The Batumi Neuroscience Conference
"Function and dysfunction of the nervous system"

August 2-6, 2010
Batumi, Georgia

IMPACT OF IMMUNITY ON THE NEUROCRINE FUNCTION IN THE PATHOGENESIS OF SJOGREN'S SYNDROME

Presented by
Tamar Chachibaia
Georgian Sjogren Association

Mentor Dr. Edward R. Rapp

Study of Pathogenesis

"Evaluation of Salivary Gland Dysfunction"

is ongoing since 1984

Principal investigator

Prof Robert I Fox, MD, PhD

Rheumatology and Medicine Department, Scripps Memorial Hospital, California

Robert I. Fox, MD, PhD, PC, van der Ven PF, Sonies BC, Weiffenbach JM, Baum BJ.
Xerostomia: evaluation of a symptom with increasing significance. J Am Dent Assoc. 1985 Apr;110(4):519-25.

This study is currently recruiting participants

This study will evaluate patients with complaints of dry mouth to determine the cause and severity of their salivary gland dysfunction and their possible eligibility for other NIDCR protocols.

Sponsor: US National Institute of Dental and Craniofacial Research (NIDCR)

Granted by: US National Institute of Health

NIDCR proposed to create ‘International Research Registries for Sjogren's Syndrome’

The purpose of this initiative is:

- to establish uniformly accepted diagnostic criteria for primary and secondary Sjögren's syndrome that will be used by all countries for all research purposes including clinical research, diagnosis and treatment of patients with Sjögren's syndrome; and
- to establish one or more research registries for families with Sjögren's syndrome in the *United States, Europe, Asia and Pacific Ocean countries.*

BIOBANKS

What is the aim of Georgian primary Sjogren's syndrome registry onset?

Our project aims to create a biobank of 500 individuals with Primary Sjogren's syndrome in Georgia. A biobank is a database of clinical samples (in this case blood) with corresponding relevant clinical data. The ultimate aim of the project is to facilitate high quality clinical and academic research as well as clinical trials of Sjogren's syndrome.

Georgian Sjögren Association

PROJECT of BIOBANK REGISTRY
Principal Investigator

Tamar Z. Chachibaia

Scientific Medical Advisor

Please feel free to contact us

Tel: +(995) 90 290 552 **E-mail: nanogeorgia@hotmail.com**

Mobile: +(995)99 290 552

Georgian-German Oncological Clinic, Tbilisi, Georgia
Division of Head and Neck Tumors
Chair person
Prof. Konstantin Mardaleishvili, MD, PhD
Prof. Giorgi Loladze,
Craniofacial Surgeon
Head of Crio-Biobank

Faculty of Natural Sciences
Department of Biology
Immuno-Genetic Laboratory
Assocaited Professor Leila Akhvlediani

What is Sjogren's?

- Primary Sjogren's syndrome (pSS) refers to a particular type of systemic autoimmune rheumatic disease with the hallmark symptoms of *eye and mouth dryness (sicca syndrome).*
- Primary and Secondary Sjogren's syndrome are distributed with the ratio of 50/50.

Sjogren's Syndrome

Prevalence

Incidence

SS is generally regarded as the second most common rheumatic disorder with prevalence rate of 0.5-2%, exceeded in incidence only by rheumatoid arthritis.

Epidemiology of Sjogren's

1. Predominately affects women (female/male =9/1) with two ages of median onset in the 30's and 50's
2. Patients with Sjögren syndrome develop extraglandular symptoms in 40% of cases and are similar to those in patients with other rheumatic diseases, particularly *systemic lupus rythematosus*.

Ways Sjögren's syndrome affect the body

Neurological problems, concentration-memory (brain fog)

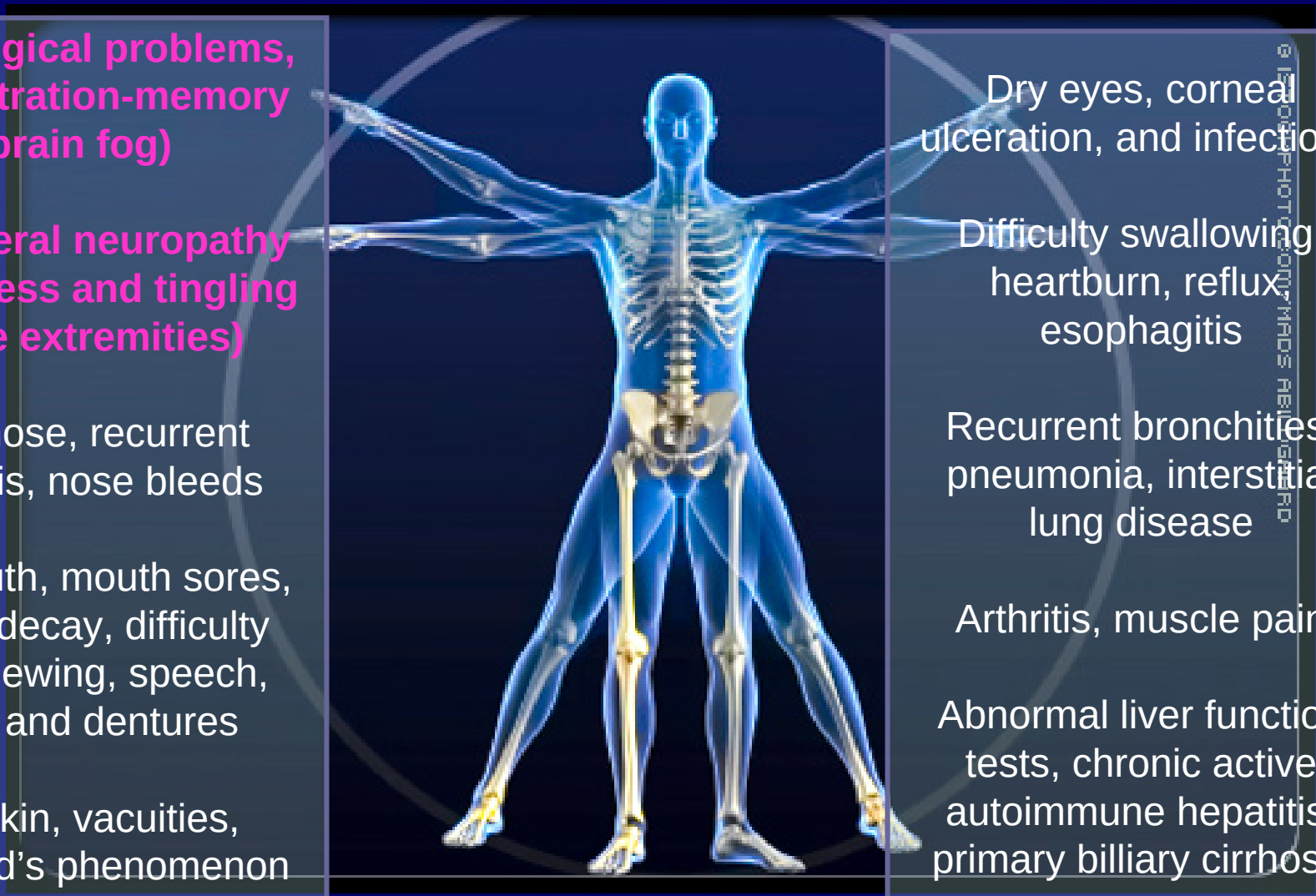
Peripheral neuropathy (numbness and tingling in the extremities)

