The History of Pyrazinamide

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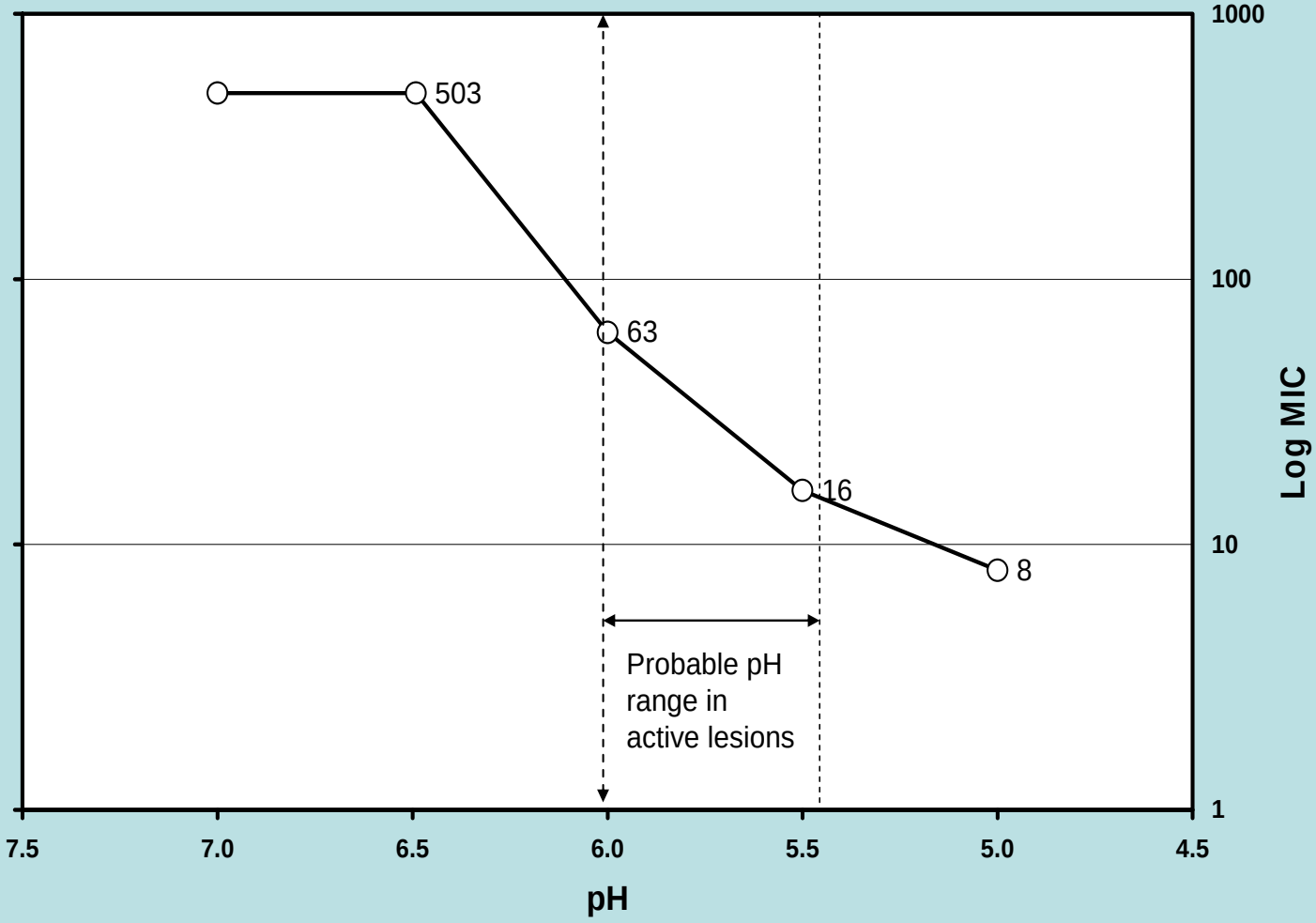
Discovery

- Nicotinamide (Vit B3) found to inhibit TB (Chorine)
- 1952 PZA found to be most active B3 analogue in mice (Lederle and Merk labs)
- But inactive in guinea pig TB and in culture
- Actively explored in Walsh McDermott's lab at Cornell (McCune, Tompsett). First use of long term mouse model.

