

**Tufts University, Medford, Massachusetts**

**Bio 195: Treatments Therapies and Cures - are we treating an organ or a human being?  
(Pharmacology of Multiorgan Diseases)**

- Instructor:** Theoharis C. Theoharides, B.S., M.S., M.Phil., Ph.D., M.D. (Yale University) Professor of Pharmacology, Internal Medicine and Biochemistry; Associate Professor of Psychiatry, Tufts University School of Medicine, Boston, MA  
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or [www.mastcellmaster.com](http://www.mastcellmaster.com)
- Offering:** Fall 2008, Weekly sessions, Mondays 4-6:00 PM, Barnum 113.
- Description:** This course will present key topics and drug families covered in the regular medical pharmacology course in a condensed, hopefully humorous, but intellectually stimulating way. The emphasis will be on processes rather than on individual drugs, especially those that could lead to inflammation in different organs and their treatment. During the course, there will be opportunity to address clinical trial design, the placebo effect and medical ethics.
- Content:** Examples of diseases to be discussed include autism and attention-deficit hyperactivity disorder, psychosis, psychogenic asthma, unstable angina in the heart, irritable bowel syndrome in the intestines, interstitial cystitis of the urinary bladder, infections and vaccines, as well as alternative approaches and dietary supplements.
- Reading:** Basic readings will be from: Theoharides T.C. (ed.) Essentials of Pharmacology 2<sup>nd</sup> ed., Little, Brown & Co.: Boston, 1996. The two key chapters (2 & 6) and all handouts will be available on Blackboard and will be handed out in class.
- Prerequisite:** Cell Biology (Bio 46) or its equivalent, or by permission.
- Class Size:** 15
- Advantages:** Introduction to principles of pharmacology in a friendly way, discussion of how drugs affect most organs of the body, how stress worsens many inflammatory conditions that affect multiple organs, practical and ethical consideration of clinical trials, as well as exposure to current research and opportunities for independent research.
- Evaluation:** The mid-term will be the first draft of one (15 – 20 page) paper due at the end of the course on a topic discussed in class. The mid-term draft will be reviewed and discussed in order to help with the writing of the final paper, along the lines of scientific papers; select papers may be submitted for publication. Final grade = 50:50 (class participation:final paper).

## Sessions

## Topics and readings in chronological order

### Session #1:

#### 09/10/07 Introduction-course overview-scientific discovery.

- Theoharides, T.C. Sudden death of a healthy college student related to ephedrine toxicity from a Ma huang containing drink. *J. Clin. Psychopharmacol.* 17:437-439, 1997.
- Lyckholm, L.J. Should physicians accept gifts from patients? *JAMA* 280:1942-1946, 1998.
- Burnett, J.C. Jr. Biomedical research at Mayo Clinic: A tradition of collaboration and a version for year 2000 and beyond. *Mayo Clin Proc* 75:337-339, 2000.
- Miller, E. clinical investigators – the endangered species revisited. *JAMA* 286: 845-846, 2001.
- De Smet, P.A. Herbal remedies. *N. Engl. Med. J.* 347:2046-2056, 2002.
- Marcus, D.M. and Grollman, A.P. Botanical medicines - the need for new regulations. *N. Engl. Med. J.* 347:2073-2076, 2002.
- Gordon, L.E. Mental health of medical students: the culture of objectivity in medicine. *The Pharos* 59:2-10, 1996.
- Crowley, W.F. Jr., et al. Clinical research in the United States at a crossroads. Proposal for a novel public-private partnership to establish a national clinical research enterprise. *JAMA* 291:1120-1126, 2004.
- Schwartz, R. S. Paul Ehrlich's magic bullets. *N. Engl. J. Med.* 350:1079-1080, 2004.
- Markel, H. "Who's on first?" – medical discoveries and scientific priority. *N. Engl. J. Med.* 351:2792-2794, 2004.
- Tinetti, M.E. et al. Potential pitfalls of disease-specific guidelines for patients with multiple conditions. *N. Engl. J. Med.* 351:2870-2874, 2004.
- Kintishch, E. Researcher faces prison for fraud in NIH grant applications and papers. *Science* 307:1851, 2005

### Session #2:

#### 09/17/07 "Clinical practice and research" - Conflict of interest, patient-physician-pharmaceutical industry relations

- Moreno, J. Updating protections for human subjects involved in research. *JAMA* 280:1951-1958, 1998.
- Hrobjartsson, A., Gotzsche, C. Is the placebo powerless? An analysis of clinical trials comparing placebo with no treatment. *N. Engl. J. Med.*, 344: 1594 – 1602, 2001.
- Bailar, J.C. the powerful placebo and the wizard of Oz. *N. Engl. J. Med.*, 344: 1630 - 1632, 2001.
- Brennan, T. Luxury primary care – market innovation or threat to access? *N. Engl. J. Med.*, 346: 1165 - 1168, 2002.
- Steinbrook, R. Trial design and patient safety – the debate continues. *N. Engl. J. Med.* 349:629-630, 2003.
- Blumeathal, D. Academic-industrial relationships in the life sciences - *N. Engl. J. Med.* 349:2452-2459, 2003.
- Kennedy, D. Clinical trials and public trust. *Science* 306:1649, 2004.

