Balancing the issues- models of inflammatory disease

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The Need to better understand inflammation

- Inflammation can be overt (the cardinal signs…red, hot, swollen, painful or …rubor, calor, tumor, dolor)
- Or it may be occult …producing signs and symptoms after insidious damage occurs
  - eg Liver fibrosis, kidney inflammation, atherosclerosis, heart inflammation, MS organ transplant rejection, etc

Animal Models of Inflammation

- Diverse stimuli
- Study pathophysiology and treatment
- Increasingly use transgenic/ gene knockout mice or crosses
  - Somewhat unpredictable course
  - Often allows powerful studies with small number of animals
  - Huge number of possible interventions or combinations
- In Man inflammation is commonly treated with multiple agent therapy

Key considerations

- Defining rationale for the study
- Appropriateness of the chosen animal species, strain, sex
- Existing knowledge base
- Appropriateness of the intervention
- Appropriateness of the monitoring
- Mitigation of animal stress / distress/ pain
  - Short term vs long term
  - Anticipatory stress issues
- Concomitant or peri-intervention treatments

Inducing painful inflammation

- Stimuli variable
- Stimulus → reaction → peak → settles
  - But it may not
  - Alteration to foraging lifestyle
  - Access to food / water/ warmth
  - intervention

Historical Interlude- the story of cyclophosphamide Rx for lupus nephritis

- For 40 years cyclophosphamide cytotoxic treatment has been a core component of treatment for severe lupus threatening vital organs
- It was used in uncontrolled trials in human lupus in parallel with studies in lupus prone mice
- It showed spectacular success in preventing death from lupus in mice and later comparable effects in man in the early 1970s
- Till recently no other single agent has achieved comparable success in inducing remission
- Some newer immunosuppressives look comparable in short term studies

NZB x NZW cross F1 females

Bred by W Hall 1952
selected for white colour

Helyer 1963

Male W x female B

= F1

Bred by Bielschowsky Univ Otago 1948

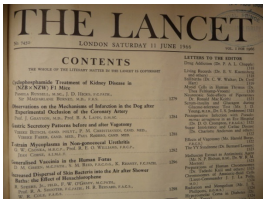
F1 males av 406 days

F1 females av 285 days

Significant features of the lupus treatment study

1. Correct hypothesis
2. Simple
3. Relevant model
4. State of the art technology
5. Well written & illustrated

The very striking effects we have obtained in preventing the development of what is almost certainly autoimmune damage to the kidney naturally suggest a similar approach to analogous forms of subacute and chronic kidney disease in man. We should, however, prefer to lay stress on the potential usefulness of the B/W female as an assay system for any immunosuppressive drugs contemplated for use in human autoimmune disease generally.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CYCLOPHOSPHAMIDE TREATMENT OF KIDNEY DISEASE IN (NZB × NZW) F1 MICE

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SEVERE renal disease has been described in NZB mice and their F1 hybrid (NZB × NZW) (Helyer and Howie 1963, Burnet and Holmes 1965, Hicks and Burnet 1966). The lesions resemble those of human systemic lupus

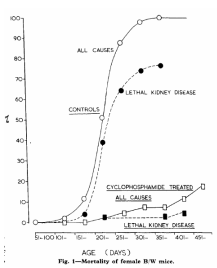


Fig. 1—Mortality of female B/W mice.

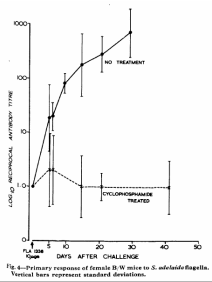
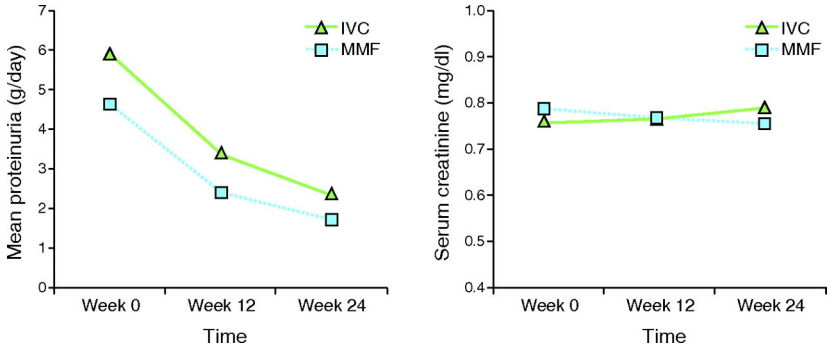


Fig. 4.—Primary response of female B/W mice to *S. schleisbi* flagella. Vertical bars represent standard deviations.

In pooled analyses, MMF was equivalent to cyclophosphamide (IVC) in inducing remission for patients with class V lupus nephritis.



Bomback A S , Appel G B JASN 2010;21:2028-2035

JASN

Is there a better therapy

- In 2010 a new cytotoxic has showed similar ?? perhaps better ?? efficacy in rodent models

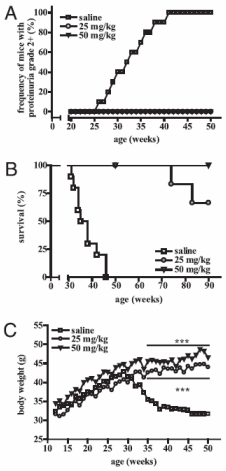


FIGURE 1. Prevention of murine lupus erythematosus by inhibition of topoisomerase I. NZB/W F1 mice were treated from week 13 with 25 mg/kg or 50 mg/kg irinotecan three times per week every fourth week ($n = 10$, control mice; $n = 12$, both groups treated with irinotecan). *A*, Frequency of mice with proteinuria. Each point reflects the frequency of mice with grade 2+ (≥100 mg/dl) proteinuria at the indicated time points. *B*, Survival of irinotecan-treated groups was significantly better compared with saline-treated groups. $p < 0.0001$; Kaplan-Meier log-rank test. At week 50/51, half of the groups treated with irinotecan were sacrificed for further analysis. *C*, Normal development of body weight in irinotecan-treated mice versus decline of body weight in saline-treated controls owing to the onset of the lupus disease. ***$p < 0.001$; two-way ANOVA.

Reversal of Established Lupus Nephritis and Prolonged Survival of New Zealand Black × New Zealand White Mice Treated with the Topoisomerase I Inhibitor Irinotecan

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Issues

- When is death (or advanced debility) as an end point acceptable
- Issues in monitoring
  - Diseases altering "usual" parameters
  - Weight issues
- How much animal data is "enough" to justify trials of toxic therapy in man