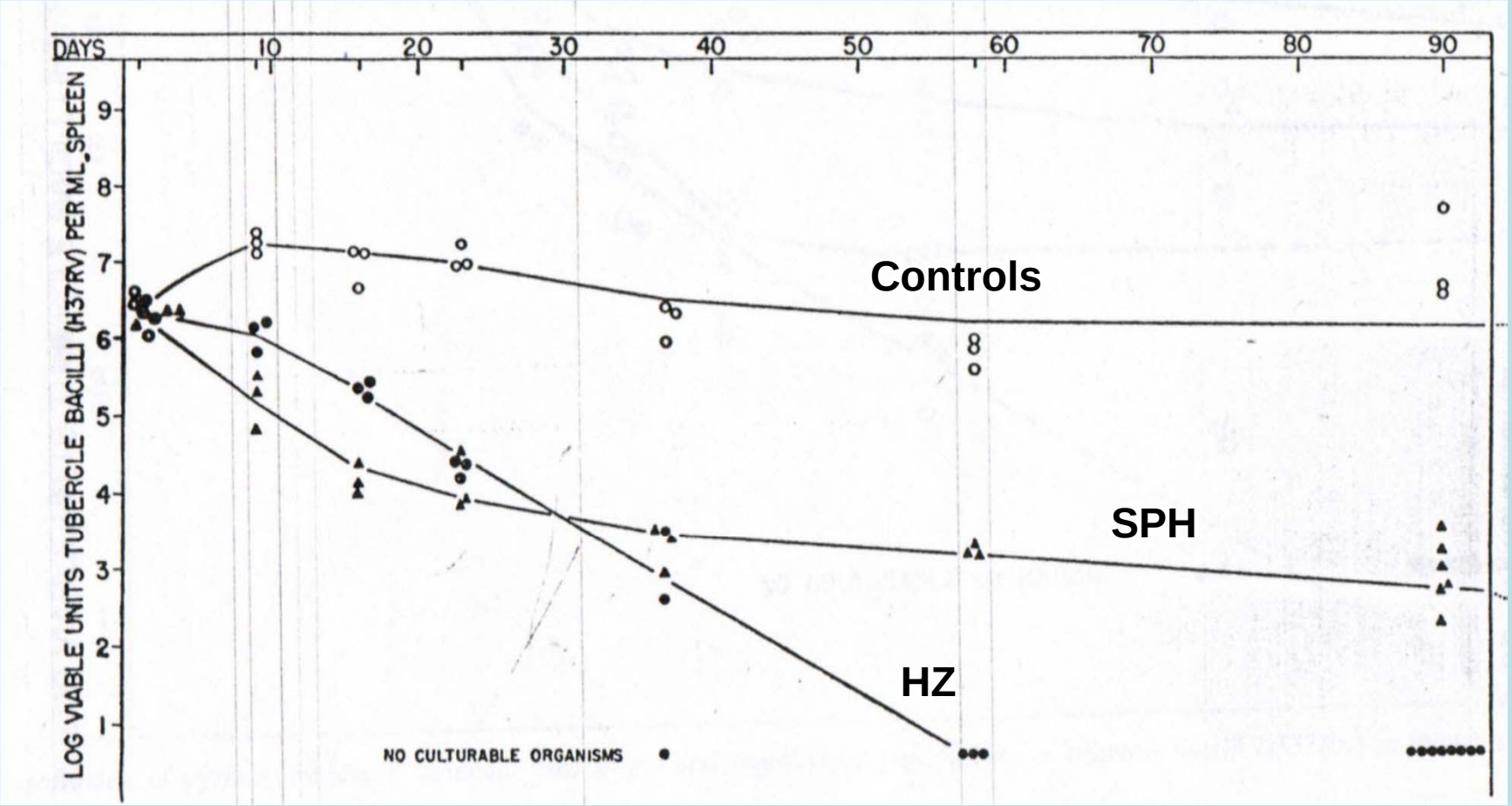


Relationship between pH and log MIC of PZA

McDermott & Tompsett Am Rev Tuberc 1954 70 748

Action of PZA+INH in long term mouse model

McCune, Tompsett, McDermott J Exp Med 1956 104 763-803



PZA is a pro-drug. Pyrazinoic acid is the active moiety

- Pyrazinoic acid (POA) is liberated when TB are exposed to PZA. POA is as active as PZA in vitro.
- The bacillary amidase that produces POA also deaminates nicotinamide.
- POA by mouth to mice was inactive against TB

Konno, Feldmann,McDermott Am Rev Tuberc 1967 95 461

INH + PZA v. INH + PAS
Veterans Administration trials

- INH 300 mg + PZA 3 g daily
- INH 300 mg + PAS 12 g daily

No difference in:

X-ray improvement, cavity closure, culture conversion.

Toxicity → discontinuation of regimen:

INH + PZA 35 (13%): 21 abnormal liver function tests, 6 jaundiced, 6 ?prodromal for hepatic dysfunction: 2 renal

INH + PAS 19 (7%): 13 gastrointestinal, 6 hypersensitivity

J Matthews Am Rev Resp Dis 1960 81 348

PZA as a reserve drug (1958-70)

- The combination

  Ethionamide / PZA/ cycloserine

  was explored and found to be an effective reserve drug combination but very toxic and difficult to give to patients for 12 months
- We now know toxicity was due to ETH/CYC but PZA was labelled incorrectly as highly toxic

East African multi-centre study (1972)

