A Brief History of Treating Rheumatoid Arthritis

By Reza Mirza, MD, (based on a discussion with Dr. Arthur Bookman)

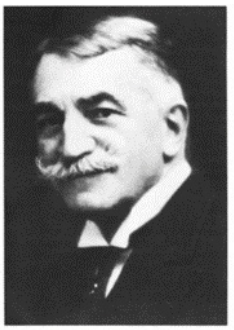
"One of the most intractable, obstinate, and crippling diseases that can befall the human body." – Lane and Griffiths, 1890

"Cases of ruin and despair, in one sense more malignant than cancer." – Spender, 1889

1920s:
"All that is gold does not glitter." *– J.R.R. Tolkien*

In 1929, Dr. Jacques Forestier—son of Henri, the founder of *La Ligue Internationale Contre Le Rheumatisme*—posited that rheumatoid arthritis (RA) and tuberculosis (TB) shared similar features: febrile illness with leukocytosis, anemia, and general malaise. He hypothesized that given gold's usefulness in TB, perhaps it would prove useful in RA.


Dr. Jacques Forestier


Dr. Henri Forestier

Over the next several years, he published a number of case series of gold trials in *The Lancet*. He injected 250 mg of gold thiopropanol intramuscular (IM) weekly x 10-12, waited a month, and in some cases gave another course.

Five of 15 patients had "excellent" response; another five had "much improved," two had "minimal response," and three were no worse. For comparison, we typically cite biologic response rates at 20% for ACR70, and 40% for ACR50+ (I say plus because people like myself forget ACR50 includes ACR70).

There remained ongoing controversary as to whether gold worked, until 1945, when Thomas Fraser published the results of the first double-blind randomized clinical trial (RCT) of any anti-rheumatic drug. It compared gold to placebo. He wasn't fortunate enough to have the Clinical Disease Activity Index (CDAI) or American College of Rheumatology (ACR) scoring system. He admitted himself: "It is difficult to decide what criteria to use." Forty-two percent (42%) had great improvement based on his impression.

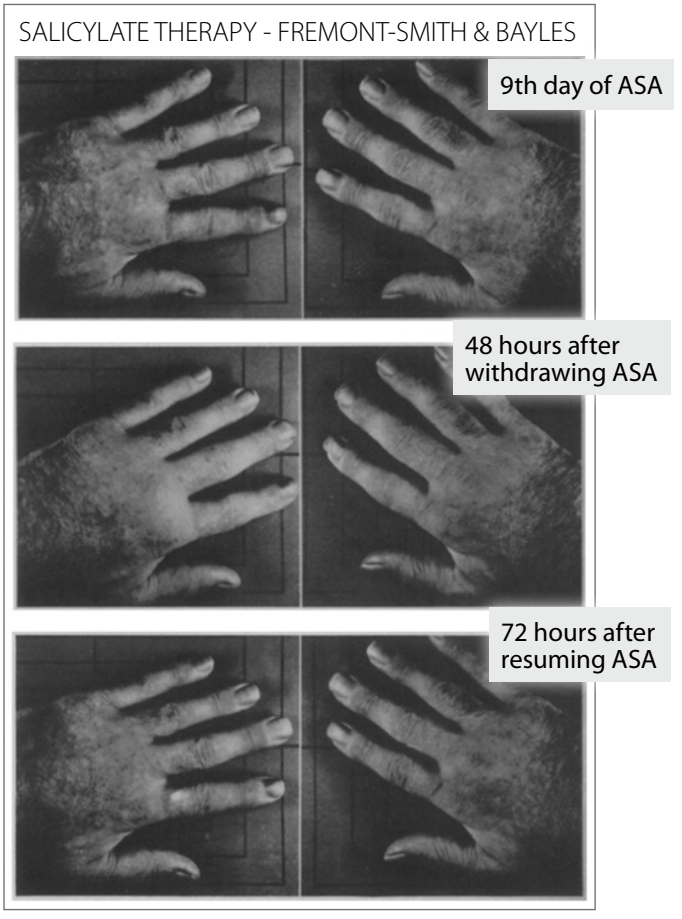
In the **1980s**, oral gold was developed: More convenient but less effective.

Overview of Gold's Clinical Properties (1998 RCT)

Efficacy: Gold was given as 50 mg IM weekly for 20 injections, then monthly maintenance. It had similar clinical, laboratory, and radiologic outcomes to methotrexate (MTX) 15 mg weekly orally.

Gold Side effects (S/E): proteinuria, rash/pruritis, thrombocytopenia, diarrhea.

Severe S/E: Mortality: ~1%, 7 deaths in a 750-patient observational cohort, due to hemorrhagic purpura (3), subacute necrosis of liver (2), agranulocytosis (1), exfoliative dermatitis (1)

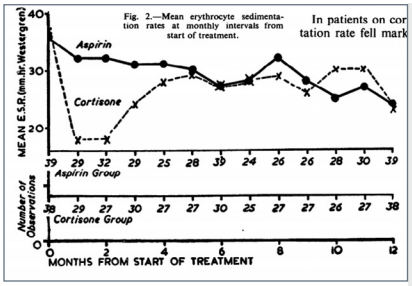


Mechanism of action (of gold):

- Patients treated with gold have decreased immunoglobulins, rheumatoid factor, and circulating immune complexes.
- Gold can dissociate antigenic peptides from MHCII, decreasing antigen presentation, demonstrated in vivo on HLA-DRB1 (the shared epitope).
- Gold blocks prostaglandin E2 production.

