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MEDICAL GRAND ROUNDS

PARKLAND MEMORIAL HOSPITAL

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"TUBERCULOSIS THERAPY"

Myth, Mumpsimus and Metamorphosis.

[David P. (D.P.) Nicholson]

Verzieht, ich halt Euch auf mit vielen Fragen,
Allein ich muss Euch noch bemuhr.
Wolt Ihr mir von der Medizin
Nicht auch ein kraftig Wortchen Sagen?
Drei Jahr ist eine Kurze Zet
Und, Gott! das Feld ist gar Su Weit,
Wenn man cinem Fingerquerg Nurhat,
Lasst sich's schol eher weiter fuhlen.

Forgive, I hold you up with many questions
But there is one more thing I'd like to see
Regarding medicine, maybe,
You have some powerful suggestions?
Three Years go by so very fast
And, God, the field is all too vast.
If but a little hint is shown,
One can attempt to find one's way.

(Student to Mephistopholes in Goethe's Faust.)

U.S.A.

The new active case rate and death rate for tuberculosis in this country have been falling exponentially for a good many years, and this fall had started well before the introduction of chemotherapy. Presently there are about 50,000 new active cases a year, and about 7,500 deaths. Dallas has between 200 - 250 new cases, and thirty deaths a year.

Tuberculosis is unpopular amongst physicians in this country for four main reasons:

(1) Treatment is now simple and along well established lines.

(2) There is little opportunity for research or original thought except in large scale cooperative trials.

(3) The incidence is falling.

(4) Tuberculosis still carries considerable but unjustifiable 'totem' and 'taboo'.

If the present fall in incidence continues, the new case rate in 1999 will be 1 per 100,000. The elimination of tuberculosis is due less to medical treatment than to the disease being in a self-eliminating phase. It is believed that ten infectious cases probably infect 100 people. (Probably less.) About five of these infected would develop pulmonary tuberculosis, and three of these would themselves be infectious. As ten infectious cases produce three new infectious cases, it is evident that the disease should eventually die out.

The 2,000 new notifications in 1999 would arise as follows:

(1) About 3,300 newly infected cases would produce 200 cases of disease.

(2) 180,000 with inactive disease under surveillance would produce 900 cases.

(3) The 1,800,000 tuberculin positive people would produce a further 900 cases.

This is assuming annual attack rates of about 5% for those recently infected (in the first year), 0.5% for those with inactive disease, and 0.05% for those with positive tuberculin tests but clear x-rays.

HISTORICAL

In 1700 Monget, while performing an autopsy on a youth observed that tubercles were so small as to resemble "millet seed" (millet seed of white poppy, and same size as hemp seed.).

In 1865 Villemin demonstrated that phthisis was a specific affliction caused by an inoculable agent or germ, and 1881 Koch isolated human tubercle bacilli. At that time one-seventh of all deaths were due to tuberculosis, and this rose to one-third in young adults.

In 1931 (Anderson, J.D., McMahon, T.M., and Pinner, M.: A Clinical Trial of Sanocrysin in Pulmonary Tuberculosis, Amer. Rev. Resp. Dis., 1931, 24, 401-435.) a study was made of one of the current treatments of tuberculosis. This was one of the first valid statistical studies undertaken of any medical therapy, and showed that gold injections were valueless in tuberculosis. Unfortunately other current treatments for tuberculosis, such as rest, artificial pneumothorax, pneumoperitoneum, and thorocoplasty, were never similarily evaluated, though undoubtedly many persons appeared to be helped by these methods. The next year, 1932, S.A. Waksman (The Conquest of Tuberculosis. Univ. of Calif. Press 1964) observed that the growth of tubercle bacilli in soil was delayed. From this arose the discovery in 1943 that certain soil actinomycetes had an anti-tuberculosis effect, and in 1944 Streptomycin was isolated from Actinomyces griseus, a soil organism first isolated 28 years earlier.

Thus was inaugurated the era of tuberculosis chemotherapy, to succeed that of the sanitarium regime and collapse therapy.

Other anti-tuberculosis agents followed: 1946 Para-aminosalicyclic acid, 1949 Pyrazinamide, and 1952 Isoniazide. The knowledge of how correctly to use these and subsequent agents was acquired painfully and slowly between 1944 and 1960, and is still being improved and refined.

The first report of the clinical use of Streptomycin in tuberculosis was in 1945, by Hinshaw and Feldman in the Proceedings of the Staff Meetings of the Mayo Clinic. They had given it to thirty-four patients. The first patient ever to receive Streptomycin was a 21 year old white female in the Mineral Springs Sanatarium, Cannon Falls, Minnesota in 1944. She survived far advanced tuberculosis, a three stage thorocoplasty, and an inadequate course of streptomycin, and was alive ten years later, well, married, and with three children. (Amer. Rev. Tuberc., 1955, 7, 752-754.)

In the ensuring years, admidst unbounding optimism, confusion, and finally from planned studies, notably by the British Medical Research Council, and the U.S. Armed Forces Veterans Administration combined studies, the limitations and place of drugs in tuberculosis therapy became appreciated.

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3. The Effect of Streptomycin upon Pulmonary Tuberculosis. Veterans Administration Co-Operative Study, Amer. Rev. Tuberc., 1947, 56, 485-507.

4. Streptomycin Treatment of Pulmonary Tuberculosis. A Medical Research Council Investigation, Brit. Med. J., 1948, 2, 769-782.

5. Treatment of Pulmonary Tuberculosis with Streptomycin and Para-Aminosalicylic Acid. A Medical Research Council Investigation, Brit. Med. J., 1950, 2, 1073-1085.