Dry nose, recurrent sinusitis, nose bleeds

Dry mouth, mouth sores, dental decay, difficulty with chewing, speech, teste and dentures

Dry skin, vacuities, Raynaud's phenomenon

Stomach upset, gastroparesis, autoimmune pancreatitis



Dry eyes, corneal ulceration, and infections

Difficulty swallowing, heartburn, reflux esophagitis

Recurrent bronchities, pneumonia, interstitial lung disease

Arthritis, muscle pain

Abnormal liver function tests, chronic active autoimmune hepatitis, primary billiary cirrhosis

Vaginal dryness, painful intercourse

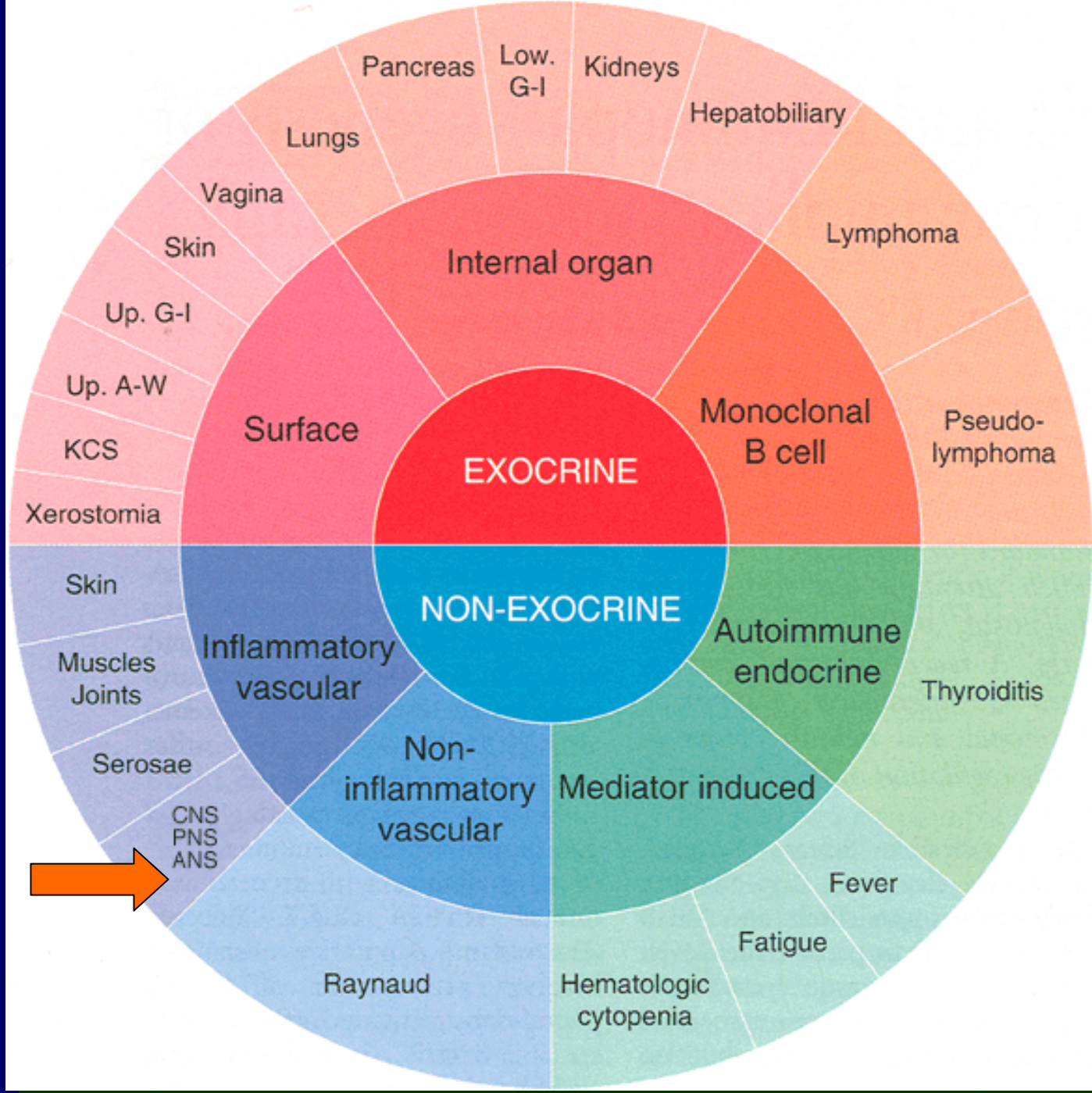
The Copenhagen wheel

The classification wheel for disease manifestations in primary Sjögren's syndrome.

