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CLEVELAND

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The relationships between dental infections and degenerative diseases, if such exist, should be demonstrable by other means than the establishment of simply an association of the two in the same person, or the development of such lesions in experimental animals with cultures taken from focal infections. In this paper I summarize some new data developed in my researches on the relation of focal infection to systemic disease, with particular consideration of dental focal infections and the degenerative diseases, and with especial reference to structural changes that take place in the supporting structures about dental focal infections, and to serologic changes in body serums.

In a previous communication [1] I have given a preliminary report, indicating that patients can be divided into three groups on the basis of the type of structural change that develops in the supporting structures of infected teeth, as the result of the presence of a given type of dental infection, as, for example, that quantity of infection that would be present in a single-rooted tooth with a putrescent pulp, in which there is infection of the dentin plus infection of the degenerated pulp tissue.

In some individuals this condition will produce a large zone of rarefaction about the apex of the tooth, which will frequently be connected with the external surface by a fistula. The medullary structure of the surrounding bone opens quite readily into the periapical chamber, the trabeculae in the surrounding osseous tissue are approximately normal in size for the age of

* Read before the Section on Stomatology at the Seventy-Fifth Annual Session of the American Medical Association, Chicago, June, 1924.

1. Price, W. A.: Volume I, Dental Infections, Oral and Systemic, Volume II, Dental Infections and the Degenerative Diseases, Cleveland, Penton Publishing Company.

that patient, and the ratio or proportion of medullary material to osseous tissue is as much as, or is more than, 50 per cent. of the total mass.

In a second group we find a condition that appears very similar to the former except that the fistula tends to be closed and the zone of rarefaction is surrounded by a zone of condensed bone, with a marked reduction in the proportion of medullary tissue and an increase in the osseous tissue immediately adjoining the chamber that has been formed in the bone about the apex of the infected tooth. The thickness of this zone of condensed bone varies in proportion to a time factor, as we shall see.

In a third group we find that this type and quantity of dental infection produces much less of a zone of rarefaction about the apex of the involved tooth, in some cases amounting to a very slight absorption as compared with the previous cases. The trabeculae are not so pronounced in the alveolar bone, and there is evidence of more or less diffuse condensation surrounding the area.

These three general types will frequently be encountered in this clear cut form. However, there will be gradations between them, which will make a differentiation between either the first or the second, or the second and third of these groups, difficult. In other words, we seem to be dealing with a combination of influences. This is illustrated in Figure 1, which shows a group of teeth with putrescent canals showing characteristic lesions of these types. I [2] have already discussed this and illustrated it in extensive detail.

RESISTANCE AND SUSCEPTIBILITY TO RHEUMATIC DISTURBANCES

I have made an intensive study of the resistance and susceptibility factor in individuals with regard to the matter of their developing, during their lifetime, certain of the rheumatic group diseases or affections, and a preliminary report of this study has been presented.[3] In the rheumatic group disturbances I have included those affections which are very frequently caused by, or associated with, streptococcal invasions associated with degenerative processes in organs and tissues, the chief of which we have included in groups, such as muscles

2. Price, W. A. Dental Infections, Chapter III.
3. Price, W. A. Dental Infections, Chapter IV.

and joints, heart, kidneys, digestive tract, nervous system, and special tissues. In these studies I have undertaken to get the history of the serious breaks in these groupings in the following individuals: the patient being studied, the brothers and sisters of the patient, the father and mother of the patient, the brothers and sisters of the father and mother, and the four grand-