6. The Prevention of Streptomycin Resistance by Combined Chemotherapy. A Medical Research Council Investigation, Brit. Med. J., 1952, 1, 1157-1162.

7. Robitzek, E.H., and Selikoff, I.J.: Hydrazine Derivatives of Isonicotinic Acid in the Treatment of Acute Progressive Causeous-Pneumonic Tuberculosis, Amer. Rev. Tuberc., 1952, 65, 402-428.

8. The Treatment of Pulmonary Tuberculosis with Isoniazid. Interim Report of Medical Research Council, Brit. Med. J., 1952, 2, 735-746.

9. Isoniazid in the Treatment of Pulmonary Tuberculosis. Second Report to the Medical Research Council, Brit. Med. J., 1953, 1, 521-536.

10. Tucker, W.B.: A Review of the Current Status of the Chemotherapy of Tuberculosis, Ann. Int. Med., 1953, 39, 1045-1061.

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14. Various Combinations of Isoniazid with Streptomycin or with PAS in the Treatment of Pulmonary Tuberculosis. 7th. Report to the Medical Research Council by Their Tuberculosis Chemotherapy Trials Committee, Brit. Med. J., 1955, 1, 435-445.

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16. Long Term Chemotherapy in the Treatment of Chronic Pulmonary Tuberculosis with Cavitation. A Report to the Medical Research Council by Their Tuberculosis Chemotherapy Trials Committee, Tubercle, 1962, 43, 201-212.

17. Johnston, R.N., Smith, D.H., Ritchie, R.T., and Lockhart, W.: Prolonged Streptomycin and Isoniazid for Pulmonary Tuberculosis, Brit. Med. J., 1964, 1, 1679-1683.

RECENT REVIEWS

18. Crofton, J.: Tuberculosis Undefeated, Brit. Med. J., 1960, 2, 679-687.

19. Fox, W.: Chemotherapy and Epidemiology of Tuberculosis, Lancet, 1962, 1, 413-417 and 473-477.

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From the accumulated experience and investigation over the years, a satisfactory approach to the therapy of all typical human tuberculous disease may be outlined briefly. These baseline rules apply to all pulmonary and non-pulmonary disease states which are con-

sidered to be active or are proven to be active, and transgression of these principles may cost the patient his existence.

1. CULTURES OF THE ORGANISM MUST BE SOUGHT DILIGENTLY, IN ORDER TO CLASSIFY THE ORGANISM, AND TO DO IN-VITRO ANTIBIOTIC SENSITIVITY TESTS.

2. MYCOBACTERIA MUST NOT BE PRESUMED TO BE SENSITIVE TO DRUGS UNTIL SHOWN TO BE SO.

3. CULTURE AND SENSITIVITY TESTS SHOULD ONLY BE DONE IN LABORATORIES FULLY EQUIPPED FOR THE PURPOSE - AND WHERE NUMBERS OF SUCH PROCEDURES ARE DONE DAILY BY STANDARD TECHNIQUES.

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1. THE THERAPY OF ACTIVE TYPICAL HUMAN TUBERCULOSIS REQUIRES A MINIMUM OF TWO DRUGS TO WHICH THE ORGANISM IS SENSITIVE.

2. SUITABLE DRUGS TO WHICH THE ORGANISM IS SENSITIVE SHOULD BE GIVEN BY A REGIMEN PROVEN TO BE EFFECTIVE (USUALLY DAILY) FOR A MINIMUM PERIOD OF ONE AND A HALF YEARS.

3. IDIOSYNCRASY - INTOLERANCE - OR HYPERSENSITIVITY REACTIONS TO A DRUG - OR DRUGS MUST BE CAREFULLY EVALUATED. SUSPECTED DRUGS MUST NOT BE WITHDRAWN SINGLY.

4. RECALCITRANT OR UN-CO-OPERATIVE SUBJECTS MAY REQUIRE SPECIAL HANDLING.

There are opinions that consider sanatorium therapy mandatory.

ADVOCATES OF SANATORIA.

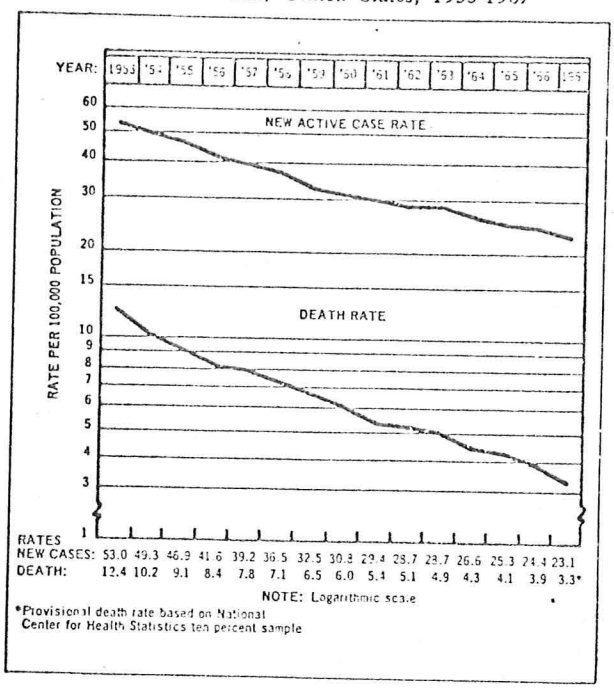
1. It gives better results.
2. Patients co-operate better.
3. Easier to educate and re-assure.
4. Guarantee patients take drugs.
5. Drug toxicity treated more easily.
6. Patients isolated when infectious.

