

In group III, Table III are the cases in which treatment has failed to produce any improvement.

As shown in Table III there was a rise in the percentage of oxygen saturation in only one case. There was a fall in one case and 4 remained the same. There was a rise in the percentage of O<sub>2</sub> saturation of the deep venous blood in one case. There was no change in 2, and a fall in 2. In one case the percentage was not recorded for the deep venous blood after treatment.

These observations show that the oxygen saturation test does *not* offer an absolute standard as to prognosis in treatment of arteriosclerotic vascular disease of the extremities with the alternate suction and pressure method. Generally speaking, however, an increase in oxygen saturation of either the superficial or the deep venous blood, or a rise in both, after one hour trial treatment indicates that some improvement will follow this form of therapy. When there is no change or a fall in the oxygen saturation after one hour trial treatment the prognosis is quite poor. There may be a wide discrepancy between the changes of the oxygen content of the deep and superficial venous blood after treatment with alternate suction and pressure therapy.

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### Thermotherapy in Experimental Tuberculosis.

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The possible value of various meteorologic factors in the prevention and treatment of pulmonary tuberculosis cannot be determined with certainty from an analysis of the fluctuating morbidity and mortality rates, which are so much more responsive to other influences.<sup>1</sup> Methods recently used in the attempt to explain the existing variations in the tuberculosis-rates in different parts of the United States on the basis of climatology would give quite different conclusions if applied to the figures of half a century ago.<sup>2</sup>

An enormous clinical experience has yielded a similar diversity of conclusions. Davos and Saranac Lake, Florida and the Riviera, Asheville and Italy, Colorado and Egypt, offer every combination of

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<sup>1</sup> Evans, G. A., *Handbook of Historical and Geographical Phthisiology*, 1888.

<sup>2</sup> Cowles, A., and Chapman, E. N., *J. Am. Stat. Assn.*, 1935, **30**, 517.

altitude, humidity and temperature to the enthusiastic but inconsistent climatologist.<sup>3</sup> Human experiments such as afforded by the group who inhabited Mammoth Cave in Kentucky<sup>4</sup> or a similar group in Alaska<sup>5</sup> have been likewise inconclusive. The effects of artificial hyperpyrexia<sup>6</sup> in the treatment of pulmonary tuberculosis still lack confirmation. Animal experiments<sup>7, 8</sup> have repeatedly disproved the reported<sup>9</sup> beneficial results of briefly exposing tuberculous animals to high temperatures. Induction of fever by the administration of dinitrophenol, 5 mg. 3 times a week,<sup>10</sup> or by exposure to the general or local condenser-field or the electromagnetic field of 6-meter wavelength 1500-watt generator twice weekly for 10-minute periods<sup>11</sup> were similarly without demonstrable effect on the course of experimental tuberculosis in guinea pigs.

On the other hand, the exposure of infected guinea pigs to continuous warmth throughout the period of infection has given definite and surprisingly good results. So far, 225 guinea pigs, kept in 45 cages, at a temperature of over 80°F., and usually between 85 and 90°, at the Olive View Sanatorium for 3 months after inoculation with from 0.1 to 0.0001 mg. of the virulent human type tubercle bacilli H37, H98, or H115 during the past 5 years have shown, on the average, just half as much tuberculosis when necropsied at the end of 3 months as did 150 guinea pigs similarly inoculated at the same time and kept in 30 cages at outside temperature. Only once did a set of guinea pigs kept in a warm cage show more tuberculosis than did the controls, while 44 different sets of 5 guinea pigs kept in the warm room showed less.

The average amount of tuberculosis, on the scale of 16 units per pig, or 80 per cage, as described previously,<sup>12</sup> was 32 units for the controls and 16 units per cage for the animals kept in the warm cages, a reduction of 50% in the amount of tuberculosis found at autopsy in the treated cages as compared with the controls. The average difference of 16 units per cage, with a probable error of less than 2.5, means that the difference here found is more than 6 times the

<sup>3</sup> Flick, L., *Trans. Nat. Tuberc. Assn.*, 1906, **2**, 442.

<sup>4</sup> Croghan, *Boston M. and S. J.*, 1843, **28**, 188.

<sup>5</sup> Welzl, Jan, *Thirty Years in the Golden North*.