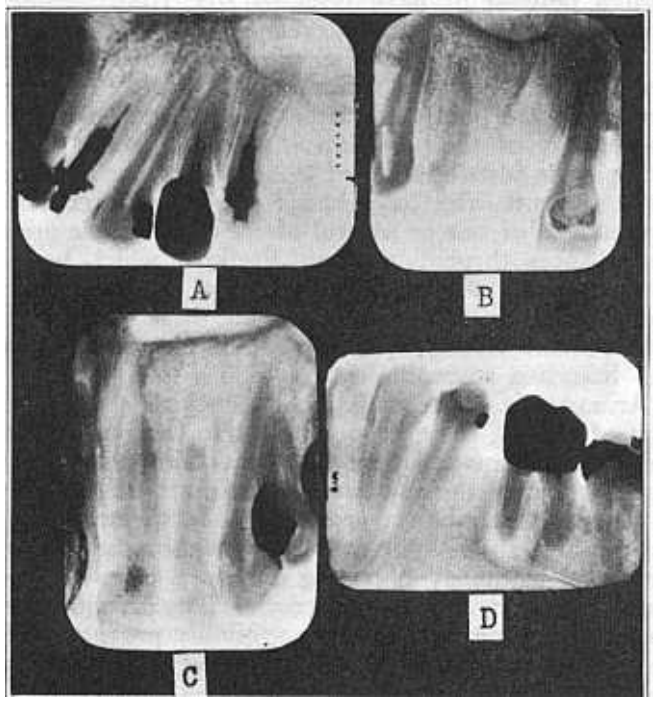

Fig. 1.—Typical different types of dental apical pathologic changes: *A*, extensive absorption opening into medulla of bone; *B*, very little bone change about apex of putrescent tooth; *C*, apical rarefaction with beginning zone of condensation; *D*, apical rarefaction with extensive zone of condensation.

parents. To secure this information has required a great deal of painstaking effort, and, because in many cases it was not possible to get in contact with reliable sources of information, such as family physicians, I have eliminated approximately 50 per cent. of the records as being inadequate.

By using 673 cases out of approximately 1,400 and comparing the data secured from this number with those

secured from an earlier group of 250 cases, we find that there is a remarkable conformity in the two sets of studies. In general, it has been found, as I have shown, that patients may again be divided into three groups on the basis of the probable presence or absence in their lifetime of serious involvements of the so-called rheumatic group lesions. These groupings are as follows: First, those persons who during their lifetime have had so high a defense or have been so free from adequate causes that they have not developed any of this group of lesions, nor have the members of their families. Second, a group very similar to the first one, except that while the persons in it have been free during the major part of their lifetime, they have had a recent break in the form of some of these disturbances. Third, those patients who have had frequent and recurring expressions of one or several of these rheumatic group disturbances throughout their lifetime, which history is more or less duplicated in various of the members of the family. I have chosen to call these groups (1) absent susceptibility, (2) acquired susceptibility, and (3) inherited susceptibility.

An analysis of the individuals constituting the members of each of these groups proves to correspond with the groupings made on the basis of differences in structural pathology, the association being as follows: Group 1, absent susceptibility, proves to have the same individuals in it as does the grouping made on the basis of structural pathology as having extensive zones of rarefaction for a given dental infection. The individuals of the group termed acquired susceptibility prove to be in general the same individuals who were in Group 2 of the other method, and are frequently, if not generally, those showing a zone of condensing osteitis around the zones of rarefying osteitis; and Group 3, those with an inherited susceptibility, prove to be the individuals with the generally lesser amount of radiolucence and cavitation about the apex of an infected tooth, with a marked tendency to fusion and obliteration of trabeculae and marked lessening of the medullary matter in the bone about infected teeth. The evidence in support of these data is now so abundant as to seem to establish without question the association of these structural and clinical phenomena.

When we take fifteen families as being typical of each of these different groups, and then divide the last group—

namely, those with an inherited susceptibility—into four groupings (one side mild, two sides mild, one side strong, two sides strong) and use fifteen families for each, we are able to make important observations which suggest elements that are involved factors, if not the fundamental causes, of some of these phenomena. This is illustrated in Table 1, in which the column headed "Susceptibility" shows the different classifications as suggested, and the section headed "Number of Lesions Per Group" shows the incidence of the rheumatic group disturbances; it will be noted that the total number of severe rheumatic group lesions (by severe I mean those that have either incapacitated or caused death) is progressively greater as the inheritance of the susceptibility increases

TABLE 1.—*Relation of Periodontoclasia to Susceptibility to Rheumatic Group Lesions (Fifteen Typical Families in Each Group)*

Susceptibility	No. of Lesions per Group		Per Cent. Caries	Per Cent. Periodontoclasia
	Severe	Severe and Mild		
Absent	16	31	40	40
Acquired	63	96	80	33
Inherited:				
One side mild	144	201	67	33
Two sides mild	227	308	93	20
One side strong	258	338	80	20
Two sides strong	483	754	93	0

in intensity. There is not opportunity in this text, since this is introductory, to review in detail those data which have previously been reported.