Experience of Madras study indicates none of the above is true. Though certain patients (viz alcoholics) may need combined in-patient therapy and rehabilitation.

The factors influencing response to treatment in order of importance are:

UNIMPORTANT	REST DIET CLIMATE	ACCOMMODATION NURSING etc.
RELATIVELY UNIMPORTANT		SEVERITY OF DISEASE
IMPORTANT		CHEMOTHERAPY CO-OPERATION OF PATIENT

FIGURE 1. *New active tuberculosis case rate and death rate, United States, 1953-1967*



Tuberculosis deaths by age, race, and sex: United States, 1966

Age Groups	Total	White			Nonwhite		
		Total	Male	Female	Total	Male	Female
All ages	7,625	5,486	4,096	1,390	2,139	1,506	633
0— 4	74	33	14	19	41	29	12
5—14	28	15	8	7	13	8	5
15—24	69	30	15	15	39	11	28
25—44	933	440	259	181	493	308	185
45—64	2,962	2,110	1,656	454	852	638	214
65+	3,551	2,852	2,139	713	699	511	188

Note: Totals include 5 deaths in white males, 1 death in a white female, 1 death in a nonwhite male and 1 death in a nonwhite female with age not stated.

Cases on current tuberculosis registers (a), United States

Type	On December 31				
	1963	1964	1965	1966	1967
Hospitalized cases	44,000	42,000	40,000	37,000	32,000
Unhospitalized active cases	61,000	63,000	60,000	53,000	45,000
Active disease cases	105,000	105,000	100,000	90,000	77,000
All other cases on current registers (b)	215,000	215,000	225,000	230,000	238,000
Total cases on registers	320,000	320,000	325,000	320,000	315,000

(a) Estimated.

(b) Cases with activity undetermined and inactive cases under current supervision.

NOTE: Tuberculosis registers include records of the active cases currently under care, the cases for which disease activity has not been determined, and inactive cases under supervision. Also retained on health department rolls are records of people who fail to respond to treatment or who have received inadequate or interrupted treatment.

New active tuberculosis cases, cities of 250,000 or more population, 1967

Cities	New active cases		
	Number	Rate per 100,000 population	Rate rank order
Akron, Ohio	42	14.0	46
Albuquerque, N. M.	39	16.7	42
Baltimore, Md.	683	75.1	1
Birmingham, Ala.	200	56.9	4
Boston, Mass.	276	41.9	18
Buffalo, N. Y.	215	46.2	10
Chicago, Ill.	1,989	56 0	5
Cincinnati, Ohio	143	28 6	28
Cleveland, Ohio	289	35.1	20
Columbus, Ohio	88	16.1	43
Dallas, Tex.	242	28.8	27
Dayton, Ohio	91	34.0	21
Denver, Colo.	88	18.4	41
Detroit, Mich.	951	59.4	3
El Paso, Tex.	96	30.2	24
Ft. Worth, Tex.	104	25.2	30
Honolulu, Hawaii	183	50.4	7
Houston, Tex.	562	47.3	9
Jersey City, N. J.	115	42.5	16
Kansas City, Mo.	143	28.2	29
Long Beach, Calif.	52	13.6	47
Los Angeles, Calif.	851	30.1	25
Milwaukee, Wisc.	173	22.4	32
Minneapolis, Minn.	73	15.8	45
Newark, N. J.	296	74.3	2
New Orleans, La.	224	32.9	22
New York, N. Y.	3,542	43.6	15
Norfolk, Va.	126	40.7	19
Oakland, Calif.	84	22.0	34
Oklahoma City, Okla.	74	19.2	39
Philadelphia, Pa.	942	45.1	12
Pittsburgh, Pa.	253	45.6	11
Portland, Ore.	118	30.7	23
Rochester, N. Y.	90	29.4	26
Sacramento, Calif.	124	44.9	13
St. Louis, Mo.	281	44.8	14
St. Paul, Minn.	62	19.8	37
San Antonio, Tex.	295	42.1	17
San Diego, Calif.	133	19.8	38
San Francisco, Calif.	368	49.2	8
San Jose, Calif.	72	18.7	40
Seattle, Wash.	142	24.5	31
Tampa, Fla.	68	21.5	35
Toledo, Ohio	63	16.0	44
Tucson, Ariz.	55	22.0	33
Tulsa, Okla.	63	21.3	36
Washington, D. C.	423	52.4	6
Wichita, Kans.	39	13.6	48
Total—48 Cities	15,625	39.8	..
San Juan, P. R.	228	46.1	..

DRUG THERAPY

There have been a number of drugs other than Streptomycin, Isoniazid, and Para-Aminosalicylic Acid developed for the treatment of active tuberculosis, more particularly since the individuals may present with bacterial insensitivity or poor tolerance to the big three drugs. For some years these second line drugs were used mainly for resistant cases. However, the position is now changing, and it is as well to review the situation briefly.

PYRAZINAMIDE. Actually an older drug, and developed before Isoniazid. However despite its demonstrable efficiency, and ability to 'sterilize' lesions in the guinea pig, it fell into disrepute for two reasons:

(1) INCIDENCE OF HEPATIC TOXICITY.

(2) RAPID EMERGENCE OF BACTERIAL RESISTANCE.

Liver toxicity was noted in 5 - 10% in early studies when dosage varied up to 200 mgm/Kgm/day. At present conventional and effective dosage, ie 25 mgm/Kgm/day (maximum dose 2.5 grams/day), toxicity is extremely rare, and is reversible. In addition the drug is well tolerated.

