

Treatment of CFS: the USA Experience

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Model of CFS Pathogenesis

Genetic Predisposition

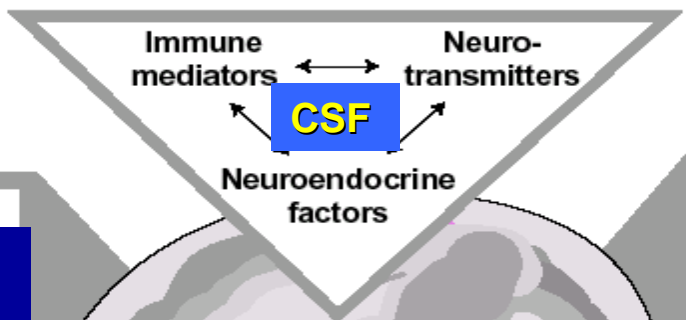


Triggering event / infection



Mediators (Immune,
endocrine, neuroendocrine,
psychosocial)

Health Outcome/Persistence

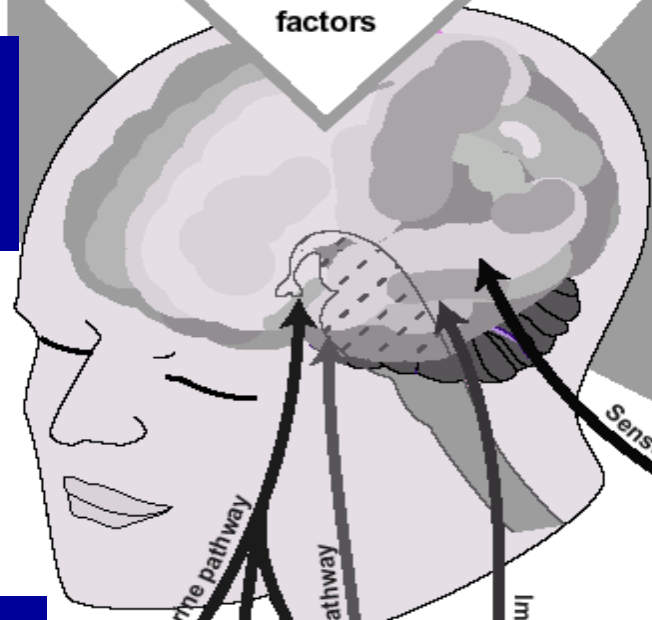


Risk factors

- Physical stress activates immune system and HPA
- Emotional stress activates immune system and HPA axis

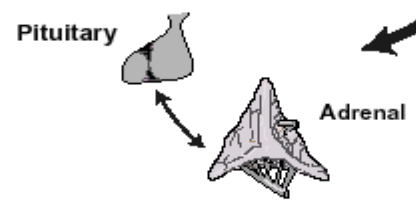
CNS Symptoms

- Altered perceptions
 - fatigue
 - pain
- Cognitive changes
 - concentration
 - memory
- Mood alterations
 - depression
 - anxiety
- Sleep disturbances
 - unrefreshing sleep
 - altered sleep-wake cycle