Abbreviations:

KCS-keratoconjuctivitis sicca;
Up. A–W upper airways;
Up. G–I, upper gastrointestinal tract;
Low. G–I, lower gastrointestinal tract;
CNS, central nervous system;
PNS, peripheral nervous system;
ANS, autonomous nervous system.

Modified with permission.



Sjogren's provides a model to study the interaction of the immune system with the neural, exocrine, and endocrine systems.

New diagnostic criteria and treatment options have been developed that should diminish confusion in clinical practice and in the research literature.

- Leading neurological clinical complications are expressed by debilitating *fibromialgia*, due to acetylcholine receptor impairment; *chronic fatigue syndrome*, due to neurotransmitter deficiency; *peripheral and autonomous neuropathy, brain fog, depression and sleep disorders.*

Fatigue & Fibromyalgia

- **Fatigue** and **cognitive change** are major causes of disability in Sjogren's syndrome.
- These complaints are so dominant that they often make clinical trials in SS or SLE difficult to interpret.

The pathogenesis of SS includes multiple different steps that include:

1) effect of the immune system on the functional neuro-endrocrine circuit that links the afferent sensory nerves, central nervous system, efferent cholinergic nerves and glandular function;
2) changes in the glandular and vascular cells that mediate the migration of lymphocytes into the tissues and effects of cytokines on glandular function;
3) activation of lymphocytes within the gland to produce cytokines and autoantibodies;

Current status of predisposing genetic loci with emphasis on potential targets for future therapy.

Patients with Sjogren's

have residual glandular tissue,

but it does not function adequately (?!)

Pathogenesis of Sjogren's:

the major misunderstanding!

Sjogren's is characterized by dry eyes and dry mouth due to lymphocytic infiltrates in the glands.

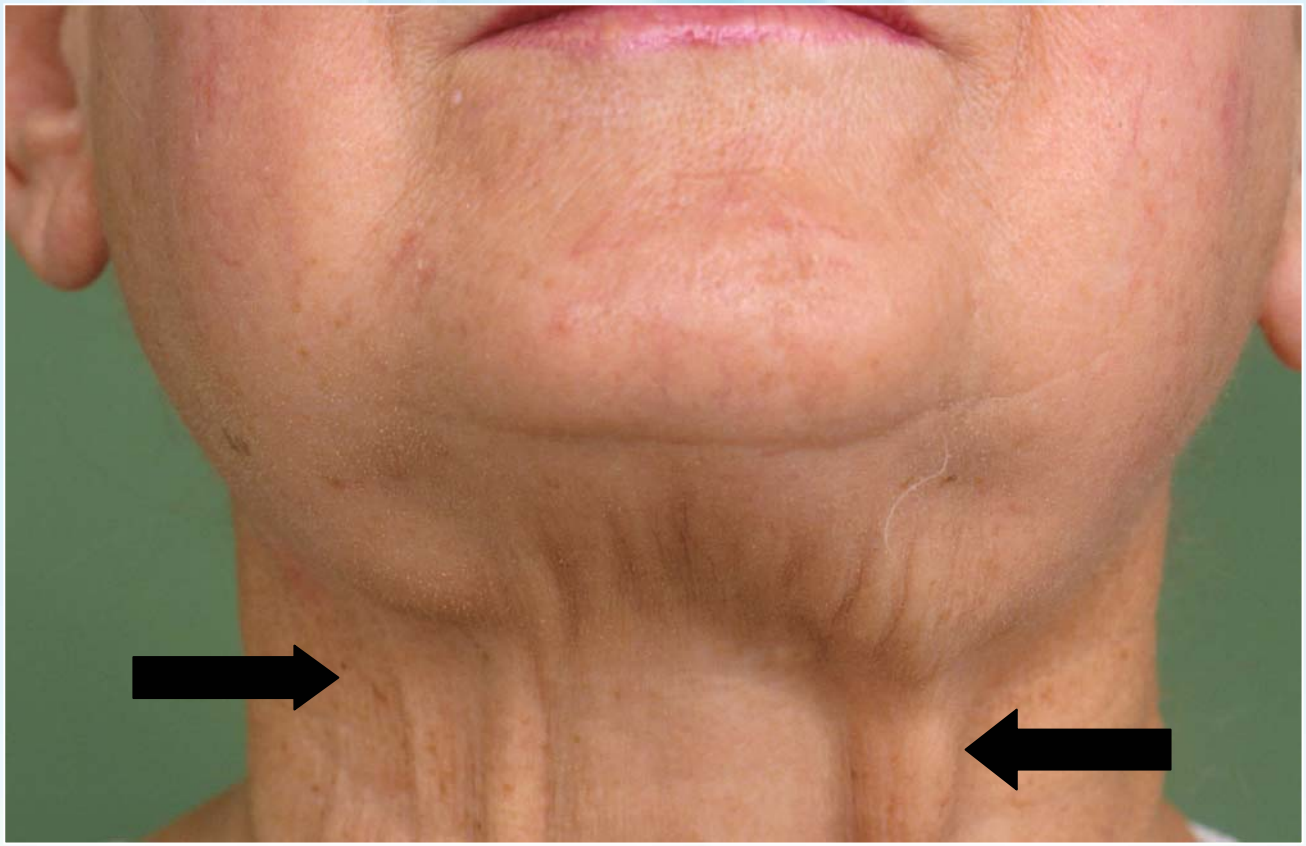
Actually salivary and lacrimal glands are not totally destroyed.