Because of the rapid emergence of bacterial resistance the dictum arose that the drug was ineffective after three months. However, resistance only emerged early (within three months), when the drug was given alone, unaccompanied by a second effective drug. To date all anti-tuberculosis drugs, when given alone, or when given in combination with an ineffective agent, result in rapid emergence of resistance to that drug. PZA is no exception, but if given in combination with another effective drug, then resistance does not emerge over long periods.

Further, in-vitro testing for bacterial resistance to PZA is unreliable. Clinically typical human bacilli are sensitive, if the patient and his bacterial population have not been exposed to the drug, alone or unprotected, in vivo.

PZA is an extremely efficient bactericidal agent against human strains of mycobacteria when used with another effective agent. At present dosage, toxicity is extremely low, and the drug is well tolerated for sufficiently long periods. Finally, since it does specifically inhibit distal tubular re-excretion of uric acid, hyperuricemia or clinical gout may arise during therapy.

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30. Phillips, S., and Horton, G.E.: Pyrazinamide - Isoniazid, Amer. Rev. Tuberc., 1956, 73, 704-715.

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32. Clinical Efficacy of Combinations of Four Anti-Tuberculosis Drugs. The Co-Operative Unit in Chemotherapy of Tuberculosis of the National Sanatoria of Japan, Tubercle, 1966, 47, 340-348.

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35. A Controlled Comparison of Four Regimens of Streptomycin plus Pyrazinamide in the Re-Treatment of Pulmonary Tuberculosis. East/African/British Medical Research Council Pyrazinamide Investigation, Tubercle, 1969, 50, 81-84.

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ETHIONAMIDE. (Iso-Ethyl Thioisonicotinamide) This drug was introduced in 1959, and shown to be effective against INH resistant organisms, and to effectively penetrate the cerebro-spinal fluid.

Ethionamide is an acceptable and efficient companion drug to INH etc, but at doses over 750 mgm a day the incidence of gastric intolerance and nausea is high. A daily dose of 500 mgm may be inadequate. Potentially toxic to the liver, the evidence of this is usually only seen in alcoholics, or in patients with prior liver disease. Rarely may cause peripheral neuritis or goitre.

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42. Hughes, I.E., Smith, H., and Kane, P.O.: Ethionamide: Its Passage into Cerebro-Spinal Fluid in Man, Lancet, 1962, 1, 616-617.

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ETHAMBUTOL. In early trials of this drug (1961-2), ocular toxicity was disturbing, but with a reduction in dosage toxicity is virtually zero, effectiveness is high, and tolerance excellent. No other toxic effects noted. Presently used in a dose of 25 mgm per Kgm for two months, and then 15 mgm/Kgm. Doses lower than this may be less effective.

It is not necessary to do visual activity and field tests before starting drug. The effects, if any, on the second nerve are of two types, and are fully reversible on the discontinuance of drug. Central axial toxicity occurs at lower doses, and periaxial at higher doses. Axial toxicity causes central scotoma and reduction in visual perception of GREEN.

Ethambutol is very well tolerated, and is displacing PAS as a companion drug with INH in basic treatment regimens. Comparative costs indicate that it is now reasonable to do this.

Leibold: Ocular Toxicity of EMB 907

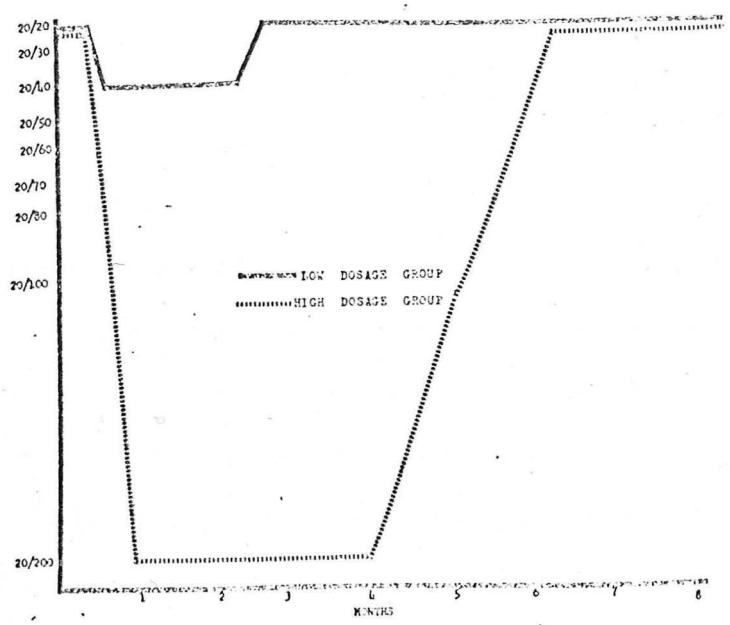

FIGURE 1. Comparison of severity of axial toxicity between low dosage groups and high dosage groups.

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53. Bobrowitz, I.D.: Comparison of Ethambutol - INH Versus INH-PAS in Original Treatment of Pulmonary Tuberculosis, Ann. N.Y. Acad. Sci., 1966, 135, 921-939.

54. Leibold, J.E.: The Ocular Toxicity of Ethambutol and its Relation to Dose, Ann. N.Y. Acad. Sci., 1966, 135, 904-909.

55. Bobrowitz, I.D., and Robins, D.E.: Ethambutol - Isoniazid Versus PAS-Isoniazid in Original Treatment of Pulmonary Tuberculosis, Amer. Rev. Resp. Dis., 1967, 96, 428-438.