Treatment for 6 months with 30 month follow-up

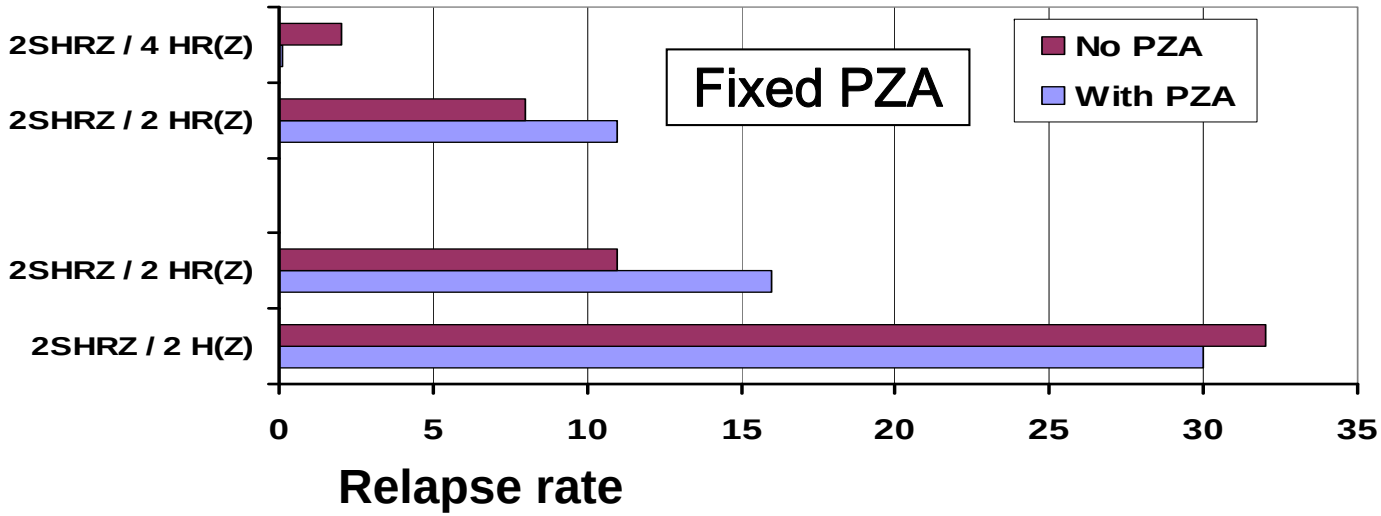
Regimen	Total patients	Cult –ve at 2 months (%)	Relapses (%)
SH	112	*49*	*29*
SHT	104	*42*	*22*
SHZ	153	*66*	*8*
SHR	152	*69*	*3*

East African/British Medical Research Council Lancet 1972; 1079:1085

R and Z act synergistically in the initial phase

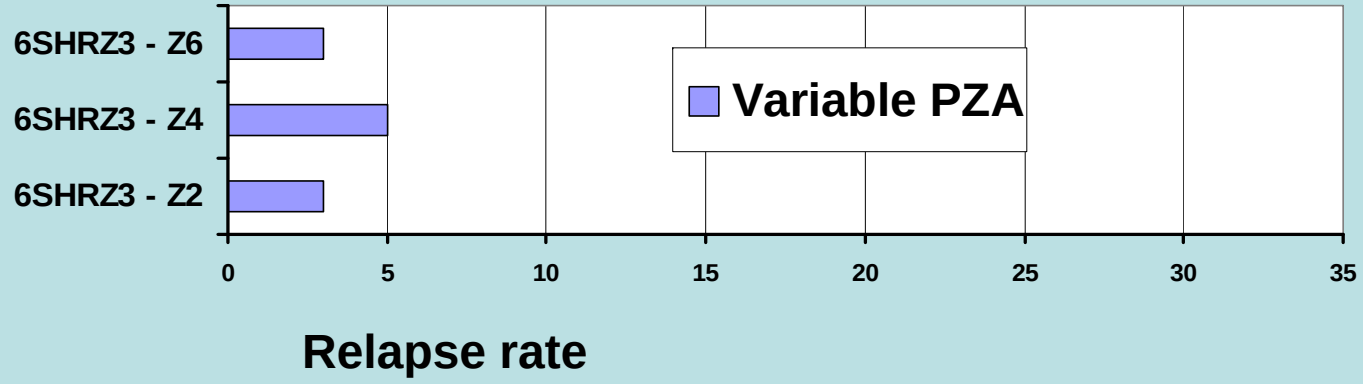
Site	Regimen	No. of patients	2-month sputum culture negative (%)	Relapse rate (%)
Africa	2SHRZ/TH	156	*87*	*13, 0*
	2SHR/TH	159	*75*	*18, 6*
	2SHRZ/TH or SHZ_2	338	*81*	-
	6SHR	171	*70*	-
Madras	$2SHRZ/SHZ_2$	132	*92*	*0*
	$2SHZ/SHZ_2$	129	*72*	*4*

Does PZA sterilize in the continuation phase?



Singapore

E Africa



Hong Kong