In fact, only 50% of the acini and ducts are destroyed.

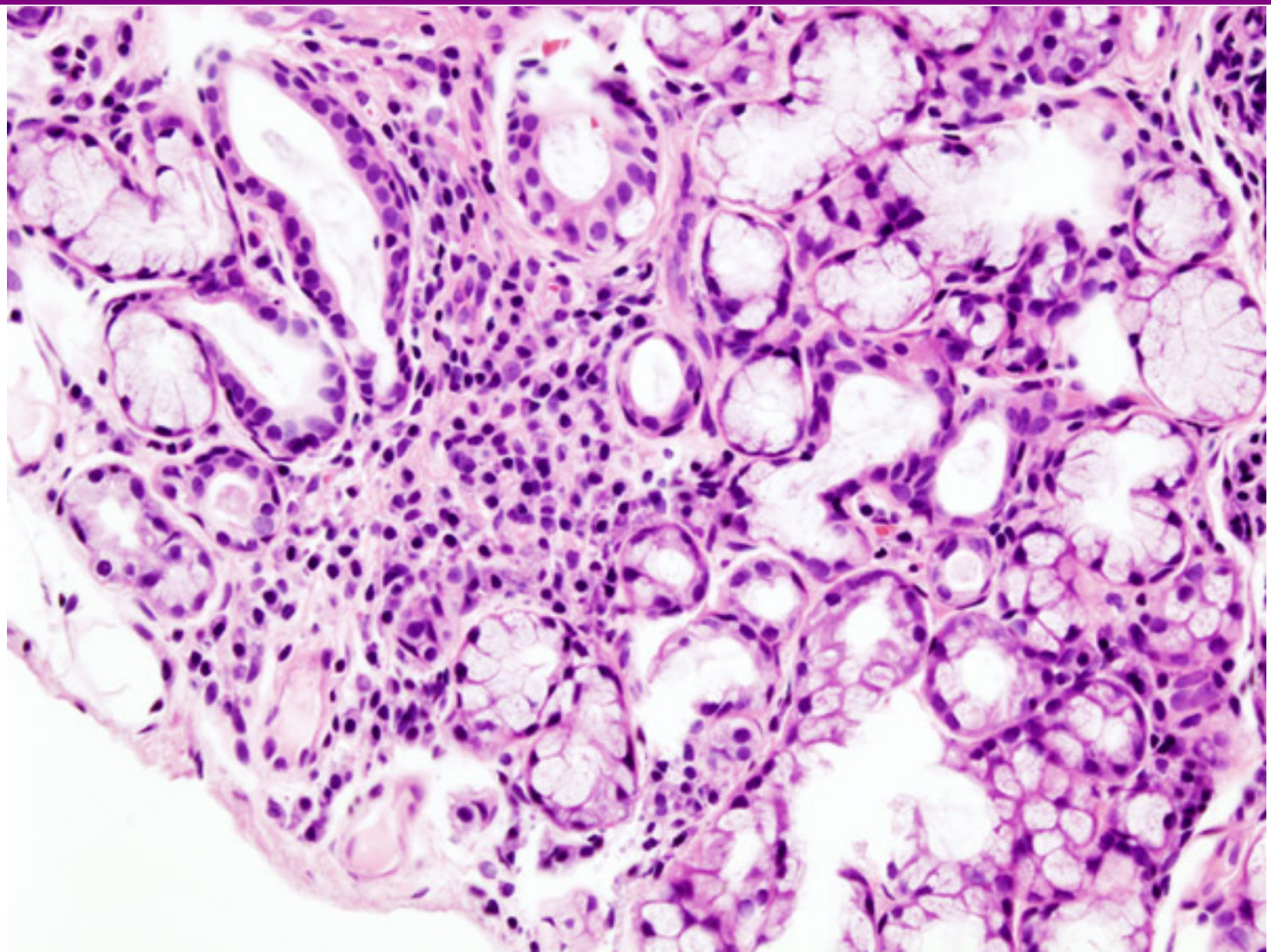
The residual glands are "paralyzed" by local release of cytokines and metalloproteinases.

Source retrieved courtesy Dr. Robert I. Fox: *Sjogren's Syndrome: New Approaches to Treatment, 2000.*

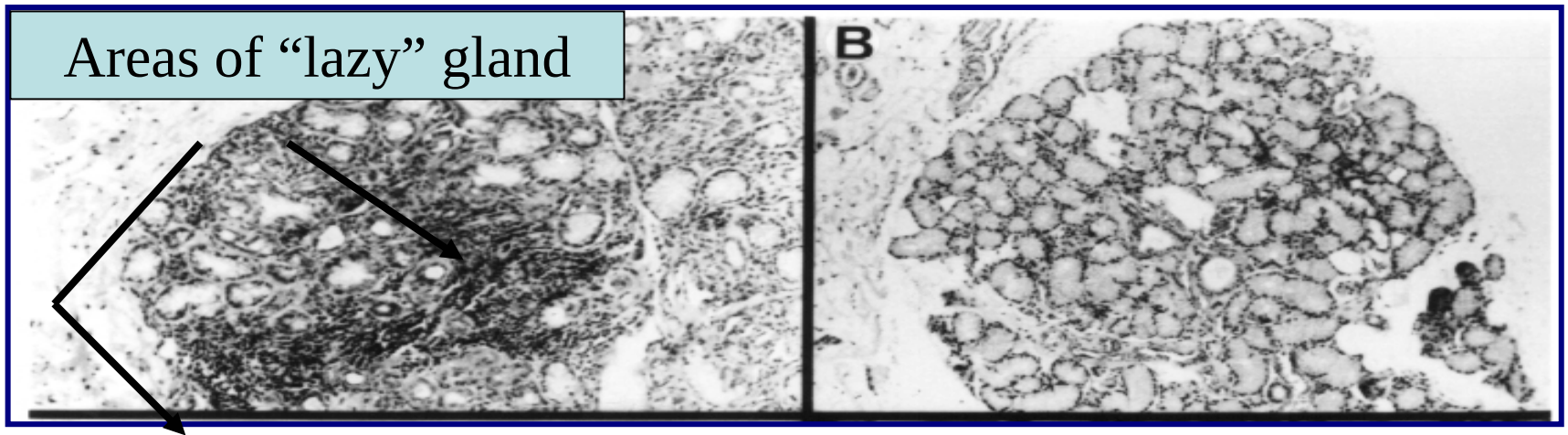
Typical features of Sjogren's Syndrome dry eyes, dry mouth and swollen glands; with swollen parotid gland - concern is infection or lymphoma.