- Rosenow, E. C. III. Patient's understanding of and compliance with medications: The sixth vital sign? *Mayo Clin Proc* 80:983-987, 2005.
- Makaryus, A.N. and Friedman, E.A. Patients' understanding of their treatment plans and diagnosis at discharge. *Mayo Clin Proc* 80:991-994, 2005
- Lerner, B.H. Subjects or objects? Prisoners and human experimentation. *N. Engl. J. Med.*, 356: 1806 - 1807, 2007.

**Session #3:**

**09/24/07 "Fantastic voyage"— nerves, muscles, glands and fluids**

Overview of the sympathetic and parasympathetic divisions of the autonomic nervous system, receptor types, distribution of receptors and pathophysiological effects at the neuromuscular and neurosecretory levels that could be used as drug targets or are involved in autoimmune diseases. Regulation of the hypothalamic-pituitary-adrenal axis will also be discussed, along with the actions of corticotropin-releasing hormone (CRH) outside the brain.

Main reading: Chapter 2 (recommended – on Blackboard)

- Chrousos, G.P. The hypothalamic-pituitary-adrenal axis immune-mediated inflammation. *N. Engl. J. Med.* 332: 1351-1362, 1995.
- Karalis, K., Sano, H., Redwine, J., Listwak, S., Wilder, R.L., Chrousos, G.P. Autocrine or paracrine inflammatory actions of corticotropin-releasing hormone *in vivo*. *Science* 254:421-423, 1991.
- Theoharides, T.C. Singh, L.K., Boucher, W., Pang, X., Letoumeau, R., Webster, E., Chrousos, G.P. Corticotropin-releasing hormone induces skin mast cell degranulation and increased vascular permeability, a possible explanation for its pro-inflammatory effects. *Endocrinology* 139:403-413, 1998.
- Theoharides, T.C. Mast cells and stress. A psychoneuroimmunological perspective. *J. Clin. Psychopharmacol.* 22:103-108, 2002.

**Session #4:**

**10/01/07 "Creativity and madness" - brain function and mental illness**

Overview of the central nervous system (CNS) and the neurotransmitters/receptors involved in the main psychiatric diseases. Emphasis will be placed on our knowledge of excitatory systems and the pathways involved in creative thinking and processing. There will be considerable discussion on the possible association between creativity and certain types of mental illness. Abuse of licit and illicit CNS stimulants (amphetamines, cocaine, ephedrine, pseudoephedrine, dextromethorphan) will also be discussed.

Main reading: Chapter 3 (optional)

- Sandblom, P. Creativity and disease: how illness affects literature, art and music. G.F. StrickleyCo.: Philadelphia, 1982.
- Arnheim, R. The artistry of psychotics. *Am. Scientist* 74:48-54, 1986.
- Konner, M. The many faces of madness. *Sciences* July/Aug: 6-8, 1987.
- Restak, R. Brain by design. *The Sciences* 33:27-33, 1993.
- Jamison, K.R. Manic-depressive illness and creativity. *Sci. Am.* 273:62-67, 1995.
- Lenhoff H. M., Wang, P.P., Greenberg, F., Bellugi, U. Williams Syndrome and the brain. *Sc. Am.* 277:68-73, 1997.
- Bennett, D. Against types. *The Boston Globe* Sept. 19: D4, 2004.
- Gardner, H. The mismeasure of man. *The Boston Globe* Sept. 19: D6, 2004.
- Beckman, M. Crime, culpability and the adolescent brain. *Science* 305:596-599, 2004.
- Lambert, C. Sonatas from syndromes. *Harvard Magazine* 108: 13-15, 2005.

**Session #5: (Columbus Classes are to be held on Tuesday, 10/09/07)**

**10/08/07 "Enemies of the state" - inflammation and auto-immunity**

Introduction to the class of molecules collectively called autacoids, especially cytokines, that are responsible for the inflammatory cascade. There will be discussion on how their inappropriate secretion can lead to autoimmune diseases, such as rheumatoid arthritis. Natural substances that may regulate these processes, including chondroitin sulfate and flavonoids, will be reviewed.