<sup>6</sup> Duncan, G. R., and Mariette, E. S., *Am. Rev. Tuberc.*, 1935, **31**, 687.

<sup>7</sup> Corper, H. J., and Gauss, J., *Am. Rev. Tuberc.*, 1920, **4**, 269.

<sup>8</sup> Rogers, J. B., *Am. Rev. Tuberc.*, 1922, **6**, 119.

<sup>9</sup> Murphy, J. B., and Sturm, E., *J. Exp. Med.*, 1919, **29**, 1, 35.

<sup>10</sup> Cutting, W. C., Mehrtens, H. G., and Tainter, M. L., *J. A. M. A.*, 1933, **101**, 193.

<sup>11</sup> Kling, D. H., and Rubin, H. M., *Am. Rev. Tuberc.*, 1936, **34**, 498.

<sup>12</sup> Bogen, E., *Trans. Nat. Tuberc. Assn.*, 1932, **28**, 163.

probable error of such figures, beyond the range of reasonable probability that this might have been a mere chance variation.

Guinea pigs in 32 of the 45 cages kept in the warmth had been inoculated subcutaneously, while in 13 they had inhaled a spray of the bacilli. The average difference between the warm cages and the controls among those subcutaneously inoculated was 18, while among those infected by inhalation the average difference was 10; but in both cases the differences appear to be significant, the lower figure among the inhalation-cages probably reflecting the greater natural variation encountered with this type of infection.

The temperature in these cages has been automatically maintained within a few degrees of the desired point by a thermostatic control operating electric lamps or resistance-coils. Temperatures above 95°F. proved fatal to the animals, while the animals kept constantly at 48°F. and at 70°F. failed to show the retardation in the development of tuberculosis noted in those kept at a warmer temperature. No definite differences could be seen, however, between the results obtained at 80-85°, 85-90°, and 90-95°F. During the summer it was necessary to cool the cages artificially during the daytime, which was done by opening the doors and by the use of ice.

In order to exclude the action of luminous or ultra-violet or infra-red light as a factor in these results, cages were heated by convection from a concealed electric heater, and shut off from outside light, but the beneficial effect of heat was observed just as in those exposed to the light of an incandescent electric bulb or to diffused sunlight. It may be noted, however, that previous studies in this laboratory<sup>12</sup> have failed to show significant effects of darkness, ultraviolet, overcrowding, dampness or other environmental factors on the development of experimental tuberculosis in guinea pigs.

Twelve of the cages, comprising 60 guinea pigs, were subjected to the warm treatment for only half of the 3 months' duration of the infection. Half of these were removed from the warm cages to the outside air after 6 weeks of warmth, while the other half were first placed in the warm cages 6 weeks after they had been infected. In both groups, the development of tuberculosis was definitely inhibited, showing no significant difference between those receiving the warmth early or later in the course of their infection. But the amount of tuberculosis developing, though less than that in the controls, was in each case greater than that developing in cages of guinea pigs which were exposed to the warmth for the entire 3 months.

TABLE I.  
Thermotherapy in Experimental Tuberculosis.

Date of Infection	Route	Months treated	Temp. °F.	No. Cages treated	Aver. Amt. Tuberculosis in treated	No. Cages Controls	Aver. Amt. Tuberculosis in Controls	% Difference from Controls
10/1/31	S.C.	3	85	1	16	1	43	-63
3/4/32	"	"	85	1	28	1	47	-40
6/7/32	"	"	90	1	27	3	38	-29
10/9/32	"	"	90	1	25	2	39	-36
1/25/33	"	"	90	1	34	2	25	+36
1/26/34	"	"	90	1	16	2	29	-45
5/9/34	"	"	90	1	24	2	28	-14
1/21/35	"	"	85	4	12	2	33	-66
"	"	"	85	1	33	A	33	0
"	"	"	85	5	19	2	36	-46
6/10/35	"	"	85	1	15	A	36	-58
1/15/36	"	"	85	3	17	4	35	-52
"	"	"	80	1	13	A	35	-64
"	"	"	90	1	7	"	35	-80
"	"	"	85	1	15	"	35	-57
7/17/36	"	"	85	6	12	3	27	-55
"	"	1½	85	3	9	A	27	-67
1/15/36	Inhaled	3	85	4	14	3	27	-48
7/17/36	"	"	85	3	14	3	22	-36
"	"	1½	85	6	17	A	22	-23
10/1/31	S.C.	3	48	1	35	A	43	-18
6/7/32	"	"	48	1	43	"	38	+13
1/25/33	"	"	48	1	18	"	25	-28
6/10/35	"	"	48	1	27	"	36	-25
1/15/36	"	"	48	1	27	"	35	-23
"	"	"	70	1	41	"	35	+17

A = recorded on preceding line. B = Beryllium. C = Cod Liver Oil. D = ½ diet.