T and B cells infiltration of Salivary Gland



In Sjogren's syndrome many acini and ducts are spared



Lymphocytic infiltrate

Sjogren's

Normal

Evaluation of the Role of the Autonomic Nervous System in Salivary Gland Dysfunction during Sjogren's Syndrome

- Researchers do not know the exact cause of SS, but they believe that it may be caused by abnormalities in the autonomic nervous system (ANS) that stimulate these glands.

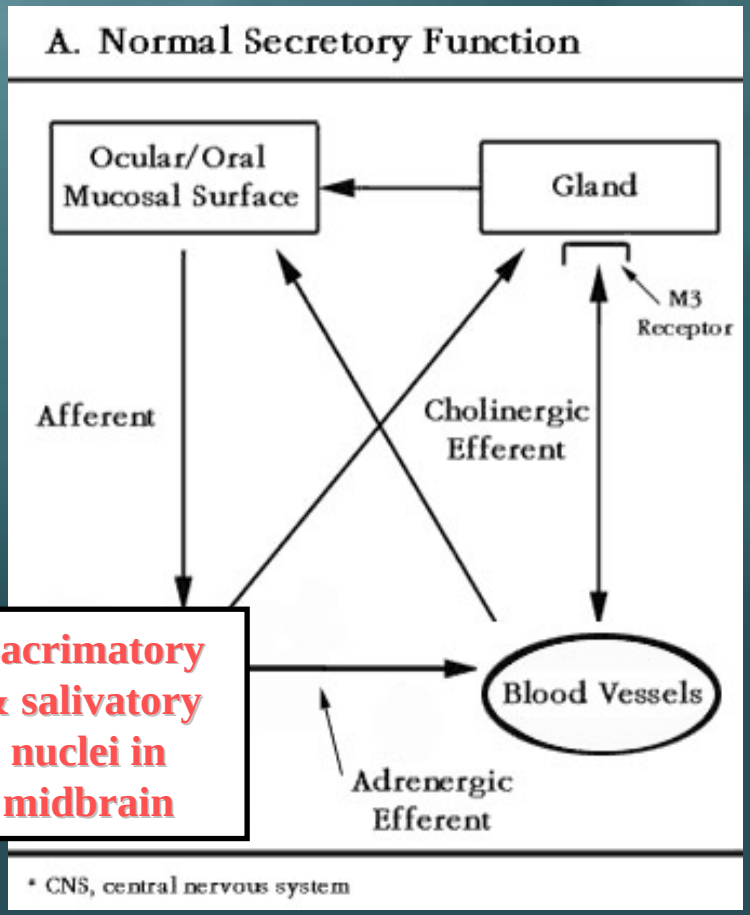
Underlying pathogenic glandular disfunction of SS

1) At least 20% of patients have no evidence of systemic autoimmunity; Animal models of SS develop glandular dysfunction long before they develop autoimmunity;
2) Discordance between severely affected function and abundance of histologically normal and ex vivo functional salivary glands;
3) Dryness and related symptoms respond poorly to immunosuppressives, including newer biologics, but fairly well to secretagogues such as *pilocarpine*;

Reasons for glandular dysfunction in Sjogren's

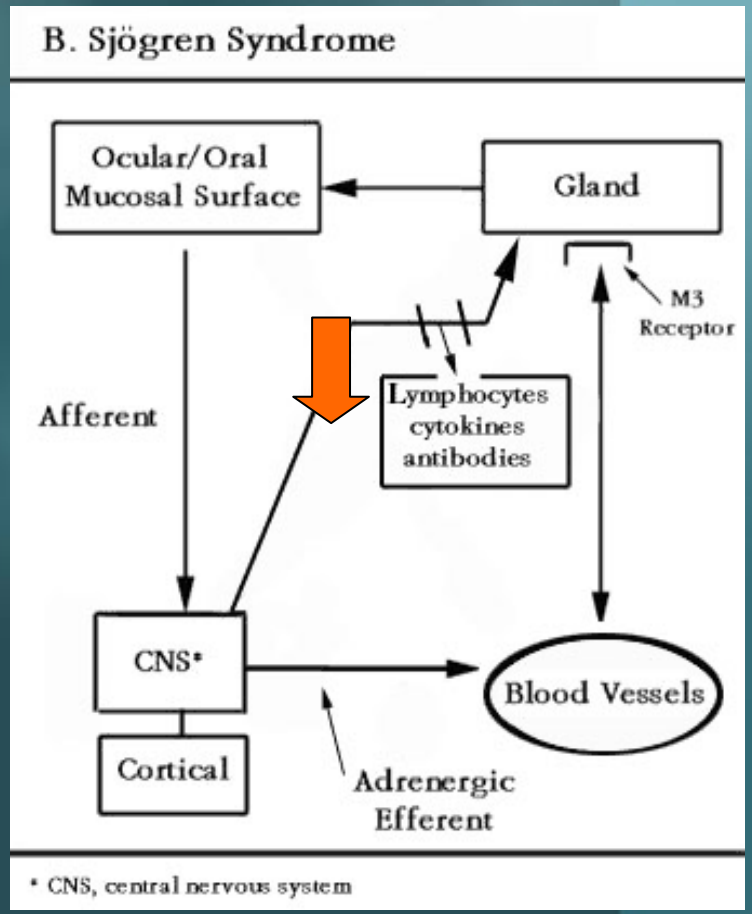
1. Cytokines (especially IL-1, TNF) interfere with release of Ach/VIP from nerve endings; and
2. Response to Ach by glandular cells Metalloproteinases interfere with Gland-extracellular matrix.

