

MEDICAL GRAND ROUNDS
April 16, 1964

TREATMENT OF TUBERCULOSIS

Charles LeMaistre, M. D.

TREATMENT OF TUBERCULOSIS

"I am quite sure we will get rid of tuberculosis before the Americans because they are much less co-ordinated and more chaotic, with a lot of private treatment and so on, much of it very bad." John Crofton, Scotland, 1961.

"The first country to eliminate tuberculosis will be that country which regards it as a serious problem to the end." Etienne Bernard, Paris, 1959.

During the past 18 years, amazingly effective chemotherapy for pulmonary tuberculosis due to *Myco. tuberculosis* var. *hominis* has revolutionized the treatment of tuberculosis. All other aspects of treatment, e.g. bed rest, collapse therapy, deforming surgical procedures, etc., have become mainly of historical interest. The patient whose organisms are initially sensitive to the standard drugs can expect rapid reversal of infectiousness and arrest of disease in virtually all instances if the drugs are properly prescribed and successfully administered for a sufficient period (18-24 mo.). On the other hand failure of initial chemotherapy for whatever cause can be expected to result in drug resistant organisms, a disaster for the patient and society.

Aims of Drug Treatment:

- (1) arrest disease
- (2) render non-infectious
- (3) prevent relapse

Standard Drugs:

1. Isoniazid (isonicotinic acid hydrazide, INH)
Para-amino-salicylic acid (PAS)
Streptomycin (SM)
2. Combinations:
 - (a) INH (300 mg.) plus PAS (15 gm.)
 - (b) INH plus PAS (as above) with Streptomycin (1 gm.) daily, first 90 days
 - (c) INH (300 mg.) plus Streptomycin (1 gm.) (daily Streptomycin usually changed to bi-weekly at 90 days)
 - (d) INH alone (for minimal, non-cavitary disease only)
3. Toxicity:
 - (a) INH: 0.5% untoward reactions, mainly peripheral neuritis or skin rash. Toxic encephalopathy encountered with higher dosage. Rarely: hemolytic or aplastic anemia, thrombocytopenic purpura, agranulocytosis, or pancytopenia.
 - (b) PAS: 7.6% untoward reactions, mainly of two types: gastrointestinal-anorexia, nausea, vomiting, diarrhea; "allergic"-fever, rash, liver damage. (a goitrogenic action is less common and dose-related-inhibition of organic binding of iodine in the synthesis of thyroid hormone).

- (c) SM: 7.8% untoward reactions, mainly fever, skin rash; toxic effect on 8th nerve both vestibular and auditory portions.
4. Duration: 18-24 months continuous chemotherapy; reduction in bacillary population occurs mainly in early weeks but bacilli not eradicated; discontinuation prior to 18 months leads to increased frequency of relapse.

Second-line Drugs:

1. Used mainly in retreatment or instances of resistance to one of the standard drugs.
2. Pyrazinamide
Ethionamide
Cycloserine
Capreomycin
- Viomycin
Ethambutol (investigational)
Tetracycline
Kanamycin
3. Properties: increased toxicity, less therapeutic effect.

Role of Steroid Hormones With Antimicrobial Therapy:

1. Effectiveness of drugs neither enhanced nor lessened by hormone administration.
2. Used primarily to lessen constitutional manifestations of illness and in severe drug reactions. Use in meningitis with block to flow of cerebrospinal fluid has become traditional although therapeutic value not yet substantiated. Possible tissue sparing effect (slight) in acute tuberculous pneumonia.
3. Use of steroid hormones should be of short duration (2-3 weeks).

TUBERCULOSIS CONTROL AND ERADICATION

Recalcitrant patients constitute only a small percentage of tuberculosis cases yet the consequences of one such patient may be seen from the following case:
Case No. [REDACTED].

Radiographic changes consistent with pulmonary tuberculosis were present on chest film of [REDACTED] 1962, at [REDACTED]. Tuberculosis Control notified but patient evaded contact until [REDACTED] 1963. Patient threatened with warrant and voluntarily entered [REDACTED] [REDACTED] 1963. INH, PAS and SM begun for far advanced pulmonary tuberculosis; chemotherapy continued until patient left hospital without notice on [REDACTED] 1963. Located and placed under warrant [REDACTED], 1963, transferred to [REDACTED] on [REDACTED] 1963.

Note: This patient was president of a PTA and taught in a nursery school. She had close contact with at least 114 children (56 positive reactors, 6 known active cases) and 12 adults (10 positive reactors, 9 inactive primary infections).