Hypothalamic-Pituitary-Adrenal Axis

- Relative Hypocortisolemia



Musculoskeletal System

- Myalgia & Arthralgia

Gastrointestinal Tract

- Altered bowel habits
- Abdominal pain

Heart and Blood Vessels

- Altered blood pressure responses
- Dizziness



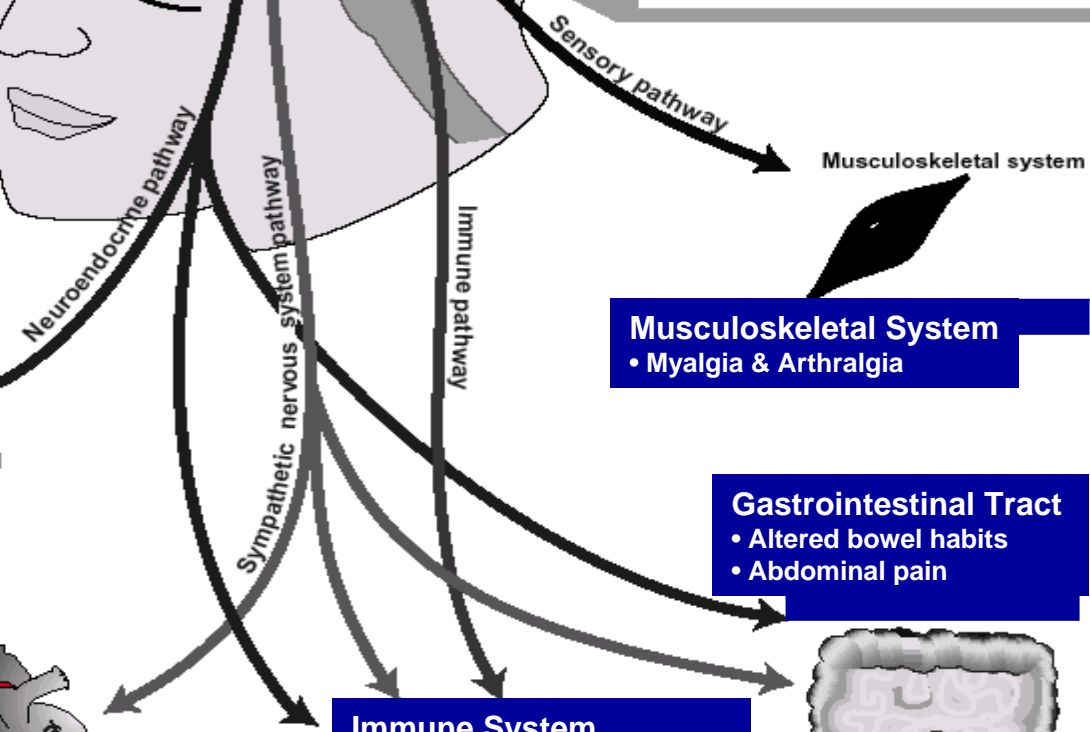
Immune System

- Lymph node tenderness
- Sore throat
- Enhanced Cytokines



• Altered bowel habits
 • Abdominal pain and

to postural change
 • Dizziness



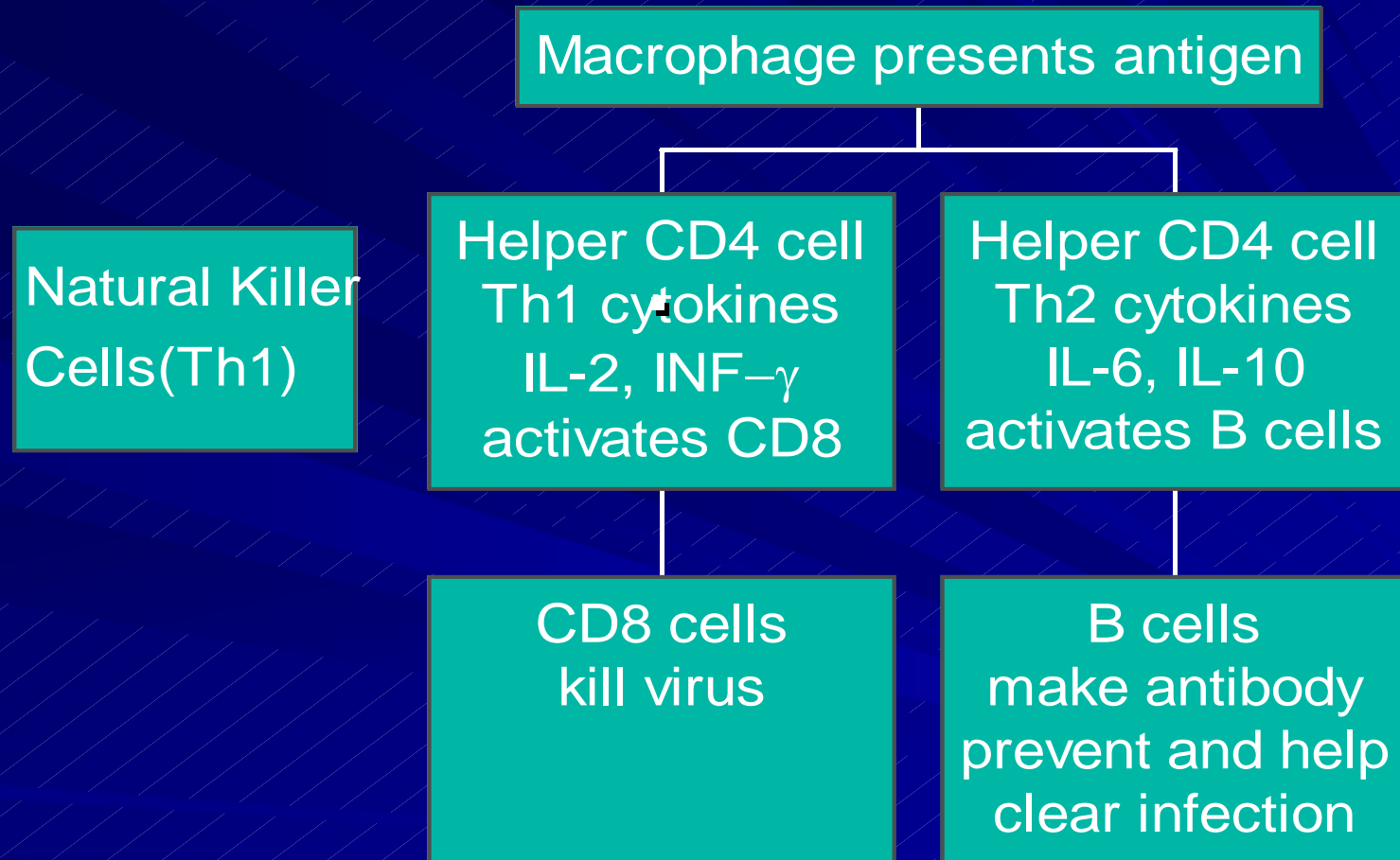
Pathogenesis Directed Interventions

- Immune - Ampligen, future immunomodulators
- HPA axis interventions - Growth hormone, cortisol
- NMH treatments (plasma expansion, sympathetic and parasympathetic stimulants/inhibitors);
- Sleep - pharmacologic and

Immune modulatory approaches

- ◆ Ampligen, a immune modulator and antiviral (Phase 3 recently completed)
- ◆ Allergy immunotherapy to down regulate allergic drive
- ◆ Future immunomodulators (trials underway): Isoprinosine, thalidomide, anti- TNF α monoclonal Ab
- ◆ Proof of concept: Autologous lymphocyte study

Immune cascade



Viral Persistence/Reactivation

HHV6 virus is present in 22 to 54% of patients in cross sectional studies (Ablashi, Krueger, Knox),

HHV6 virus is present by culture in 79% of CFS patients in longitudinal studies (HHV6 PCR assay, Knox)

HHV6 virus is present in the spinal fluid of 28 of 120 CFS patients (Peterson), and 7 of 35 CFS samples (Knox).

HHV7 and other herpes family viruses present by PCR in a subset

Enterovirus is present in 13% of CFS muscle samples (Douche-Aourik, 2003)

EBV? Still a maybe

Treating HHV6a?

Association vs. causation

- Blood PCR HHV6 a did not predict HHV6 virus is present in the spinal fluid
- CSF did not predict blood
- Of 120 CSF samples, 44 had abnormalities of protein, glucose or cells. Of the 44 , 28 were positive for HHV6(26), EBV (1), or CMV(1).
