

## Toho Journal of Medicine Vol. 4 No. 2 掲載論文の紹介

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### *Biological and Clinicopathological Features of Pulmonary Large-cell Neuroendocrine Carcinoma-A New Era of Research*

Iyoda A

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**要約 :**

Large-cell neuroendocrine carcinoma (LCNEC) of the lung, categorized as a lung neuroendocrine tumor, shows clinicopathological features similar to those of small-cell lung carcinoma (SCLC), although there are some differences between them. As patients with LCNEC have a very poor prognosis, and surgery alone does not provide a cure for it, a new treatment strategy including adjuvant chemotherapy after surgery is needed. Several studies have compared the biological behaviors of LCNEC and SCLC, which, in addition to their clinicopathological features, are very similar. Recently, the biological features of LCNEC related to molecular targeted therapies have been investigated, and new treatment strategies, such as mTOR (mammalian target of rapamycin) inhibitors, have been proposed for patients with LCNEC. Here, I discuss the current biological and clinicopathological features of LCNEC and introduce recent new research on it. LCNEC was reclassified from a variant of large-cell carcinoma to a neuroendocrine tumor. Consequently, the focus of studies on LCNEC switched from clinicopathological features to molecular targeted therapies, and research on LCNEC entered a new era. Further studies are needed to improve the prognoses of patients with LCNEC.

**KEYWORDS: large-cell neuroendocrine carcinoma, lung, surgery, adjuvant chemotherapy, profiling**

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### Concept, Assessment, and Management of Disease Activity in Rheumatoid Arthritis

Kameda H

Toho J Med 4 (2): 43—48, 2018

**要約 :**

As a concept, disease activity should be time-differentiated organ damage, and high disease activity should be associated with the high-speed progression of organ damage, mainly joint destruction in rheumatoid arthritis. This concept has been validated by the retrospective analyses of joint destruction during given periods: time-integrated disease activity correlated well with joint destruction. A mathematical description of disease activity as time-differentiated organ damage indicated a new concept, “negative activity,” which means the improvement of organ damage, and it should be clearly distinguished from “zero activity,” which means neither worsening nor improvement of organ damage. However, current composite activity measures do not distinguish “negative activity” from “zero activity,” and the correlation of the time-integrated disease activity score to joint destruction during a given period is considerably insufficient. A formula with the modification of Newton’s motion equation indicated the difference between synthetic compounds and biological agents in the importance of patient “capacity.” Thus, the primary objective of the serum trough monitoring of biological agents is to avoid the lack of effectiveness due to underdosing, whereas that of synthetic compounds is to avoid dose-dependent adverse events due to overdosing.

**KEYWORDS: activity, damage, joint destruction, rheumatoid arthritis**

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### Effect of Phosphodiesterase-3 Inhibition on Experimental Autoimmune Neuritis

Hagiwara W, Konno S, Kihara H, Inoue M, Fujioka T

Toho J Med 4 (2): 49—57, 2018

**要約 :**

**Background:** The phosphodiesterase-3 inhibitor cilostazol (CLZ) is widely prescribed as an antiplatelet agent in treatment for peripheral arterial disease. The immune modulating effect of CLZ has been unveiled in experimental autoimmune encephalomyelitis, the animal model for human multiple sclerosis; however, the effect of CLZ on immune-mediated peripheral nerve disease is unclear.

**Methods:** Female Lewis rats were immunized with synthetic peptide from bovine P2 protein to induce experimental autoimmune neuritis (EAN). Ten or 30 mg/kg/day of CLZ was administered daily from 1 day post immunization (dpi) or after onset of paralysis. Immunohistochemistry and real-time PCR were studied on sequentially removed cauda equina (CE).

**Results:** Motor paralysis developed at 11 dpi in all rats; however, subsequent paralysis was suppressed by 30 mg/kg/day of CLZ. CLZ administered after onset of paralysis suppressed motor disturbance compared with sham-treated EAN rats. Improvement of motor function roughly correlated with shrinkage of demyelination foci and inflammatory cell accumulation. Real-time PCR analysis for proinflammatory cytokine interferon (IFN)-gamma, anti-inflammatory cytokine interleukin (IL)-10, or cell adhesion molecule E-selectin (E-sel) mRNA expression revealed an upregulation of IL-10 message before motor paralysis onset and suppression of IFN and E-sel messages at the paralysis onset phase.

**Conclusions:** CLZ treatment ameliorates EAN via IL-10 upregulation with reciprocal suppression of IFN and E-sel expression in peripheral nervous system.

**KEYWORDS:** experimental autoimmune neuritis, phosphodiesterase-3 inhibitor, interferon-gamma, interleukin-10, E-selectin

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### Cost of Illness of the Obstetrical Diseases in Japan: a Time-trend and Future Projection Analysis

Hayata E, Matsumoto K, Kitazawa T, Seto K, Morita M, Hasegawa T

Toho J Med 4 (2): 58—65, 2018

**要約 :**

**Background:** Many problems associated with pregnancy and childbirth are associated with public health policies and require the attention of society as a whole. We chronologically observed the social costs for obstetrical diseases to obtain an overview of the changes and determine future prospects.