Main reading: Chapter 6 (recommended – on Blackboard)

- DiNarello, C.A. The role of the interleukin-1-receptor antagonist in blocking inflammation mediated by interleukin-1. *N. Engl. J. Med.* 343:732-734, 2000.
- Middleton, E., Jr., Kandaswami, C., Theoharides, T.C. The effects of plant flavonoids on mammalian cells: Implications for inflammation, heart disease and cancer. *Pharmacol Rev.* 52:673:751, 2000.
- Theoharides T.C. and Cochrane D.E. Critical role of mast cells in inflammatory diseases and the effect of acute stress. *J Neuroimmunol*, 146:1-12, 2004.
- Theoharides, T. et al. Differential release of mast cell mediators and the pathogenesis of inflammation. *Immunul. Rev.* 217:65-78, 2007.

**Session #6:**

**10/15/07 "Sprains, strains and pains" - how and why it hurts**

The basic elements of the physiology of pain will be addressed using such conditions as arthritis, cancer and headaches. Emphasis will be placed on the effect of emotional stress on neuropeptide release and neurogenic inflammation, as well as on the use of dietary supplements to reduce symptoms.

Main reading: Chapter 7 (optional)

- Crofford, L.J. Rational use of analgesic and antiinflammatory drugs. *N. Engl. J. Med.* 345:1844-1845, 2001.
- Fored, C.M., Ejerblad, E., Lindblad, P.Fryzek, J.P., Dickman, P.W., Signorello, L.B., Lipworth, L., Elinder, C., Blot, W.J., McLaughlin, J.K., Zack, M.M., Nyren, O. Acetaminophen, aspirin, and chronic renal failure. *N. Engl. J. Med.* 345:1801-1808, 2001.
- Goadsby, P.J., Lipton, R.B., Ferrari, M.D. Migraine - current understanding and treatment. *N. Engl. J. Med.* 346:257-270, 2002.
- Levin, M. The many causes of headache. *Postgrad. Med.* 112:67-82, 2002.
- Topol, E.J. Failing the public health – rofecoxib, Merck, and the FDA. *N. Engl. J. Med.* 351:1707-1709, 2004.
- FitzGerald, G.A. Coxibs and cardiovascular disease. *N. Engl. J. Med.* 351:1709-1711, 2004.
- Drazen, J.M. COX-2 inhibitors – a lesson in unexpected problems. *N. Engl. J. Med.* 352:1131-1132, 2005.
- Psaty, B.M., Furberg, C.D. COX-2 inhibitors – lessons in drug safety. *N. Engl. J. Med.* 352:1133-1135, 2005.

**Session #7:**

**10/22/07 "Breaths of fresh air" - the challenge of asthma**

The physiology of asthma will be presented, especially with respect to its epidemic status in spite of the fact that better sanitary conditions, air conditioners, more potent antibiotics and specific bronchodilatory drugs are available. The effect of stress will be explored as most of asthma cases do not have an allergic basis, but are considered "intrinsic" or "psychogenic" in nature. Possible novel interventions will be highlighted.

Main reading: Chapter 6 (optional)

- Bach, J.F. Mechanisms of disease: the effect of infections on susceptibility to autoimmune and allergic diseases. *N. Engl. J. Med.* 347:911-920, 2002.
- Lim, K.G. Management of persistent symptoms in patients with asthma. *Mayo Clin. Proc.* 77:1333-1339, 2002.
- Weiss, S.T. Eat dirt-the hygiene hypothesis and allergic diseases. *N. Engl. J. Med.* 344:930-931, 2002.
- Smit, J.J. et al. Ramp-ing up allergies. *Trends in Immunol.* 25: 342-347, 2004.

#### Session #8:

##### 10/29/07 "How to write a scientific paper"

Style, references, journals, impact factor, multiple authors, repetitive results.

11/05/07 Dr. TCT will be away and 11/12/07 Veterans' Day Observed

#### Session #9:

##### 11/19/07 "When too much of a good thing can kill you" - cancer

The ability of tissues to regenerate, such as the skin, is wonderful and there is considerable discussion presently about harvesting fetal or stem cells for possible tissue engineering for damaged organs. The mutation and tissue organization theories of cancer will be reviewed and ways the tumor escapes surveillance, increases its vascular supply or metastasizes will be discussed as potential targets for therapy.