- 5 of 8 CSF PCR positive treated until CSF cleared returned to full time employment (Peterson); in his experience TK inhibitors did not clear CSF, patients required foscarnet or cidofovir
- Open label valgancyclovir 9 of 12 responders in high titer EBV plus HHV6 selected cohort , (Jose Montoya of Stanford)
- Placebo control trials have not been completed

Autonomic Dysfunction

Neurally mediated hypotension (Rowe)

Orthostatic hypotension (Streeten)

Parasympathetic dysfunction (Sisto)

Sympathetic over activation (Pagini, De Becker)

Balancing Act



Autonomic Nervous System

- Haemodynamic Instability Score taken during tilt table testing predicts CFS with 90% sensitivity. ¹
- Heart Rate variability as a predictor of CFS ²
- Gastric emptying delayed in 23/32 CFS subjects ³

■ 1 Naschitz QJ Med 2003 96(133-142)

■ 2 Yamamoto Exp Biol Med 2003 228(2):167-74

Autonomic Dysfunction

- Exhaustive treadmill testing results in cognitive function decline (LaManca et al)
- Perfusion abnormalities of brain stem, cerebellum (Costa et al)
- Drops in BP followed by CFS relapse
- Mid cerebral reduced perfusion (Schwartz et al)

Implications for treatment - NMH

- “Pipes and a pump”, wired by the autonomic nervous system
- Fill the space - fluid vs. cells
- compress the space - alpha 1 agonists, antiphlebotic stockings
- regulate the pump - beta blockers

HPA Axis dysregulation

- Demitrack low basal cortisol levels in CFS subjects, hypothalamic dysfunction-
- Dinan and colleagues - evidence of deficiency of hypothalamus, pituitary, and adrenal hypofunction.
- Small adrenal gland in depressed and non depressed CFS subjects, enlarged adrenal in depressed control group.
- Bennett et al studied 500 FM patients with basal IGF-I levels which were significantly lower than controls.