Normal

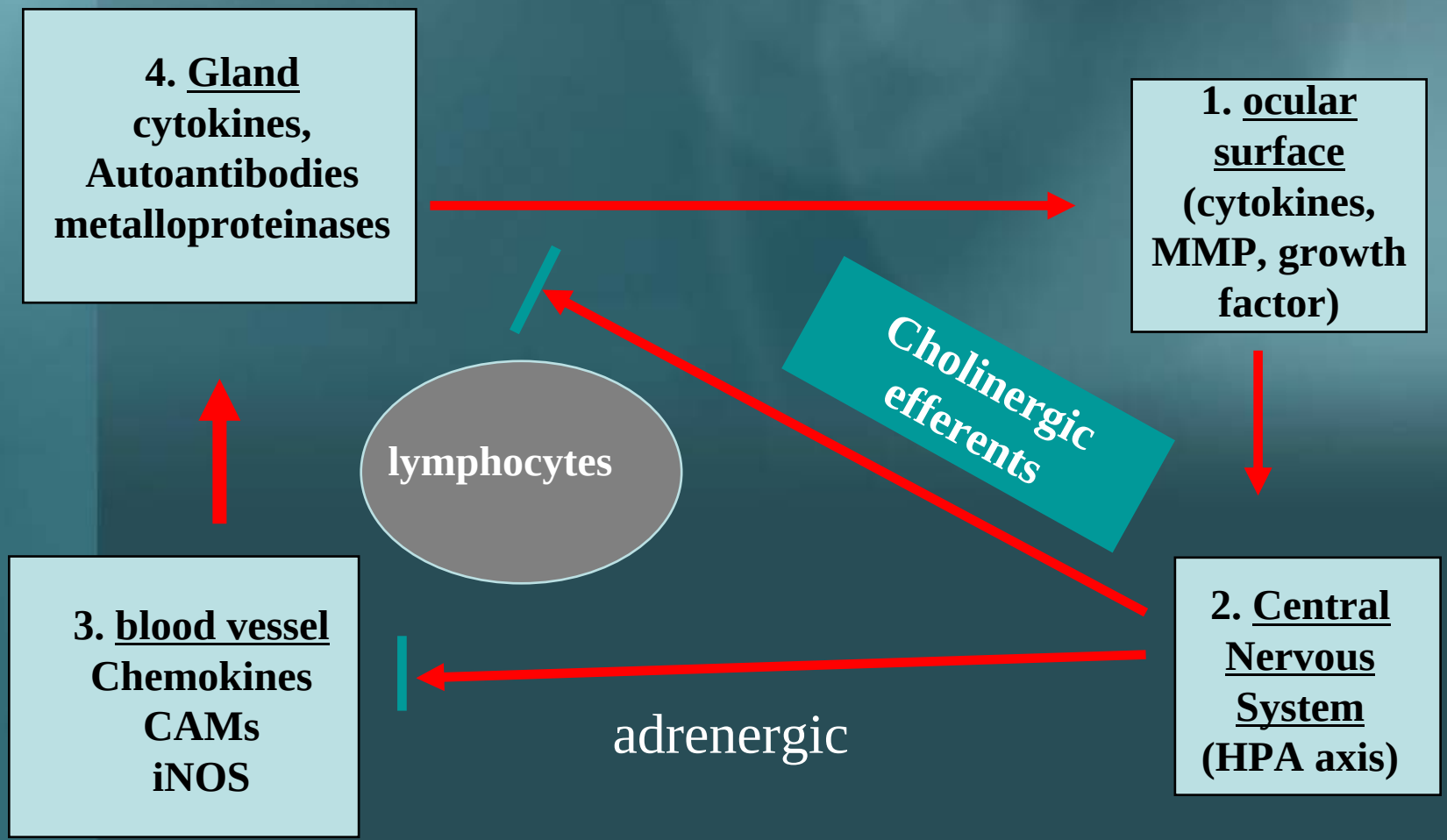


Lacrimatory & salivatory nuclei in midbrain

Sjogren's



Sjogren's syndrome affects functional unit



Muscarinic Receptors

There are at least 5 receptors (M1-M5), but we will concentrate on M1 and M3 mAChR that are found on the salivary gland.

The muscarinic receptors are members of the super family of G-protein coupled receptors.