Main reading: Chapter 10 (optional)

- Lichtenstein, P., Holm, N.V., Verkasalo, P.K., Iliadou, A., Kaprio, J., Koskenvuo, M., Pukkala, E., Skytthe, A., Hemminki, K. Environmental and heritable factors in the causation of cancer--analyses of cohorts of twins from Sweden, Denmark, and Finland. *N Engl J Med.* 343:78-85, 2000.
- Ahlgren, M., Melbye, M., Wohlfahrt, J., Sorensen, T.I. Growth patterns and the risk of breast cancer in women. *N Engl J Med.* 351:1619-26, 2004.
- Chodosh, L.A. The reciprocal dance between cancer and development. *N Engl J Med.* 347:134-6, 2002.
- Hamilton, A.S., Mack, T.M. Puberty and genetic susceptibility to breast cancer in a case-control study in twins. *N Engl J Med.* 348:2313-22, 2003.
- Theoharides, T.C. and Konstantinidou, A. Antidepressants and cancer: a case of misguided associations and priorities? *J. Clin. Psychopharmacol.* 13:1-4, 2003.
- Theoharides, T.C. and Conti, P. Mast cells-the Jekyll and Hyde of cancer growth. *Trends Immunol.* 25:235-41, 2004
- Michels, K.B., Willett, W.C. Breast cancer--early life matters. *N Engl J Med.* 351:1679-81, 2004.
- Pollard, J.W. Tumour-educated macrophages promote tumor progression and metastasis. *Nature Reviews* 4:71:78, 2004.

#### Session # 10:

##### 11/26/07 "Heart and vessel squeeze" - cardiovascular disease

One of the major health concerns of the industrialized world is cardiovascular disease. However, the old "plumbing" theory of arteries clogged by cholesterol deposits has been superseded by the concept of coronary inflammation and the predictive value of the inflammatory markers C-reactive protein (CRP) and interleukin-6 (IL-6). These findings will be discussed in light of the effect of acute stress on cardiovascular inflammation, especially in unstable angina.

Main reading: Chapter 4 (optional)

- Chester, A.H. Mast cells feel the strain. *Cardiov. Res.* 55:13-15, 2002.

- Huang, M. Pang, X., Letoumeau, R., Boucher, W., Theoharides, T.C. Acute stress induces cardiac mast cell activation and histamine release, effects that are increased in Apolipoprotein E knockout mice. *Cardiov. Res.* 55:150-160, 2002.
- Libby, P. Fire within-inflammation's link to heart attacks. *Atherosclerosis: The new view. Sci. Am.* 286:46-55, 2002.
- Taubes, G. Does inflammation cut to the heart of the matter? *Science* 296:242-245. 2002.

### Session #11:

#### 12/03/07 "Guts and runs"- Do they affect the brain?

Our gastrointestinal (GI) tract comprises the largest surface area of our body, larger than the skin. As such, it can be critical in the absorption or loss of fluid, and the uptake of nutrients. However, the gastrointestinal tract is also exposed to pathogens and food related antigens. Moreover, it is intimately connected to specialized areas of our brain with bidirectional input. The GI system and the bladder also constitute major ways to excrete unwanted substances, but they are also affected by them. Emphasis will be placed on the pathophysiology of irritable bowel syndrome interstitial cystitis.

Main reading: Chapter 12 (optional)

- Gershon, M.D. The enteric nervous system: a second brain. *Hospital Practice* 34:31-52, 1999.
- Mayer, L. Mucosal immunity. *Pediatrics* 111:1595-600, 2003.
- White, J.F. Intestinal pathophysiology in autism. *Exp. Biol. Med. (Maywood)* 228:639-49, 2003.
- St. Sauver, J.L. *et al.* Early life risk factors for attention-deficit/hyperactivity disorder: a population – based study. *Mayo Clin. Proc.* 79:1124-1131, 2004.
- Theoharides, T. Treatment approaches for painful bladder syndrome/interstitial cystitis. *Drugs* 67:215-235, 2007.

### Session #12:

#### 12/10/07 "Bugs, pumps and epidemics" - the origins of infections and antibiotics

The structure of the mammalian cell surface will be compared to that of microorganisms from the perspective of how the latter adhere and infect cells, while evading antibacterial agents. The different ways of antibiotic synthesis and selection will be reviewed, including serendipity, trial and error, chemical synthesis and molecular mimicry. Emphasis will be placed on antibiotic abuse and the emergence of multiple drug resistance, as in tuberculosis that has reemerged as a health challenge.

Main reading: Chapter 9 (optional)

- Dajer, T. Saint Vitus's dance. *Discover* 11:86-90, 1990.
- Heymann, L., Aylward, B. Eradicating polio. *N Engl J Med* 1275-1284, 2004.
- Jasmer, R.M., Nahid, P., Hopewell, P.C. Latent tuberculosis infection. *N. Engl. J. Med.* 342:1860-1866, 2002.
- Khan, K., Muennig, P., Behta, M., Zivin, J.G. Global drug-resistance patterns and the management of latent tuberculosis infection in immigrants to the United States. *N. Engl. J. Med.* 342:1850-1859, 2002.
- Editorial. Antibiotic abuse. *The Boston Globe* Aug.8: A10, 2005.

### Session #13:

#### 12/17/07 Student paper presentations