Endocrinology

Reduced Cortisol output via several mechanisms

A) heightened negative feedback

B) heightened receptor function

C) impaired ACTH and cortisol responses to challenge

DHEA functional abnormality (early data)

Abnormal serotonin function

IL-6 increase associated with low cortisol, CRH mediated

Cleare AJ Endocr Rev 2003 24(2):236-52

Papanicolaou Neuroimmunomodulation 2004 11(2)65-74

HPA axis interventions -

- Growth hormone – phase 1
(Antwerp study)
- Cortisol – conflicting phase 2
study results (London, NIH)
- Restoration of sleep cycle
(circadian rhythm)

Sleep Physiology

- Circadian Sleep - Wake neuroendocrine and immune functions in CFS (Modofsky)
- altered diurnal patterns in cortisol, prolactin
- altered diurnal patterns of NK cell function
- alpha wave intrusion on sleep EEG , reduced stage III and IV
- Higher %REM (Twin study, 22 discordant twins)¹

1 Watson et al Sleep 2003 26(3):32-8

Sleep

- Re-establish circadian rhythm

Conditioned response to bed - avoid bed for resting, reading, use bed for sleeping.
Establish "bedtime".

- Avoid short acting hypnotics (alpha trappers)
- tricyclics, doxepan are longer acting, and don't trap in alpha wave
- mirtazapine (Remeron), sodium oxybate or gamma hydroxybutyrate, (Xyrem) act as stage 4 inducers

Nutritional interventions

- Oxidative stress studies suggest interventions such as glutathione, N-acetylcysteine, alpha lipoic acid, NADH
- Vitamin studies suggest B vitamins, Vitamin C, magnesium, sodium, zinc, l-tryptophan, L carnitine, co-Q10, and essential fatty acids

Nutritional interventions

- Dangers:
- Licorice root – potassium deficiencies
- “supplements” that are actually hormones
- “supplements” that have iffy contents – eg. St John’s wort, melatonin
- Products that make unsubstantiated claims
- Under and over hydration

Reconditioning

- Poor orthostatic resilience leads to substantial changes in usual reconditioning programs
- Limit upright head up time to 5 minutes alternating with 5 minutes flat, use flat or near flat aerobic conditions (swimming, recumbent bike)
- Concentrate on muscle bulking exercises, increasing metabolic rate (weight training, light weights)
- Flexibility , stretching and balance as core component.

Recent reports - interventions

- Brewers Yeast Extract - in a mouse model , using a chronic immune activation model, the BYE prep quieted the immune response and prevented further over activation in subsequent immune challenges. Activity level increased in the treated animals as compared to placebo
- Use of antibiotics for *Coxiella burnetii* infection(Q fever). TCN was given to 4 CFS patients and 58 ICFS PCR positive patients: all cleared the infection, CFS patients failed to improve, ICFS patients improved in performance and in temperature and headaches scores.
- Neurotropin - 6 mo treatment resolved all symptoms. Neurotropin is a immune modulator that is currently used in Japan to treat RSD and other painful conditions.
- Toda Hiroshima J Med Sci 2006 mar 55(1) 35-77.
- Takasha Evid based Compl Alt Med 2006 mar 3(1)109
- Twakami et al Intern Med 2005 Dec 44(12):1258-63

Recent reports - interventions

- Melatonin 29 patients, 5mg open label study, 8 of 27 normalized fatigue scores. Measured patients dim light melatonin onset, patients whose result was later than 22 hours were more likely to respond to treatment.
- Methylphenidate (ritalin) in CFS 10 mg BID study in 60 patients, placebo control: 17% reported decreased fatigue, 22% improvement in concentration. ..further studies needed.
- Modafinil not helpful (N=14 cross over study) – mixed effect on cognitive testing, some dose effect.
- Van Heukelom et al Eur J neurol 2006 Jan 13(1):55-60
- Blockman D et al Am J Med 2006 feb 119(2):167
- Randall DC et al J Psychopharm 2005 nov 19(6): 647-60

Recent reports - interventions

- Walking program notes an initial ability to meet goals (4 to 10 days), then develop exercise intolerance and worsening symptomatology
- Patients report: of 155 patients taking everything under the sun, most helpful supplements coQ10 (69%) DHEA (65%), ginseng (56%). Vitamins, exercise, yoga, predicted improvement. Yoga seemed the most helpful.

■ Black CD and McCully KK. Dyn Med 2005 Oct 28;3:10

■ Bentler SE J Clin Psychiatry 2005 may 66(5):625

University of Miami CFS Research and Clinical Center— Research Protocols

- SMART Energy Study (CBT)
- Erythropoetin (Procrit) phase 2 protocol
- Pathogenesis of NK cell defect in CFS
- Thalidomide Phase 1 protocol
- Isoprinosine Phase 2 protocol
- Natural history study

Conclusion

- There has been significant progress in our understanding of CFS .
- The neuroendocrine, immune, and central nervous system are linked, and can't be considered separately.
- More effective therapies, based on this new understanding are available, with others under study.