56. Place, V.A., Pyle, M.M., and de La Huerga, J.: Ethambutol in Tuberculous Meningitis, Amer. Rev. Resp. Dis., 1969, 99, 783-785.

RIFAMYCIN-RIFAMPIN. (1957). Rifamycin was obtained from Streptomyces mediterranei, and this and an oxidation produce Rifamycin SV were found to be active against a variety of organisms including mycobacteria. Given intravenously, the drug was concentrated quickly in the liver and excreted in the bile. A semi-synthetic derivative, Rifampin (RMP), is absorbed orally and excreted slower.

Typical human strains, including strains resistant to INH, are susceptible at 0.01 - 2.0 micrograms/ml. Mycobacterium kansasii at 0.5, and some group III organisms

at 2 - 5 micrograms/ml. Given before a meal, doses of 450 - 600 mgm orally produce blood levels of 16 - 32 micrograms/ml at two hours, 8 - 16 at six hours, and 1 - 2 at twelve hours. Toxicity is very low, and tolerance is high. Natural resistance occurs quickly in all organisms, so the drug is unlikely to become of much value in coccal and bacterial infections. If used alone in human tuberculosis, resistance develops by a one step mutation in $1 \times 10^{7-8}$ generations, or a little slower than resistance develops against INH or Streptomycin.

The drug is highly effective clinically, along with another drug, against human tuberculosis. Experimentally in mice it is the single most effective agent, and completely sterilizes lesions in 21 weeks. Neither Rifampin, nor INH, given alone, will completely sterilize all lesions in 12 weeks, though Rifampin has a greater effect. However, the drugs given together will completely sterilize all lesions in 12 weeks.

This ability to sterilize lesions may open up possibilities of clinical cure with less than 18 months treatment. Furthermore, the drug remains active against the mycobacteria for several days, after a relatively short period of exposure. Thus this agent may be ideally suited, along with Ethambutol, which shares this property, for intermittent dose regimens.

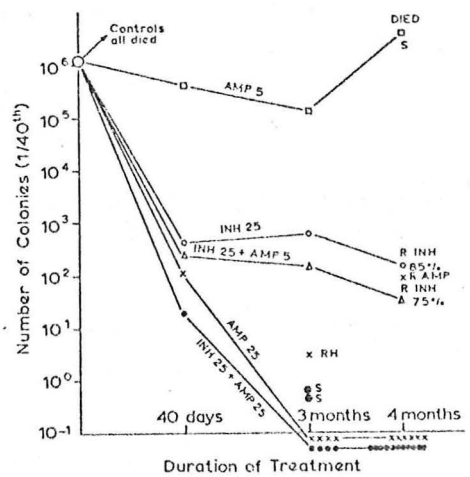

FIG. 5
Comparison of the efficacy of rifampicin (AMP) and isoniazid (INH) in various doses and combinations. S = sensitive; R = resistant.
(CRUMBACH)

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ANTI-TUBERCULOSIS DRUG ACTIONS.

ISONIAZID	D.N.A. and cell intermediary metabolism.
CYCLOSERINE.	CELL WALL SYNTHESIS.
ETHAMBUTOL.	R.N.A.
RIFAMPICIN.	INHIBITS D.N.A. dependent R.N.A. polymerase.
PYRAZINAMIDE.	'UNKNOWN'
STREPTOMYCIN.)	
KANAMYCIN etc.)	PROTEIN SYNTHESIS.
ETHIONAMIDE.)	
PAS.	INTERMEDIARY METABOLISM, competes with PABA.

COST OF ONE YEARS TREATMENT

		Dollars	Cents
ISONIAZID	(100 mgm T.I.D.)	1	60
SODIUM PAS	(15 GM/day)	33	00
NEOPASALATE	(12 GM/day)	67	00
TRIPAC	(INH + PAS T.I.D.)	106	92
ETHAMBUTOL	(400 mgm B.I.D.)	68	00
ETHIONAMIDE	(250 mgm T.I.D.)	180	00
PYRAZINAMIDE	(500 mgm T.I.D.)	138	00
INH + ETHAMBUTOL		70	00
STREPTOMYCIN		60	00
KANAMYCIN		1230	00
VIOMYCIN		507	00
RIFAMPICIN		ASTRONOMICAL	

ANTI-TUBERCULOSIS DRUGS

DRUG	USUAL DOSE	ADDITIONAL	TOXICITY	
Isoniazid	100 mgm. t.i.d.	B_6 in small doses.	Impairment of concentration. Peripheral Neuropathy.	Rashes. Hepatitis.
Streptomycin	1 gram a day, or three times a week.		Vertigo. Peri-oral paraesthesiae.	Rashes Renal damage.
P.A.S.	10 - 12 grams of P.A.S.		G.I. disturbances. Goitre. Anemia.	Rashes, acne. Hepatitis.
Ethionamide	250 mgm. three - four times a day.	B_6 in small doses.	G.I. disturbances. Goitre. Peripheral Neuropathy.	Rashes. Hepatitis.
Ethambutol	25 mgm./kgm/day 10 - 12 weeks then 15 mgm./kgm/day.		Optic Neuritis.	Rashes, but rare.
Cycloserine	250 mgm. t.i.d.	B_6 in high doses.	Psychoses. Convulsions.	
Pyrazinamide	25 - 30 mgm./kgm/day. Maximum 2.5 grams.		Hyperuricemia.	Hepatitis.
Kanamycin Viomycin	4 grams a week.		Ototoxicity.	Renal damage. Rashes.
Rifampin	Promising drug, under study. 450 mgm./day			

OUT-PATIENT INTERMITTENT CHEMOTHERAPY

A number of factors have led to trials of intermittent dose regimens in the treatment of pulmonary tuberculosis.