Inasmuch as it was suggested that the effect of the warmth might be to conserve caloric expenditure, and thus improve the animals' nutrition, one cage of animals was maintained in the warm temperature on only half of the usual ration of food. This had absolutely no effect on the beneficial effect of the warm temperature, the cage of animals receiving the half-diet showing just about the same amount of tuberculosis as those on full diet, whether in the warm cages or in the controls (D). Another cage of animals receiving cod-liver oil in addition to the warm temperature also showed no difference from the animals warmed on the regular diet (C), again confirming the failure to find effect of cod-liver oil on experimental tuberculosis in guinea pigs previously experienced.

On the other hand, the repeated injections of beryllium, as previously reported,<sup>13</sup> not only increased the amount of tuberculosis developing in the infected animals at room temperature, but when administered to animals in the warm cages caused them to develop just about the same amount of tuberculosis as the untreated controls (B), in other words, the deleterious effect of the beryllium exactly balanced the beneficial effect of the warmth.

Three different strains of guinea pigs were used for these experiments, the cross bred Olive View stock and the 2 highly inbred families, family 13 and family 39, which were studied many years ago by Lewis and Wright. All 3 families seemed to respond similarly to the warm temperatures, with the development of lower amounts of tuberculosis than when at room temperature.

The mechanism by which this retardation of the development of tuberculosis in infected guinea pigs is brought about is still obscure. No demonstrable increase in body-temperature could be noted in the animals kept in the warm cages, as compared with the controls, both averaging 101°F. rectally. Blood studies for possible leukocytosis or lymphocytosis as a result of the warmth have been, so far, inconclusive. Although, as might be expected, the infected animals, kept from developing so much tuberculosis by the warmth, did show considerably better weight curves than those in which the disease advanced more extensively, healthy animals placed in the warm cages showed no greater gain than did healthy animals kept under control conditions.

One possible interpretation of the results is suggested by the behavior of the animals under these conditions. The guinea pigs in the warm cages appear to be uncomfortable if they move, and so tend to remain much more quiet than do the controls. In other words, they are here subjected to an enforced intensive rest treatment, from

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<sup>13</sup> Loomis, R. N., and Bogen, E., *Am. Rev. Tuberc.*, 1935, **32**, 475.

which they stir only for eating and other functions, or when alarmed. The animals, remaining more quiet because of the discomfort induced by movement in the warm cages, may thereby be spared some of the spread of the disease secondary to muscular activity, and the increased lymphatic and circulatory drainage that such activity induces, and thus show a more marked localization of the disease. It has been impossible for us so far to determine what effect rest obtained in any other way might have on the course of experimental tuberculosis in guinea pigs, but we cannot deny the possibility of such benefit.

This simple explanation, if true, would obviate any practical application of the warmth treatment, or moderate thermotherapy, in the treatment of pulmonary tuberculosis in man, in whom rest may be achieved by other, perhaps more pleasant means, but furnishes additional evidence for the generally accepted belief that rest is an important factor in aiding recovery from tuberculous infection.

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**A Cinematic Study of Bronchiolar Reactions.\***

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A cinematic record was shown of directly observed bronchiolar reactions. These were obtained by applying drugs to microscopic cross-sections of fresh bronchioles, and photographing through a low-power microscope.

*Method.* The excised lungs are filled with a warm solution of 10% gelatin in Ringer's, by intratracheal injection. The gelatin is hardened by placing the lungs in iced Ringer's, where excitability of the muscle is retained for several days. Free-hand sections are made with a razor. Each section is pinned onto a perforated piece of cork attached to the bottom of a Petri dish, and the dish is filled with Ringer's solution. The dish is placed on the warm-stage of a microscope, and drugs applied after a preliminary warming, approximately to body temperature, for at least 30 minutes. Reactions are recorded either by means of camera lucida drawings, or, as in this case, by taking cinematic records.

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