seem to be in a very high degree "suggestible" and impressionable and respond nobly to every therapeutic effort.

Circulatory changes in tumors offer an interesting group of clinical symptoms. The observation has often been made, especially in ulcerated new growths, that treatment is associated with swelling, peripheral hyperemia, and an altered character of the discharge. In spite of the fact that there is no reasonable relationship between this congeries of symptoms and the actual cure of the tumor, they generally receive considerable emphasis and are cited as an indication of the specific local action of the agent employed. It is also true, however, that the growth may continue to advance in spite of their presence. It is of some importance to inquire into the mechanism which produces these circulatory changes and into their clinical interpretation. It is a well-known fact that many drugs, when introduced into the body either by the mouth or through the skin, are excreted not only by the normal channels of elimination, such as the kidney or the intestine, but also from such ulcerated surfaces as may be present on the body. This is easily shown to be true, for example, of certain of the anilin dyes, which, when introduced by way of the veins, produce an intense discoloration of the dressings over ulcers. It is likewise true of certain of the metals, such as arsenic. In order to understand the series of events previously enumerated it is therefore only necessary to assume that the therapeutic agent is excreted from the ulcerated surface of tumors. If an irritant, it will tend to produce hyperemia of the margins of the ulcer, and an increase of the secretions. If an astringent, however, it may produce just the opposite of these effects. Such a result, however striking, is purely accidental, and has no necessary bearing on the growth or destruction of the tumor itself. It constitutes a symptom on which no reliance should be placed.

Excluding from consideration all of these secondary factors, we may conclude that the observation of the size of the tumor itself is the sole criterion on which we can place reliance in judging of the effect of therapeutic measures. This implies, in the first place, that a tumor must be accessible to fairly accurate measurement. Tumors of the uterus, for example, and intra-abdominal growths will only exceptionally fall into this class. In the second place, indirect evidence of a decrease in the size of tumors, such as is afforded by the increased permeability of obstructed passages, as in the case of tumors of the esophagus, pylorus or intestine, must be accepted only with great reserve. Remissions in the obstructive symptoms characteristic of such tumors are a frequent feature of the normal evolution of the clinical history of such growths. The relief of obstruction, however, may be due either to necrosis of the obstructing portions of the tumor, while the remainder continues to grow progressively, or to a relief of the accompanying muscular spasm. Finally, evidence of decrease afforded by the roentgenogram is not sufficiently exact in most cases to afford ground for so important a conclusion as that at present in question.

Not only must there be unquestionable evidence, however, of the diminution in size of the tumor, but this diminution must be of a kind not ordinarily attributable to the natural evolution of the tumor. . . . It is safe to say that multiple tumors offer enormous difficulties in the matter of interpreting therapeutic results. At present we have in the wards of the hospital a patient with multiple metastatic carcinomas of the skin. For several months we have at intervals made accurate measurements of certain of these tumors and have found that some have undergone retrogression, others have entirely disappeared, while still others have continued to grow steadily. In the case which afforded the ascitic fluid used in Hodenpyl's experiments, many of the lymphatic metastases underwent complete retrogression, while the metastatic process in the liver, as was demonstrated at necropsy, increased progressively, and ultimately almost destroyed that organ. Thus, in multiple carcinosis, the retrogression of individual nodules is no indication that therapeutic intervention has produced an improvement.

I shall not delay to emphasize those variations in the size of solid tumors which accompany hemorrhage and its absorption, edematous swelling, necrosis in the depths, and other familiar factors which clinically simulate, or induce, the softening and the reduction that are so often attributed to therapeutic interference. But it is important to draw attention to a similar feature in that type of superficial epithelioma known as rodent ulcer. These new growths not infrequently advance at one point of the periphery, while they recede at another, and thus cicatrization and contracture may simulate a partial recovery. This effect is due in part to alterations not in the growth itself, but in the accompanying ulcerative process. The secretions from the growths, especially if confined under dressings, may have eroded and destroyed the surrounding skin, and it is tempting to interpret a recession of the associated ulcerative disease as an indication of a favorable effect on the new growth. It is unquestionably this aspect of rodent ulcers which plays so generously into the hands of the numerous nostrum venders for this disease.

In brief, the demonstrable reduction in size of a tumor, of a kind not to be attributed to the natural processes of evolution of that tumor or of its associated lesions, is the one essential feature of effective therapeutic intervention.