REFERENCES

Chemotherapy:

1. McDermott, W. Antimicrobial therapy of pulmonary tuberculosis. Bull. Wld. Hlth. Org., 1960, 23: 427-459.

Basis for effective therapy and preferred drug regimens discussed in scholarly manner; emphasis placed upon isoniazid superiority.

2. Grofton, J. Drug treatment of tuberculosis. Brit. Med. J. July 30, 1960, 2:370-373; Aug. 6, 1960, 2:449-451.

A complete discussion of standard chemotherapy (INH, PAS, SM) and detailed guide for treatment of the patient with drug-resistant organisms.

3. McDermott, W. The chemotherapy of tuberculosis. Amer. Rev. Resp. Dis, 1962, 86:323-335.

Discussion of biologic concepts involved in drug therapy of tuberculosis; microbial persistence and drug resistance are major concern.

4. M. R. C. Tuberculosis Trials Committee. Long-term chemotherapy in the treatment of chronic pulmonary tuberculosis with cavitation. Tubercle 1962, 43:201-267.

A high rate of bacteriological quiescence was achieved by the end of one year of chemotherapy even in patients with extensive cavitation in chronic pulmonary tuberculosis. Excellent study with emphasis upon potency of anti-tuberculosis chemotherapy when successfully used; second year of chemotherapy reduces relapse rate.

5. Fox, W. The chemotherapy and epidemiology of tuberculosis. Lancet 1962, 1:413-417, 473-478. (Presented more extensively in Adv. Tuberc. Res., 1963, 12: 28-149).

Excellent study of ambulatory chemotherapy in India. Clinical and epidemiological studies show remarkable success in both ambulatory and sanatorium patients with few relapses; increased risk to contacts during home treatment of the index case could not be established.

6. D'Esopo, N. D. The present status of treatment of pulmonary tuberculosis. Ann N. Y. Acad. Sc. 1963, 106: 85-95.

Conservative approach to initial therapy, management of "open-negative" cases, retreatment, surgery, and optimum duration of chemotherapy.

7. Lepper, M. H. and Spies, H. W. Present status of the treatment of tuberculosis of the central nervous system. *Ann. N. Y. Acad. Sc.* 1963, 106: 106-123.

Careful study of 159 cases of tuberculosis meningitis; improvement of results by isoniazid emphasized; failure of steroids to produce definite effect upon survival or decrease of residue noted. Excellent references.

8. Lattimer, J. K. et al. Genitourinary tuberculosis: current status. *Trans. 22nd Res. Conf. in Pulmon. Dis. (VA-Armed Forces)*, 1963. p. 47-51.

Brief summary of the dramatic change in management of renal tuberculosis due to chemotherapy. Triple drug (INH, PAS, SM) regimens slightly better than INH and PAS, although both regimens remarkably successful.

9. Strangaard, E. Sputum conversion on chemotherapy in fresh cases of pulmonary tuberculosis. *Acta Tuberc. et Pneumologica Scand.*, 1962, 41: 187.

A study of 136 patients with conversion of sputum to negative in 89% after three months of chemotherapy; conversion occurred in all (100%) by end of the sixth month.

10. Russell, W. F., Jr. and Middlebrook, G. Chemotherapy of tuberculosis. 1961. *Chas. Prophylactic chemotherapy: Thomas, Springfield, Ill.*

A monograph presenting the National Jewish Hospital approach to clinical and laboratory aspects of chemotherapy.

11. Ferebee, S. et al. The use of chemotherapy as a prophylactic measure in tuberculosis. *Ann. N. Y. Acad. Sc.*, 1963, 106: 151-156.

Isoniazid prophylaxis (5 mg./Kg.) safe and reduces the incidence of tuberculosis by three fourths whether the risk be high or low; chemoprophylaxis strongly recommended for close contacts of a newly discovered active case.

12. Des Prez, R. M. and Muschenheim, C. The chemoprophylaxis of tuberculosis. *J. Chronic Dis.* 1962, 15: 599.

Side Effects and Toxicity:

13. Kalinowski, S. Z. et al. Complications in the chemotherapy of tuberculosis. *Amer. Rev. Resp. Dis.*, 1961, 83:359.

A review with analysis of experience in 3,148 patients; treatment interrupted in 379 patients (12.2%). Responsible drug: SM (7.8%), PAS 7.6%, INH (0.5%).

14. Dewlett, J. H. et al. The toxicity of INH and PAS in 513 patients. Dis. of Chest. August 1959.

Chemotherapy Plus Steroid Therapy.