(1) A number of studies, using 'spot' urine tests, home checks and pill counts have shown that only 60 - 70% of patients take their medicines as prescribed, and that many patients miss up to 40 - 50% of their doses. Yet, despite this, 90 - 98% of patients do well and achieve a stable and inactive status.

(2) Social 'mores' no longer accept or require the prolonged physical detention of the co-operative or of the recalcitrant patient.

(3) The cost or prolonged hospital and daily drug therapy is becoming expensive for the affluent, and is prohibitive for the less wealthy, where most of the problem remains. In any event modern drug therapy does not require prolonged hospital care.

(4) Animal experiments have shown that intermittent chemotherapy produces acceptable results, and that certain drugs may be even more effective given in this way.

As yet, intermittent regimens have not been shown to produce as effective long term control of the disease as have daily regimens, and short term results are enhanced by a preliminary 8 - 12 week period of daily therapy.

At least the future holds the prospect of short periods of hospital care, followed by supervised intermittent chemotherapy, perhaps for periods less than a year and a half. However, intermittent regimens are clearly more fragile in certain respects, and fast inactivators

of Isoniazid do less well than slow inactivators.

The greater the interval between doses, following exposure of organisms to drug, the less the effect of the drug on the organisms. Exposure time is important as is the interval between doses. In both respects SM is the most efficient potential intermittent agent, being effective for upwards of eight days after less than 24 hours exposure. Isoniazid, to be effective, requires 24 hours exposure, and rapidly looses efficiency if intervals between doses is greater than three days. Thus, suitability of drug for intermittent chemotherapy depends primarily on length of time bacterial multiplication is inhibited after exposure to it. If growth not suppressed between doses, there may be a rapid emergence of resistance.

Ethiomamide, experimentally, appears moderately suitable. Ethambutol, however appears to increase in efficiency if the interval between doses is increased to two or three days. Intermittent short exposure to high dose being more effective than prolonged contact with lower concentrations.

A number of studies have now been undertaken of intermittent chemotherapy regimens (mainly using SM with INH), and results have been very favourable in all but two of these studies, that of Fridmodt-Möler in Rural India, and that of Burzoni in Morocco. The Madras trial has reported on a four year follow up of 119 patients who had bacteriologically quiescent disease at the end of a year of chemotherapy with either a fully supervised twice-weekly regimen of INH + SM (66 patients) or a standard self administered daily regimen of INH + PAS (52 patients).

SERIES	TOTAL PATIENTS	PATIENTS WITH BACTERIOLOGIC RELAPSE					
				YEAR OF RELAPSE			
		NO.	%	2nd.	3rd.	4th.	5th.
SHTW	66	8	12	3	3	1	1
PH	52	8	15	3	3	1	1

Follow up experience was the same in both treatment groups. Treatment was only for one year, which may not be sufficient - actual relapse rates are rather high, but similar, indicating on identity between Intermittent Supervised, and Unsupervised Daily regimens.

From these and other experiences certain preliminary conculsuions may be inferred:

(1) Efficient Intermittent Chemotherapy regimens are of great value in treating the recalcitrant patient, and may become of greater efficiency, and so be suitable for all cases.

(2) At the present time all intermittent regimens should be preceeded by a period, probably 12 weeks, of efficient daily therapy, by which time all cases should be bacteriologically negative.

(3) The Intermittent Regimen should be maintained for 1-1/2 years, and at this time should be one of SM/INH or possibly SM/Ethambutol, provided toxicity is more closely related to mean dose, rather than to the size of the individual doses.

(4) The total weekly dose of a drug in an Intermittent Regimen needs to approach the weekly dose total shown to be effective for that drug if given daily.

ie. daily INH 4 mgm/Kgm. BIW 15 mgm/Kgm. BIW
daily SM 10 mgm/Kgm. BIW 30 mgm/Kgm. BIW

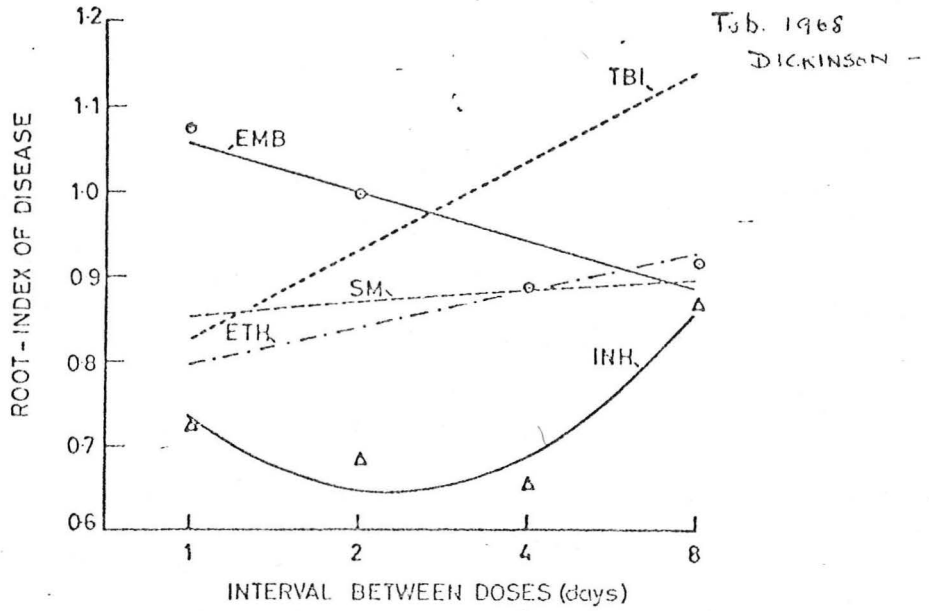

FIG. 3

Mean root-indices of disease related to interval between doses in guinea-pigs treated with isoniazid (△), ethambutol (⊙), thiacetazone, streptomycin or ethionamide (points for individual means with these three drugs have been omitted).