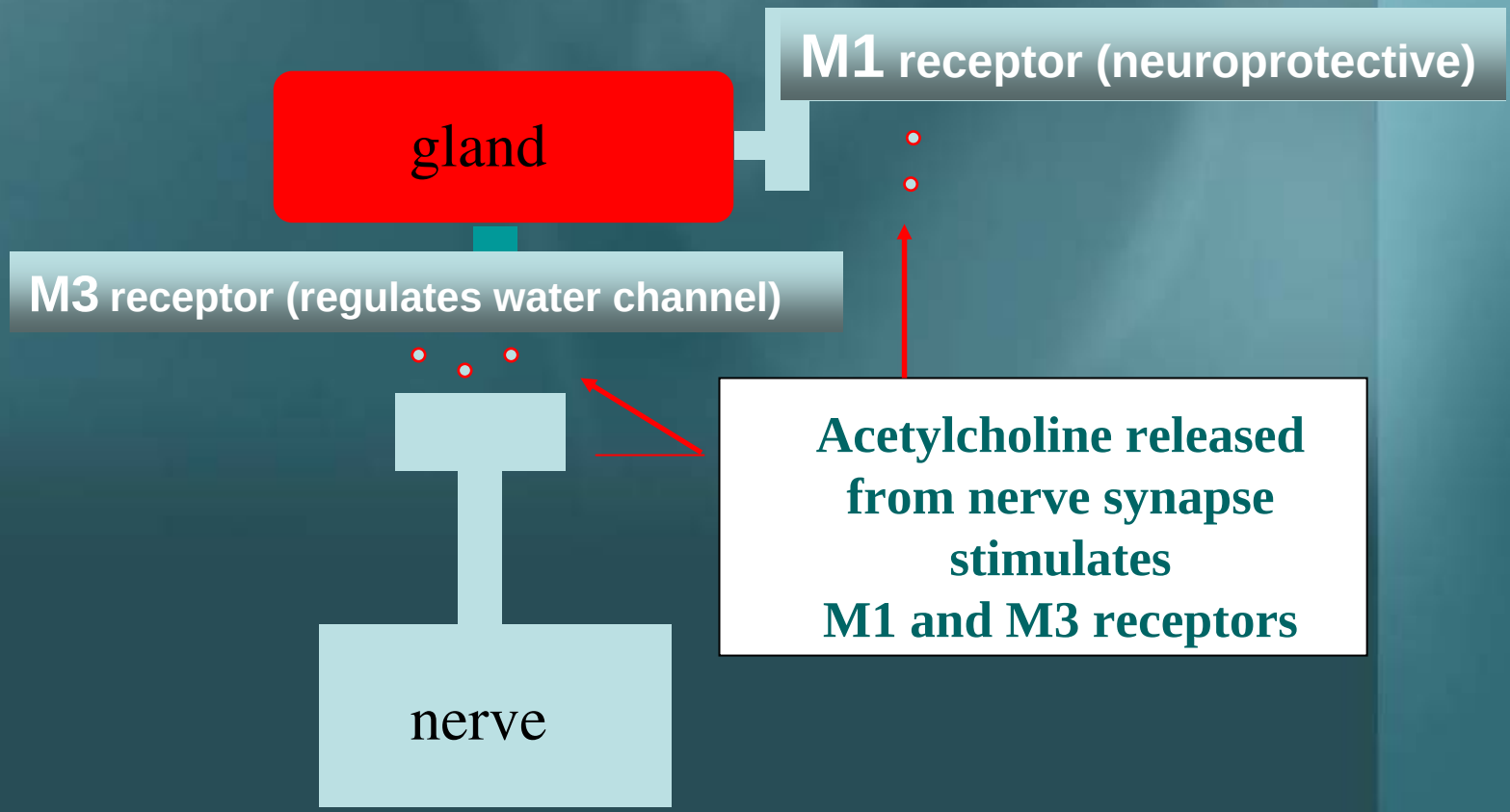
Muscarinic Receptor Actions

a) **M1 receptor:** neuroprotective and anti-apoptotic properties for neurons

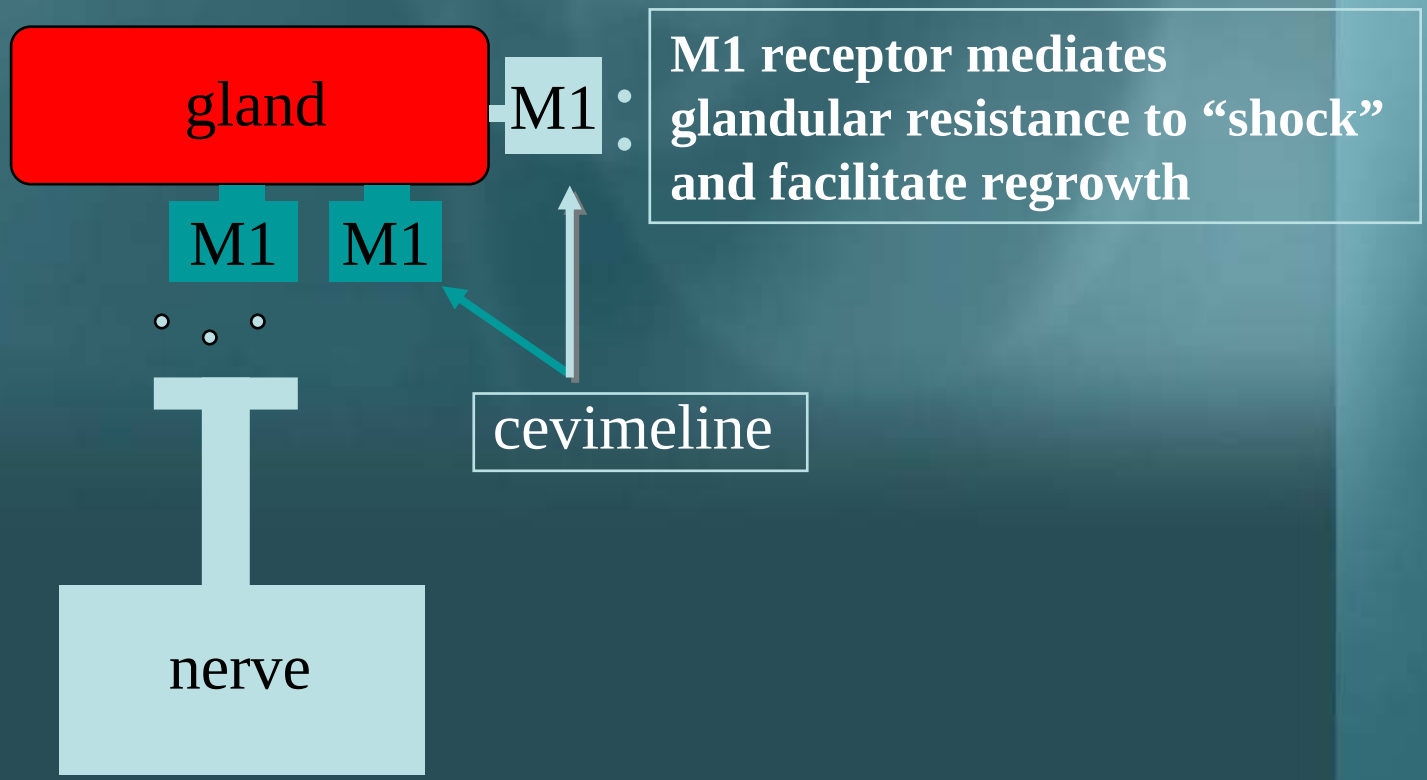
b) **M2 receptor:** (found on cardiac tissues)

c) **M3 receptor:** secretory function of gland

Acetylcholine Receptors of Muscarinic Type 1 and 3 are found on salivary and lacrimal glands