15. McLean, R. L. The role of adrenocorticotrophic and adrenocorticosteroid hormones in the treatment of tuberculosis. Ann. N. Y. Acad. Sc., 1963, 106:130-147.

A review of the development of information pertaining to steroid therapy, significance of the accelerated x-ray response and analysis of the tissue sparing effect.

16. McLean, R. L. Early corticosteroid effect upon acute tuberculous pneumonia. Trans. 22nd Res. Conf. Pulmon. Dis., 1963, p. 97-102.

Marked improvement in gas diffusion in steroid treated cases is interpreted as evidence of the long sought tissue sparing effect.

17. LeMaistre, C., Tompsett, R. et al. Effects of adrenocorticotrophic hormone and cortisone in patients with tuberculosis. J. Clin. Invest., 1951, 30:445-456.

Early assessment of physiologic changes which result in altered appearance of laryngeal tuberculosis and pulmonary lesions on x-ray.

Transmission:

18. Loudon, R. G., et al. An analysis of 3,485 tuberculosis contacts in the city of Edinburgh during 1954-1955. Amer. Rev. Tuberc. and Resp. Dis., 1958, 77:623-643.

Careful study of spread of tuberculosis to contacts. Contacts at greatest risk when sputum, laryngeal swab or gastric contents of the source case positive on microscopy. Greater risk of household contacts confirmed.

19. Chapman, J. S. The adequacy of present criteria of noninfectiousness as measured by tuberculin conversion in the offspring of adults with active tuberculosis of the lung. Amer. Rev. Resp. Dis., 1961, 83:436.

20. Riley, R. L., et al. Aerial dissemination of pulmonary tuberculosis: A two year study of contagion in a tuberculosis ward. Amer. J. Hyg. 1959, 70: 185-196.

Classic experiment establishing droplet nuclei containing tubercle bacilli as the predominant route for transmission.

21. Riley, R. L., et al. Infectiousness of air from a tuberculosis ward. *Amer. Rev. Resp. Dis.*, 1962, 85: 511-525.

Ultraviolet irradiation of air prevented transmission; infectiousness of patients rapidly reduced by chemotherapy, regardless of whether organisms resistant or susceptible. Certain forms of tuberculosis (laryngitis) more infectious (perhaps certain people are better transmitters also).

Chemotherapy: A Tool for Eradication:

22. The Arden House Conference on Tuberculosis, 1959, Public Health Service Publication No. 784, U. S. Gov't. Printing Office, Wash., D. C.

Conferees conclude that eradication of tuberculosis is a perfectly feasible objective in the United States and that the basis should be widespread application of chemotherapy as a public health measure.

23. Canetti, G., The eradication of tuberculosis: Theoretical problems and practical solutions. *Tubercle*, Lond. 1962, 43:301-321.

Sound, basic considerations important in eradication on an international scale are reviewed. Importance of effective chemotherapy stressed; chemotherapeutic regimens for "developing" and "developed" countries clearly defined. Eradication as a long range goal considered feasible.

24. Soper, F. L. Problems to be solved if tuberculosis is to be eradicated. *Amer. J. Public Health*, 1962, 52:734.

Enthusiastic endorsement of a concept of eradication which considers tuberculosis fundamentally as a medical administrative and public health problem.

25. MacLeod, C. M. Biological implications of eradication and control. *Amer. Rev. Resp. Dis.*, 1963, 88:763-768.

Pessimistic views concerned with improbability of eventual eradication voiced by eminent microbiologist. Biological objections drawn from possibly irrelevant analogies with other diseases and inadequacy of use of current tools.

26. Krohn, E. F. Tuberculosis control. *Amer. J. Public Health*, 1963, 53:473-479.

Public health aspects of global control considered; enormity of problem in lands other than United States apparent.

27. The use of chemotherapy as a public health measure in tuberculosis.
ATS statement. Amer. Rev. Resp. Dis., 84:609, 1961.

Chemotherapy recommended for (1) tuberculin positive children less than three years of age (2) tuberculin positive adults with pulmonary lesions whose activity is uncertain (3) tuberculin positive patients who must receive prolonged corticosteroid therapy, or who have had gastric resection, or who are unstable or severe diabetics, or who have nodular silicosis. Chemotherapy considered "discretionary" for household contacts of patients with sputum positive for tubercle bacilli (recommended strongly by other groups).

28. The future of tuberculosis control. A report to the surgeon general of the Public Health Service by a task force on tuberculosis control. 1963, PHS No. 1119, U.S. G.P.O., Washington, D. C.