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URINE TESTS FOR TBc DRUGS

ACETYLISONAZID TEST.

Solution A. 10% KCN in distilled water.
B. 10% Chloramine-T (Eastman-Kodak) in distilled water.
Four drops urine, four of A and 10 of B successively in small p rcelain well.
Positive → Red.

PARA-AMINOSALICYLIC ACID.

(1) 2 ml urine, 6 drops fresh Ferric Chloride solution. Turns purple in presence of PAS or ASPARIN.
(2) PHENISTIX paper. Turns red-brown in presence of PAS, SALICYLATES, and PHENOTHIAZINES.

PYRAZINAMIDE.

ACETEST tablet on white tile, add one drop of urine. Turns pink within 2 - 10 minutes.

ETHIOAMIDE. See reference Eidus and Harnanansingh, 1968.

ETHAMBUTOL.

Bromthymol blue and benzene extraction. (Lederle Laboratories, Medical Communication Department.)

RIFAMPIN.

Drug and metabolities are chromogens, which can be extracted with chloroform.

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STEROIDS AND TUBERCULOSIS

Since the work of Lurie in rabbits, there has been a good deal of experimental evidence that glucocorticoids reduce native resistance to tuberculosis and other infections. Although the organisms do not multiply faster in the mononuclear cells, steroids allow more cell injury from 'bacterial' cytotoxins. Clinically it is not common to see 'spread' of inactive disease in patients on steroids, nevertheless the risk is sufficient to warrant certain precautions:

(1) Known positive skin reactors (P.P.D. Intermediate greater than 9 mm) placed on steroids should receive Isoniazid 100 mgm t.i.d.

(2) Patients with lymphoma, leukemia, or myelo-proliferative disease placed on steroids or anti-metabolities should also receive Isoniazid, regardless of the status of the skin test.

There are of course other times when Isoniazid chemoprophylaxis should be given, and though we are not specifically concerned at this time, it might be as well to list the indications:

(1) INACTIVE TUBERCULOSIS. Previously untreated, and presently sputum negative.

(2) CONTACTS OF NEW ACTIVE CASES. If negative by sputum but positive by skin test.

(3) KNOWN SKIN TEST CONVERTORS.

(4) MEASLES OR PERTUSSIS IN SKIN TEST POSITIVE CHILDREN.

(5) PREGNANCY. If evidence of inactive, untreated disease.

(6) POSITIVE REACTORS.

(a) Post-Gastrectomy.

(b) Diabetic.

(c) Silicosis.

A number of trials have been undertaken of the effect of steroids in the treatment of active pulmonary tuberculosis, and several conclusions may be made:

LONG TERM EFFECTS.

There is no evidence that steroids in combination with tuberculosis chemotherapy affects the long term result, either functionally or radiographically. Patients treated with steroids do have a marked early subjective improvement, and radiographic resolution is enhanced at three months, but not at six months.

SHORT TERM EFFECTS.

Systemic symptoms of tuberculosis, such as fever, anorexia, anemia, and 'toxaemia' are immediately ameliorated by steroids. In particular this is true of painful lesions, such as oro-pharyngeal or ano-rectal ulcers, which may enable a patient to survive long enough for drug therapy to be effective, and certainly on occasions, more comfortably.

Steroids will not allow all patients to survive. Severly ill patients with very far advanced disease will still die, often of respiratory failure. Severly ill patients with moderately advanced disease should survive, and in certain circumstances steroids may improve the outlook.

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STEROIDS IN TUBERCULOUS SEROSITIS.

A. PLEURAL EFFUSION.

Early observations revealed that tuberculous pleural effusion was followed by active pulmonary tuberculosis in 30% of patients, over a five year follow up. This breakdown rate was NOT altered by treatment with bed rest, but was reduced to less than 5% with one year of a suitable two drug regimen. However, drug therapy, whilst it did decrease the duration of the fever, did not enhance the rate of resolution of the fluid, nor did it affect the extent of residual pleural thickening. Similarly, removing as much fluid as possible by thoracentesis, and repeating the proceedure as fluid re-collected did not affect the duration of the effusion, or the result, as judged radiographically.

The concomitant use of steroids (systemically or intra-pleurally) with drug therapy is a vexed question. There are virtually no definitive studies, and at least in the so called 'developed' countries, the incidence of tuberculous pleural effusion is dwindling fast. It is

difficult also to analyze some studies as the series may include a fairly high percentage of bacteriologically unproven cases. Nevertheless it is abundantly clear from the data available that systemic steroid therapy, and possibly intra-pleural instillation of steroids at the initial thoracentesis, has a remarkable effect.

(1) The effusion resolves in an average of four weeks, against 8 - 12 weeks without steroids.

(2) Fever, and subjective symptoms resolve almost at once.

(3) There is a marked reduction in residual radiological abnormality.

Thus, morbidity can be reduced, hospital stay shortened, and a return to work on chemotherapy advanced.