When the various methods of treatment which have been discussed in this paper are judged by the standard advocated above, it is apparent that none of them can lay claim to therapeutic effectiveness. The modifications of the disease attributed to them are modifications which occur spontaneously in a very large proportion of cases as a result of the natural evolution of the disease process. This is a fact which cannot be too strongly emphasized. Owing unfortunately to the hopeless character of cancer, men are not prone to study with care all the lesser changes which the disease and the patient present under ordinary conditions; but when a "cure" is under investigation, the patient and his medical attendant note every apparent improvement with painstaking attention and enthusiasm. As a result, some evidence of improvement in treatment is entered on the books.

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THE SIGNIFICANCE OF BACILLUS COLI IN PASTEURIZED MILK*

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The presence of *Bacillus coli* or of any other nonsporulating gas producer in pasteurized milk is usually taken to indicate either improper pasteurization or subsequent contamination of the milk. For according to most authorities the thermal death points of *B. coli* and similar organisms are below the temperature of pasteurization. Thus Kolle and Wassermann[1] give the following summary of the various findings for *B. coli* up to the year 1903:

C	Minutes	
62-63	1	Von Geuns
59	5	Von Geuns
60	15	Kitasato
60	10	Weisser
60-61	5	Chantemesse and Widal
59	15	Chantemesse and Widal
55-60	120	Fränkel

However, more recently De Jong and De Graef[2] have described seven strains of *B. coli* which survive 65 to 67 C. (149 to 152.6 F.) for thirty minutes in milk or broth. These strains would not be killed by the degree of heat commonly used in pasteurization and

* From the Laboratory of Bacteriology and Hygiene, Johns Hopkins University.

1. Kolle and Wassermann: Handb. d. Path. Mikroorg., 1903, ii, 385.
2. De Jong and De Graef: Quoted by Rullmann, Centralbl. f. Bakteriol., Part 2, 1914, xli, 269.

in consequence the presence of *B. coli* in pasteurized milk could no longer be taken as an index of improper pasteurization or subsequent contamination.

With the object of confirming these observations I examined samples of the various brands of milk pasteurized in Baltimore, twenty-two in all, and with one exception succeeded in isolating some aerobic, nonsporulating gas producer from every sample. Thirty-one strains were recovered along with thirteen strains from unpasteurized milk of excellent quality and their thermal death-points were determined.

The method employed was to transfer by means of a sterile pipet 1 c.c. of the milk from below the cream line to 2 per cent. dextrose broth in a fermentation tube. Then the milk in the original container and the fermentation tube was incubated. The following day gas usually would appear in the fermentation tube. From this preparation and from the cream on top of the milk specimen plates of dextrose-litmus agar were made. After from twenty-four to forty-eight hours incubation red colonies were replated, recovered and identified.

In this way there were isolated from the cream of the pasteurized specimens two strains of *B. coli communis,* one strain of *B. coli communior,* one strain of *B. coli communis immobilis,* two strains of *B. cloacae,* one strain of *B. coli liquifaciens,* and five of *Bact. aerogenes.* From the milk were recovered five strains of *B. coli communis,* four strains of *B. coli communior,* one strain of *B. coli communior immobilis,* seven strains of *B. cloacae,* and two of *Bact. aerogenes.* From the unheated milk were isolated four strains of *B. coli communior* and one of *Bact. aerogenes,* and from the unheated cream eight strains of *Bact. aerogenes.*

The majority of these organisms gave typical reactions in the usual culture mediums and could be identified easily. However, three strains of *B. cloacae* gave no gas or acidity in lactose broth when isolated, but later acquired this power. In addition, many of the cultures of *B. coli* showed no motility even in six-hour broth cultures when first recovered. But after about three months' artificial cultivation the greater number acquired this power and in young broth cultures showed violent motility. In two strains, however, no independent movement was ever observed. Yet they show no capsule when stained by the same method which was employed successfully in demonstrating the capsules of the various cultures of *Bact. aerogenes* isolated. In consequence these two strains could be identified neither as *Bact. acidi lactici, Bact. aerogenes,* nor *B. coli,* but resembled rather the *B. coli immobilis* of Germano and Maurea with which they were classed.