**Methods:** Using the cost-of-illness (COI) method based on official government statistics, we calculated COI for obstetrical diseases (ICD10 Code: O01-99) from 1996 to 2014 and estimated future COI projections, that is, for the period from 2017 to 2029. COI includes both direct and indirect costs (morbidity and mortality costs).

**Results:** COI increased by 28.5% between 1996 and 2014 mainly because of increased direct costs during this period. COI of a single birth increased by 54.5% between 1996 and 2014. Our future predictions included an estimation of changes in the constant trends of COI, assuming that current trends of health-related indices would persist (estimated COI in 2029: 250.6-307.0 billion yen, depending on the model used). COI per birth was estimated to increase until 2029 and (331,000-407,000 yen, depending on the model used).

**Conclusions:** We estimated that COI would remain unchanged in the future, provided current trends of health indices remain constant. Although the number of birth would reduce, the economic burden pertaining to each pregnancy and delivery would increase. Accelerated social participation of women and the promotion of measures to prevent the declining birth rate may lead to future increases in COI.

**KEYWORDS:** cost of illness, perinatal disease, health economics, health policy

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### Thymidine Phosphorylase Expression in Gastric Cancer Tissues is Associated with Thrombocytosis but not with Serum Thymidine Phosphorylase Concentration

Kikuchi Y, Ito M, Nemoto T, Yajima S, Shiozawa K, Suzuki T, Ooshima Y, Nanami T, Watanabe M, Igarashi Y, Shimada H  
Toho J Med 4 (2): 66—73, 2018

**要約 :**

**Background:** The relationship of thymidine phosphorylase (TP) expression and patient outcomes has been investigated in various cancers. This study investigated the association of TP expression, serum TP, and platelet counts in patients with gastric cancer.

**Methods:** A series of 77 patients with gastric adenocarcinoma were enrolled in the study. Pretreatment serum TP was determined by enzyme-linked immunosorbent assay and the patient characteristics, including platelet count, gender, age, tumor stage and histological grade, and immunoreactivity of surgically resected tissue specimens, were recorded.

**Results:** The serum TP level was significantly higher in poorly differentiated and signet ring cell adenocarcinomas than in more differentiated types. TP expression was observed within well- and moderately differentiated adenocarcinoma cancer cells, but was significantly weaker in poorly differentiated adenocarcinomas and signet ring cell carcinomas. There were no significant differences in the survival of patients with different histological types and serum TP levels. Although the differences were not statistically significant, high TP expression and high platelet counts were poor prognostic factors. TP expression was not correlated with serum TP levels, but was slightly correlated with the platelet count.

**Conclusions:** TP expression in gastric cancer tissue was slightly related to the platelet count rather than to the serum TP concentration. Therefore, a larger number of patients should be evaluated to assess the relationship between platelet count and capecitabine treatment response in gastric cancer patients.

**KEYWORDS:** gastric cancer, thymidine phosphorylase, ELISA, immunohistochemistry, platelet count

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Effect of 7-ketocholesterol on Hyaluronic Acid Synthase 2 in Human Aortic Smooth Muscle Cells  
Nagumo-Yoshikawa A, Ishihara N, Watanabe F, Shirai K, Tatsuno I  
Toho J Med 4 (2): 74—80, 2018

**要約 :**

**Background:** Hyaluronic acid (HA) is a component of the soft extracellular matrix in the arterial wall, and is involved in the elasticity of the arterial wall; however, its regulation and role in the progression of atherosclerosis remain unclear. We investigated the effects of 7-ketocholesterol (7KCHO), an oxysterol found in the atheromatous lesion, on the synthesis of HA in the cultured human smooth muscle cells (SMCs).

**Methods:** The cell count was done using a hemocytometer. Messenger ribonucleic acid (mRNA) and protein “hyaluronic acid synthase 2 (HAS2)” was measured by real-time reverse transcription polymerase chain reaction (RT-PCR) and Western blot, respectively. Production of the intracellular reactive oxygen species (ROS) was measured by fluorescence-activated cell sorting.

**Results:** Treatment with 7KCHO increased ROS and decreased HA production in SMCs. N-acetyl cysteine, an antioxidative compound, restored the 7KCHO-induced decrease in the HA production. No changes were observed in the mRNA and protein expression of HAS2 by 7KCHO treatment.

**Conclusions:** These results suggest that HA production is decreased by 7KCHO treatment through stimulation of ROS. The 7KCHO-induced decrease of HA production may be involved in the loss of elasticity and the enhancement of arterial stiffness.

**KEYWORDS:** hyaluronic acid, smooth muscle cell, 7-ketocholesterol, reactive oxygen species

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