TBc EFFUSIONS: HYDROCORTISONE and CONTROL GROUPS
Mathur et al 1960

		ABSORPTION OF FLUID			
	No.	Striking	Good	Fair	Poor
HYDROCORTISONE	25	18	3	2	2
CONTROL	25	0	2	7	16

There are arguments against the use of steroids. Some patients fail to appreciate the necessity of taking two anti-tuberculosis drugs for at least one year, and after a brief illness accompanied by the sense of well being imparted by steroids, this necessity may be even harder to accept.

Finally, it has been shown in children that steroids have no beneficial effect on pulmonary function after the effusion, and in fact it was concluded that tuberculosis ef-

fusion in childhood does not impair the ventilo-respiratory function of the lung.

There is no similar data in adults, and whilst one might surmise that the ultimate pulmonary function would be improved there is no proof yet that this is so.

In conclusion, it would appear that whilst primary uncomplicated tuberculous effusion requires two "effective" drugs for a minimum of one year, that the use of steroids initially is optional, and possibly 'harmful'. Certainly it is important to keep the patient active and encourage deep breathing exercises, which may be as important in maintaining ventilatory function as any other factor.

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B. PERICARDIAL EFFUSION.

Tuberculous pericardial effusion untreated will proceed to constrictive pericarditis and death in around 80% of cases. Since the advent of drug therapy the incidence of constriction has fallen to 40%, and is probably less in instances where treatment has been instituted very early.

There is a rather sparse literature pertaining to the point, but such evidence as there is strongly suggests that the addition of steroid therapy probably further halves the incidence of 'chronic' constriction. Certainly in early cases there is a rapid resolution of the fluid, and practically no sequelae. If the fluid is very turbid, or the situation is one of pericardial tuberculous empyema, then steroids have less effect. If at pericardial biopsy there is evidence of thickened pleura or of constriction, then pericardiectomy should be done at the time. Similarly, pericardiectomy should be done during follow up any time there is evidence of constriction. The only exception to this is a lone rise in jugular venous pressure, without other clinical signs of constriction, when a week or so of observation is permissible, since on oc-

casions the rise in jugular venous pressure may abate.

The results of pericardiectomy have improved since the advent of drug therapy.

RESULTS OF SURGERY FOR CONSTRICTIVE PERICARDITIS.

AUTHOR		NO.	MORTALITY IMMEDIATE	LATE	TOTAL
Evans	1952	30	1	4	5 15%
Cooley	1958	72	14	13	27 37.5%
Johansson	1959	50	6	1	7 14.0%
Malm	1963	15	2	3	5 33.3%
Blakemore	1960	28	3	?	? 3 10.7%
Effler	1961	26	2	7	9 34.5%
Glenn	1962	33	2	13	15 45.5%
Portal	1966	56	2	2	4 7%
Dayem	1967	22	1	1	2 9%

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C. PERITONEAL EFFUSION.

There is very little data on the use of steroids in tuberculous peritonitis, though probably one can extrapolate from the results in tuberculous pleural effusion. A recent

article, however, indicates that steroids help to reduce the incidence of intestinal obstruction during follow up.

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TUBERCULOUS MENINGITIS.

The outlook in tuberculous meningitis has steadily improved over the years since the advent of drug therapy.

SURVIVAL RATES.

1947-52	SM and PAS	309.	60% Survived.
1952-53	SM, PAS, and Isoniazid	112.	88% Survived.

Mortality is highest in infants, and in those with stage three disease.

CLINICAL GRADES MRC (1948).

1. FULLY CONSCIOUS. NO C.N.S. SIGNS.
2. NEITHER 1 OR 3.
3. DEEP COMA - INACCESSIBLE.

Since the introduction of Isoniazid there has been no good indication for the use of intrathecal Streptomycin, and the daily intra-muscular dose can be kept at levels that rarely lead to ototoxicity, ie 10 - 15 mgm/Kgm/day.

Despite the enthusiasm of the Oxford group for intrathecal tuberculin, this is not shared by other workers, and nor is there presently any remaining enthusiasm for the intrathecal use of fibrinolytic agents in impending C.S.F. block.

Indeed the prevailing consensus of opinion is to use systemic steroids in all infants, in empending block in older age groups, and in clinical stage 3 disease. Neurosurgical drainage may still be required despite steroids, particularly in case diagnosed late in the course of the disease. The Oxford group do agree, however, that steroids are indicated in the face of (1) cerebral edema, (2) hyperpyrexia, and (3) circulatory failure.

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INDICATIONS FOR USE OF STEROIDS IN TUBERCULOSIS.

(1) Severe systemic symptoms which prejudice survival in the face of treatable disease.

(2) Severe drug hypersensitivity, but combined with suitable and effective alternative drug therapy.

(3) Tuberculous Meningitis in all infants, and in stage 3 (and possibly stage 2) disease in older children and adults.

(4) Tuberculous Pericarditis.

LESSER INDICATIONS.

(5) Tuberculous pleural and peritoneal effusions.

(6) During essential drug desensitisation. Rarely necessary, and two other effective drugs must be given concurrently.

In Tuberculous Meningitis steroids should be given, if indicated, until the C.S.F. protein is less than 40 mgm %. Initial dose would be 40 mgm daily of Prednisilone or equivalent, and maintenance dose 20 mgm daily. For drug desensitisation the maintenance dose should be sufficient to suppress symptoms over a 4 - 6 week course of desensitisation. In the remaining situations steroids may be given for 4 - 8 weeks, with an initial dose of prednisilone of 40 - 60 mgm a day, or equivalent, and decreasing in successive step wise fashion throughout the course.