As soon as recovered and identified as gas producers, the various cultures were tested roughly as to their ability to withstand a temperature of 60 C. (140 F.) for fifteen minutes. The method employed was to transfer the organisms to peptone solution in test tubes and immediately heat in the water-bath for fifteen minutes. Then the tubes were cooled rapidly and incubated. At the end of from twenty-four to forty-eight hours turbidity indicated survival. Transfers were then made to dextrose broth in fermentation tubes and gas formation after incubation was taken to mean the survival of the organism tested. In my experience this method is inaccurate and misleading, but it has the advantage of being easy to accomplish and was used in this work merely to divide the organisms into two classes, one capable of surviving 60 C., the other killed by this temperature.

Of the thirty-one strains of gas producers recovered from pasteurized milk, eleven survived this process, twenty were killed. None of the thirteen strains isolated from unheated milk survived. Of the eleven strains which 60 C. failed to destroy, four were classed as *B. coli communis,* three as *B. coli communior,* one as *B. coli communior immobilis,* two as *B. cloacae,* and one as *B. coli liquifaciens.* Seven of these cultures were recovered from the milk, four from the cream.

As a control to these results about 10 c.c. of each specimen of milk examined was transferred by means of a sterile pipet to a sterile test-tube and heated in the water-bath for fifteen minutes at 60 C. This preparation was incubated and on the following day 1 c.c. was transferred to dextrose broth in the fermentation tube in an effort to recover *B. coli.* No gas was produced by this means in the dextrose broth however, and no culture of *B. coli* could be recovered from the milk so heated in the laboratory.

On the completion of the preliminary work the thermal death-points of the various cultures were determined in the following manner adapted from the method of Sternberg:[3]

First, small test-tubes were procured with a diameter just sufficient to admit the ordinary glass rod used in transferring. In these tubes bulbs were blown capable of holding about 2 c.c. Then they were filled with Dunham's peptone solution, corked with cotton, and sterilized in the autoclave. When cooled they were inoculated from twenty-four hour agar cultures of the strains to be tested. No definite amount of the organism was transferred, but roughly as much as could be taken conveniently on the end of the platinum wire. These preparations were sealed by melting the glass mouths in the flame of the Bunsen burner. Next they were weighted and immersed deeply in a water bath heated to the desired temperature. They were kept in this fashion fifteen, and in some cases, thirty minutes, and then were immersed in cold water. When cooled the ends of the tubes were filed and broken and the contents expelled into test-tubes of sterile litmus milk by means of gentle heat applied to the bulb. The milk tubes were incubated and on the appearance of acidity transfers were made to dextrose broth in fermentation tubes. The evolution of gas in these was taken usually to indicate the survival of the original culture tested, but in the case of those strains showing high thermal death-points the organisms were recovered from the milk and identified. Two thermometers were used in the experiments, one touching the bottom of the water-bath in contact with the bulbs; the other suspended in the water. The Bunsen burner used was kept with a small flame and was placed at the side away from the bulbs. In spite of these precautions Sternberg's limit of error of two degrees was taken as a fair figure.

The various strains first were tested at 60 C. for fifteen minutes. Those surviving this process were subjected to 61 C. for fifteen and thirty minutes, and then at each experiment the temperature was raised one degree until none survived. Those killed by 60 C. were subjected to decreasing degrees of heat for fifteen minutes until all survived this treatment. In this way the following results were obtained:

3. Sternberg: Text-book of Bacteriolgy, New York, William Wood & Co., 1892, p. 147.

STRAINS FROM PASTEURIZED MILK

	Thermal Death-Point, C.	
B. coli communis	15 Minutes	30 Minutes
Strain 30	+ 66-67	+ 62-63
Strain 6	+ 65-66	+ 63-64
Strain 11	+ 65-66	+ 63-64
Strain 12	+ 62-63	+ 60-62
Strain 26	+ 58-59	
Strain 2	+ 57-58	
Strain 14	+ 57-58	
B. coli communis immobilis		
Strain 1	+ 57-58	
B. coli communior		
Strain 29	+ 67-68	+ 64-65
Strain 16	+ 64-65	+ 62-63
Strain 34	+ 64-65	+ 62-63
Strain 7	+ 59-60	
Strain 13	+ 58-59	
B. coli communior immobilis		
Strain 33	+ 63-64	+ 62-63
B. aerogenes		
Strain 4	+ 59-60	
Strain 8	+ 59-60	
Strain 19	+ 59-60	
Strain 20	+ 59-60	
Strain 27	+ 59-60	
Strain 31	+ 59-60	
Strain 28	+ 58-59	
B. cloacae		
Strain 18	+ 63-64	+ 60-62
Strain 10	+ 60-61	— 60
Strain 9	+ 59-60	
Strain 17	+ 59-60	
Strain 15	+ 57-58	
Strain 32	+ 57-58	
Strain 5	+ 54-55	
Strain 21	+ 53-54	
Strain 25	+ 53-54	
B. coli liquifaciens		
Strain 22	+ 60-61	— 60
From Unheated Milk		
B. coli communior		
Strain 109	+ 58-59	
Strain 112	+ 56-57	
Strain 104	+ 54-55	
Strain 114	+ 54-55	
B. aerogenes		
Strain 105	+ 59-60	
Strain 115	+ 59-60	
Strain 108	+ 58-59	
Strain 107	+ 57-58	
Strain 103	+ 56-57	
Strain 111	+ 56-57	
Strain 113	+ 56-57	
Strain 106	+ 55-54	
Strain 110	+ 55-54	
Control		
Stock B. typhosus	+ 54-55	

SUMMARY

Of the thirty-one strains of various gas producing aerobes isolated from pasteurized milk, eleven possessed a thermal death-point above 60 C. for fifteen minutes. Three of these survived 63 C. for thirty minutes and three others survived 62 C. for the same length of time. One strain, identified as *B. coli communior*, possessed a thermal death-point of 68 C. at fifteen minutes and 65 C. at thirty minutes. This was the most resistant strain of *B. coli* recovered. The least resistant in this group were two cultures obtained from unheated milk which were killed by an exposure to 55 C. for fifteen minutes. The highest thermal death-point of *B. cloacae* was found to be 64 C. for 15 minutes, 62 C. for thirty minutes. The lowest belonged to two strains which originally failed to ferment lactose broth but which later acquired this power. These cultures were killed on being subjected to 54 C. for fifteen minutes. No culture of *Bact. aerogenes* isolated survived 60 C. for fifteen minutes. Different strains of this organism varied comparatively little in regard to their thermal death-points. All those recovered from pasteurized milk were killed by 59 or 60 C. for fifteen minutes. Two strains from unheated milk failed to survive 56 C. for the same length of time.

CONCLUSIONS

1. As observed by De Graef and De Jong, certain strains of *B. coli* are not killed by a temperature exceeding that commonly used in pasteurization.

2. The thermal death-point of this and similar organisms is not a constant quantity but varies for different strains of the same bacterium. In the case of *B. coli communior* this variation was found to be as great as thirteen degrees.

3. The presence of *B. coli* in pasteurized milk cannot be taken as an index of its improper pasteurization or subsequent contamination.

THE SMALL HEART IN TUBERCULOSIS

A SUGGESTED PHYSIOLOGIC EXPLANATION

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The small heart, often found in tuberculosis, has long been looked on as being a predisposing factor in this disease. That small hearts and hearts smaller than normal are common in tuberculosis, and this, in early as well as late tuberculosis, seems to be well-established. Ordinary methods of examination, as well as orthodiagraphic records of excellent observers,[1] prove this to be a fact.

It will be recalled that Brehmer,[2] the founder of modern phthisiotherapy, being convinced by the researches of Louis, Rokitansky and Beneke that the small heart was a predisposing cause of tuberculosis, founded his method of treatment on the idea that the cure of the disease could best be furthered by strengthening and increasing the capacity of the small heart. Exercise, particularly graduated hill climbing, was a very important part in his program.

The small heart in tuberculosis has been accounted for by Martius[3] as being due to constitutional weakness and as being associated with narrowing of the arteries. Grödel[1] says that it is an expression of malnutrition. He also says that the small heart is found in those suffering from enteroptosis and particularly those having narrow chests. If the small heart is found in tuberculosis, enteroptosis and those having narrow chests, it is well to make inquiry in order to find out whether or not there are factors affecting the

1. Grödel: Lehman's Med. Atlanten., München, 1909, vii.
2. Brehmer: Die Etiologie der chromischen Lungenschwindsucht, 1885.
3. Martius: Pathogenese innere Krankheiten.