All CFS patients can
experience a better quality of
life with compassionate care
and a multidisciplinary
approach.

Thank You!

Professional links:

AACFS on line: www.aacfs.org

CDC on line: www.cdc.gov

NIH on line: www.nih.gov

Advocacy organizations:

CFIDS Association of America

On-line: www.cfids.org Information: info@cfids.org

American Fibromyalgia Syndrome Assn.

Online: www.afsafund.org

National Gulf War Resource Center online:

www.ngwrc.org

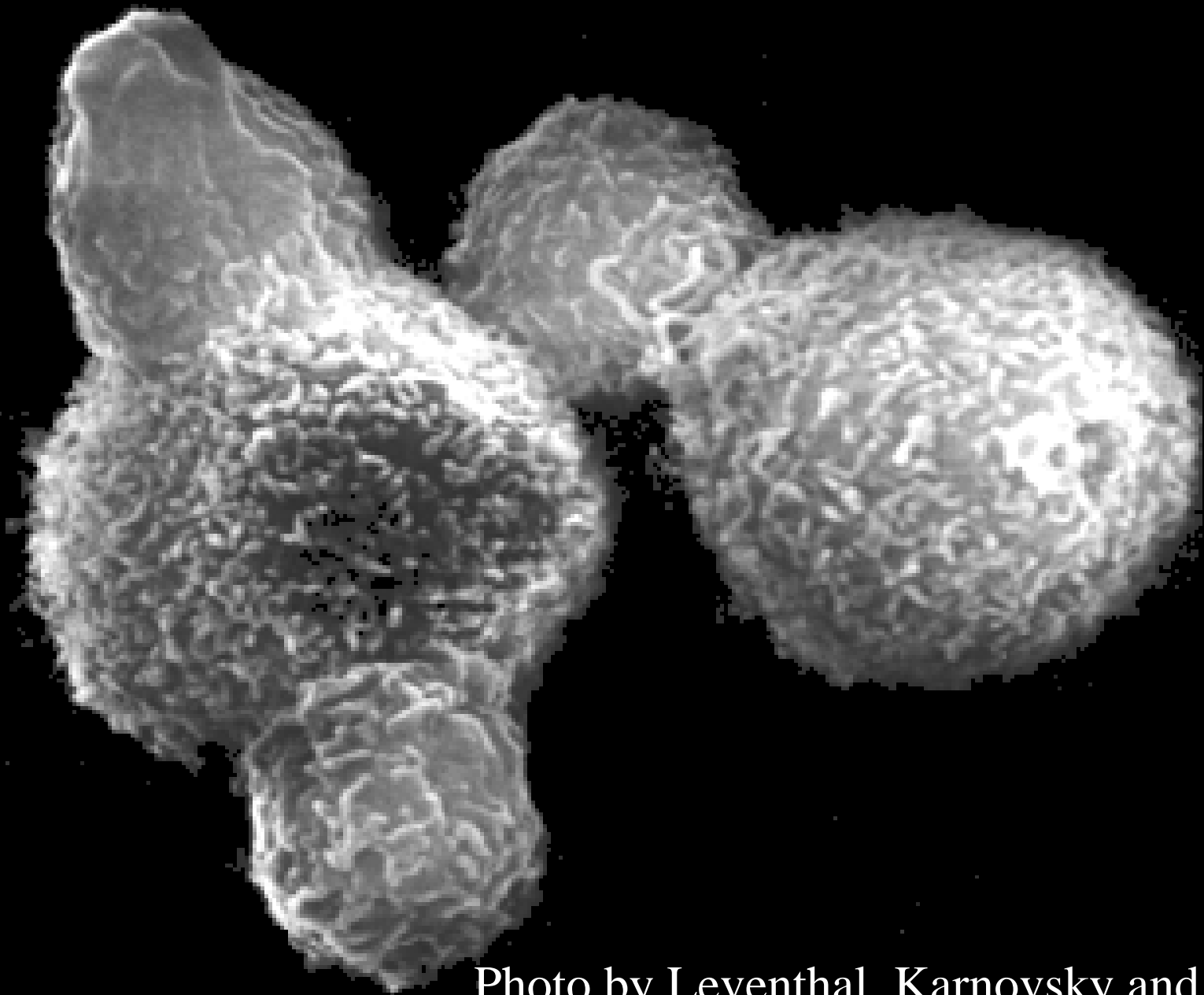


Photo by Leventhal, Karnovsky and Martz