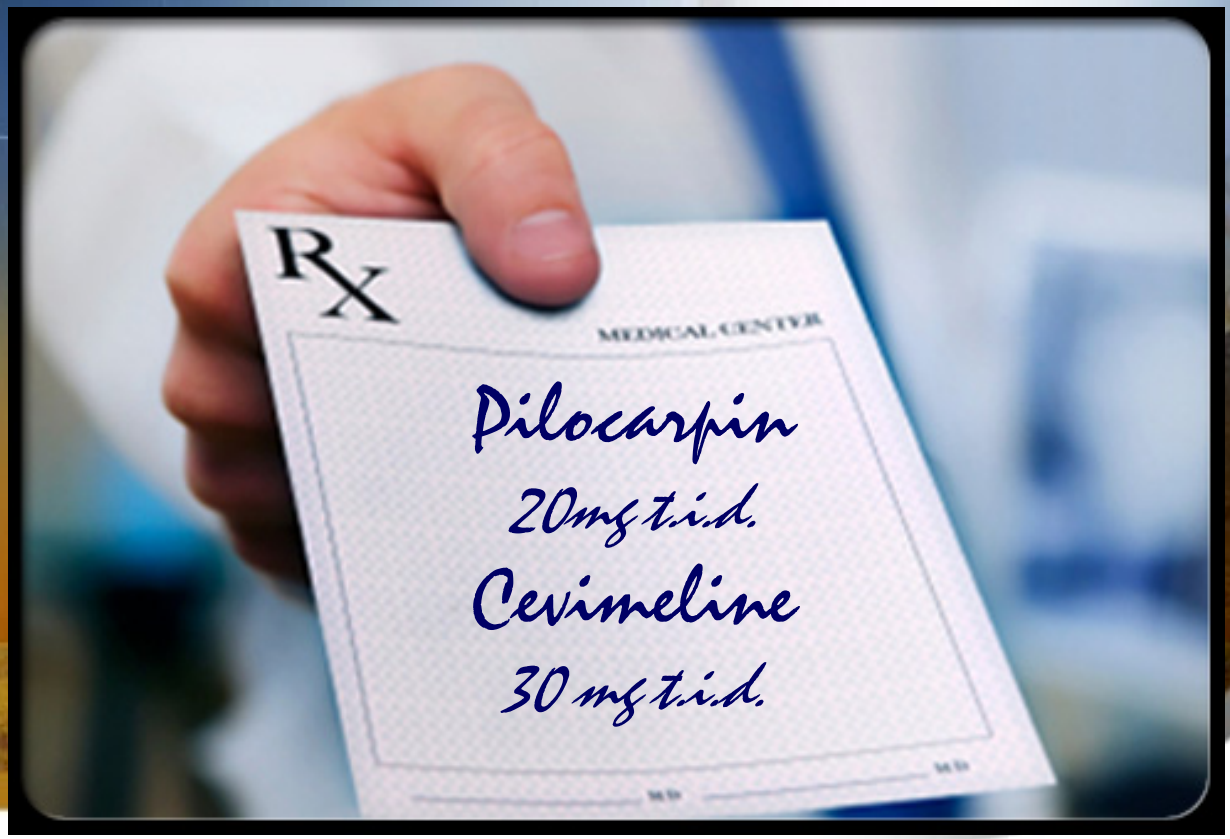


CEVIMELINE is a neurotransmitter that mimics acetylcholine and binds to Muscarinic Type 1 and 3 receptors



Pilocarpin 20 mg t.i.d.

Cevimeline 30 mg t.i.d.



Cevimeline and Pilocarpin provides an opportunity

to explore the new frontiers of neurobiology.

Why is a “neurotransmitters” useful in an autoimmune disease?

- Two muscarinic agonists *(Pilocarpine* and *Cevimeline)* have recently been approved as secretagogues for the treatment of symptoms of xerostomia in Sjögren’s syndrome (SS) [Reference: Vivino, 2001;Petrone, 2002].
- These agents stimulate the M1 and M3 receptors present on salivary glands, leading to increased secretory function.

New Approaches to the Stimulation of Salivary and Lacrimal Function in Sjögren Syndrome

Both Pilocarpine and Cevimeline

are effective in decreasing symptoms of *dry mouth and oral discomfort.*

Both Pilocarpine and Cevimeline are approved by FDA for dry mouth and further study pending for dry eyes.

Cevimeline actions

1. A sterically constrained form of Ach
2. Selected for its M1 and M3 activity :
    a) Stimulates water transport, benefit in stimulating saliva and tears (M3 receptor)
    b) Protects the gland from stress (M1 receptor)
    c) Alzheimer's model of rat maze learning

3. Up regulates new proteins (defensins/histatins)
4. Alters post translational modification of salivary proteins
5. Stabilizes aquaporin 3 and 5 (both receptors are important in brain and gland)

Relative binding to transfected receptors

agonists	pilocarpine	cevimeline
receptor		
M2 (cardiac)	10	1
M1 (anti-apoptotic)	1	25
M3 (secretory)	100	100

Thank you for your time