I would like to thank Dr. Madias for his comment on our report. The T wave amplitude was not measured in the patients who underwent mTWA testing. We concentrated only on the issue of reproducibility in this study.

**T. Fuchs MD FHRS**
Director, Electrophysiology Laboratory, Assaf Harofeh Medical Center, Zerifin, Israel
[therese@fuchs.org]

## GENERIC ATORVASTATIN-INDUCED THROMBOCYTOPENIC PURPURA: A RAISED RED FLAG

**To the Editor:**

Atorvastatin is one of the most frequently prescribed HMG-CoA reductase inhibitors. An adverse reaction of thrombocytopenia has been described in a few cases, all regarding thrombotic thrombocytopenic purpura (TTP) [1-3]. We describe a patient with severe thrombocytopenia, without microangiopathic hemolytic anemia, following the administration of a newly introduced generic form of atorvastatin.

A 77 year old woman was admitted to the emergency room after a fall that resulted in a hip fracture. Her past medical history was insignificant except for a transient ischemic attack. Four days prior to her hospitalization, simvastatin treatment was replaced by Litorva® (atorvastatin, Teva, Israel) 40 mg/day. The day following intake of the first pill, she developed diffuse non-palpable purpura and ecchymoses on her lower limbs, which gradually spread to her trunk and face. Administration of atorvastatin was halted, but over the next 3 days she felt increasingly weak, eventually falling while walking at home. There was no overt bleeding, fever, change in urine color or mental status, and the extent of the purpura was unchanged. Laboratory tests performed on admission revealed a platelet count of 1,000/μl, hemoglobin level 5.1 g/dl and a normal white blood cell count. Blood smear and normal range levels of bilirubin, haptoglobin and lactate-dehydrogenase excluded microangiopathic hemolytic anemia. Prothrombin time, partial thromboplastin time and C3 levels were within the normal range, and a direct Coombs test was negative. Computed tomography of the abdomen and pelvis demonstrated no pathological findings except for a hip fracture. Treatment was initiated with intravenous steroids, blood and platelet transfusions. Platelet count reached normal levels after 2 days of therapy, and the patient underwent a

successful surgery for the hip fracture. Over the next months, her blood indices remained stable.

The temporal relation between the initiation of therapy with the generic form of atorvastatin and the onset of purpura, along with exclusion of other etiologies, suggest a cause-and-effect relationship. Unlike earlier documented cases of atorvastatin-induced thrombocytopenia, the current event did not meet the criteria for TTP, and prior administration of simvastatin was not associated with similar adverse reactions. Therefore, it is conceivable that the development of severe thrombocytopenia was not related to the active ingredient but to other ingredient(s) of the generic form of the drug. The use of generic forms of drugs has spread worldwide in recent years. Physicians as well as health organizations should be alerted to report novel adverse effects and to strive to incorporate them in current guidelines for treatment [4].

**A. Gurevich BMedSc MPhil[1], L. Epstein BMedSc[1], S. Fuchs MD[1,2] and G.Y. Stein MD PhD[1,2]**

[1]Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, and [2]Dept. Of Internal Medicine B, Rabin Medical Center (Beilinson Campus), Petah Tikva, Israel [gidi.stein@gmail.com2]

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## Capsule

### NLRP3 is activated in Alzheimer's disease and contributes to pathology in APP/PS1 mice

Alzheimer's disease is the world's most common dementing illness. Deposition of amyloid-β peptide drives cerebral neuroinflammation by activating microglia. Indeed, amyloid-β activation of the NLRP3 inflammasome in microglia is fundamental for interleukin-1β maturation and subsequent inflammatory events. However, it remains unknown whether NLRP3 activation contributes to Alzheimer's disease in vivo. Heneka et al. demonstrate strongly enhanced active caspase-1 expression in human mild cognitive impairment and brains with Alzheimer's disease, suggesting a role for the inflammasome in this neurodegenerative disease. Nlrp3−/− or Casp1−/− mice carrying mutations associated with familial Alzheimer's disease were largely protected from loss of spatial memory and other sequelae associated with Alzheimer's disease, and demonstrated reduced brain caspase-1 and interleukin-1β activation as well as enhanced amyloid-β clearance. Furthermore, NLRP3 inflammasome deficiency skewed microglial cells to an M2 phenotype and resulted in the decreased deposition of amyloid-β in the APP/PS1 model of Alzheimer's disease. These results show an important role for the NLRP3/caspase-1 axis in the pathogenesis of Alzheimer's disease, and suggest that NLRP3 inflammasome inhibition represents a new therapeutic intervention for the disease.

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Eitan Israeli

## Capsule

### Mammalian heart renewal by pre-existing cardiomyocytes

Although recent studies have revealed that heart cells are generated in adult mammals, the frequency of generation and the source of new heart cells are not yet known. Some studies suggest a high rate of stem cell activity with differentiation of progenitors to cardiomyocytes. Other studies suggest that new cardiomyocytes are born at a very low rate, and that they may be derived from the division of pre-existing cardiomyocytes. Senyo et al. show, by combining two different pulse-chase approaches – genetic fate-mapping with stable isotope labeling, and multi-isotope imaging mass spectrometry M – that the genesis of cardiomyocytes occurs at a low rate by the division of pre-existing cardiomyocytes during normal aging, a process that increases adjacent to areas of myocardial injury. The authors found that cell cycle activity during normal aging and after injury led to polyploidy and multinucleation, but also to new diploid, mononucleate cardiomyocytes. These data reveal pre-existing cardiomyocytes as the dominant source of cardiomyocyte replacement in normal mammalian myocardial homeostasis as well as after myocardial injury.

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Eitan Israeli

**"A fanatic is one who can't change his mind and won't change the subject"**

Winston Churchill (1874-1965), British politician, best known for his leadership of the United Kingdom during the Second World War