1940-50s: Rx. ASA 325 mg 3 tablets QID—You read that right!

The Empire Rheumatism Trial (1955) was the CYCLOPS trial of its day.[1] It proved acetylsalicylic acid (ASA) was no different than cortisone in terms of improvements in joint count and erythrocyte sedimentation rate (ESR) and ushered in an era of proliferating nonsteroidal anti-inflammatory drugs (NSAIDs)!



Enteric-coated ASA given in increasing doses until maximally tolerated. The usual optimum dose was 975 mg QID (3.9 g OD). You titrated to tinnitus then dropped the dose. Not the only instance rheumatologists invoked such a rule.

> Dr. Bookman: *"Nobody had an MI on high-dose aspirin. We thought rheumatoid protected from coronary disease until we switched to ibuprofen and naproxen."*

1950s: Cortisone

TABLE XI
AVERAGE HAEMOGLOBIN LEVELS AT BEGINNING, MIDDLE, AND END OF FIRST YEAR
(g. per cent.)

Time of Examination	Cortisone Mean ± S.E.	Aspirin Mean ± S.E.
Beginning of Year	12·5 ± 0·22	12·5 ± 0·27
Middle of Year	13·3 ± 0·27	12·5 ± 0·31
End of year	13·3 ± 0·15	13·1 ± 0·20

No evidence of bleeding (Hb went up)!

The first realization there may be an agent to put RA into remission came when physicians realized patients with RA who became jaundiced underwent spontaneous remission. The hunt was on for "Nature's Dramatic Antidote": "Volunteers with rheumatoid arthritis were given bile salts by mouth, a derivative of a bile acid (decholin) orally and intravenously, liver extracts parenterally, ox bile by proctoclysis [per rectum], and large amounts of human bile by stomach tube…" None of these worked!

Another clue came from women with RA who dramatically improved during pregnancy. The focus switched to hormones. In 1948, Dr. Kendall (a biochemist who isolated thyroxine and several adrenal hormones including cortisone) and Dr. Hench of Mayo Clinic trialed "Compound E" (cortisone) on a patient with rheumatism at a dose of 100 mg IM daily, and she improved dramatically within three days.

And so, they won the Nobel prize! Dr. Laurence Rubin insists you read their Nobel lecture on the discovery.[2] It is very good.

The next 60 years introduced the drugs we are familiar with, so we can leave their tales brief:

1960s: NSAIDs. The first was ibuprofen (patented 1962, marketed 1969); the second was naproxen (patented 1967, marketed 1976). At one point there were 15 NSAIDs on the Canadian market. Heart attack rates shot up. Hospitalizations for ulcer complications became epidemic.

1970s: Methotrexate and Cyclophosphamide. Rex Hoffmeister, a practicing rheumatologist from Spokane, Washington, reported positive effects with intramuscular MTX in 1972. At the ACR meeting people laughed him off. It took the stodgy rheumatology community until the 1980s to do the first double-blind trial.

1990s: Leflunomide received approval in 1998 in the U.S.: the same year as etanercept.

Conclusion

Rheumatology is the specialty with the most patient-important advances in the past several decades, as I see it. My colleagues and I cannot wait for what the future holds. Only a few beasts await to be tamed: Scleroderma, Sjogren's syndrome, the many-faced wolf (SLE), and the vasculitides.

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References
1. de Groot, K, et al. "Pulse versus daily oral cyclophosphamide for induction of remission in antineutrophil cytoplasmic antibody—associated vasculitis: a randomized trial." Annals of internal medicine. 2009; 150(10): 670-680.
2. Kendall, E. C. The development of cortisone as a therapeutic agent. Antibiot Chemother (Northfield). 1951; 1(1): 7-15.

The Toronto Wellesley Hospital (1963-1998), a 40-bed Inpatient Rheumatology Ward: *A Reflection by Dr. Bookman*

Patients were brought in from all over Ontario, sometimes from the back of a barn, many times completely immobile. Patients would be admitted for several weeks.

They were brought to hospital for physiotherapy, occupational therapy, rehabilitation, medication management, reconstructive surgery, splints, springs, and slings. Everyday at noon, physiotherapy was conducted over the intercom and patients followed along in their beds.

There was a heated therapeutic pool. Immobile patients would be lifted in using a cradle. Hands were dipped in warm paraffin wax (heated using a double-boiler) to relieve AM stiffness prior to hand physiotherapy.

Rheumatology trainees would inject several joints at a time in each patient each day. The only drugs available were gold, NSAIDs, cortisone, and chloroquine. Chloroquine worked much better than hydroxychloroquine, but had higher rates of retinal toxicity and also caused corneal toxicity affecting night vision.