In the column headed "Severe and Mild" we have included the mild lesions with those that are severe (by mild I mean those that have produced severe inconvenience and discomfort, but not caused death or incapacity), and here again it will be noted that there is presented the number of these lesions in the different families. These data suggest that the members of the families in the last group—namely, those with two sides strong—are subject to a probability for the development of these lesions from twenty to thirty times as great as those in the families of the groups classed as absent susceptibility. This furnishes a very important factor in each diagnosis, prognosis and treatment, for the factor of safety of the last of these groups is very much less than that of the preceding groups.

These data immediately suggest the answer to the paradox that has produced probably more of the difference of opinion than any, if not all, other factors combined: namely, why it is, in our general clinics, that those patients who apparently have the most dental infection in their mouths, as judged by flowing pus from fistulas and number of broken down and abscessing roots or suppurating pyorrhea pockets, generally present themselves without a history of the rheumatic group disturbances, as they appear in general or accident clinics; and, conversely, why it is that the patients who do show severe or frequent breaks with the rheumatic group disturbances are so often those who have very little evidence of oral suppurative, infective processes. Whereas in the former group there is a history of recurring tenderness of the teeth to make certain that the teeth are infected, in the latter group there is usually little or no history of such inflammatory reactions or painful disturbances.

RELATION OF CARIES AND PERIODONTOCLASIA

The application of these new principles constitutes a new basis for practice, as I have indicated in the previous report. I am limiting this discussion to the significance and nature of some of the structural and biochemical changes that are associated with these phenomena.

In the column headed "Per Cent. Caries" (Table 1) I have shown the incidence of dental caries in relation to these various factors, and it will be noted that whereas only 40 per cent. of the patients in the group called absent susceptibility show caries, this factor increases to 80 per cent. in the next group, those with an acquired susceptibility, and progressively increases, as the intensity of inherited susceptibility develops, to 93 per cent. This has tremendous meaning and significance, for it indicates that those patients who would be in greatest danger of injury from an apical focal infection (because apical infections are the result of loss of vitality of the pulp, due generally to the approach of caries), will have most opportunity for the infection, and, further, these individuals, who would be most in danger, would be the ones who would have zones revealed by roentgenograms as small or negative zones, as the local structural expression of the dental focal infection.

TABLE 2.—*Dominance of Special Tissue Lesion in Both Patients and Families (Ten)*

Group	No. of Males	No. of Females	Number of Lesions in Ten Patients							Number of Lesions in Families								Local Expressions of Dental Infections					
			Tonsils	Rheumatism	Heart	Neck	Nerves	Internal Organs	Special Tissues	Tonsils	Rheumatism	Heart	Neck	Nerves	Internal Organs	Special Tissues	Total: Severe	Total: Severe and Mild	Caries	Periodontoclasia	Open	Locked	Rarefying	Condensing
Rheumatism.....	2	8	5	10	2	6	4	4	3	8	59	7	9	19	19	10	104	131	9	1	1	6	4	5
Heart.....	3	7	7	6	10	5	7	3	8	12	24	57	6	25	13	19	121	156	10	1	2	8	3	5
Nerves.....	2	8	5	6	2	7	10	7	7	10	15	9	10	142	38	19	180	233	9	3	3	9	5	5
Internal organs..	2	8	6	4	0	6	9	10	6	6	13	9	10	30	90	12	136	170	7	3	3	7	4	3

In the column headed "Per Cent. Periodontoclasia" (Table 1), I have shown the incidence of periodontoclasia, or so-called pyorrhea alveolaris, and find (and this was a great surprise although it has been abundantly verified) that as the tendency to caries increases, not only does the tendency to periodontoclasia decrease, but the periodontoclasia tends to decrease as the intensity of the inheritance of susceptibility for the rheumatic group lesions increases. This has profound importance, since it immediately indicates that the phenomena of structural change, whether at the apex of a tooth or at a gingival margin (for in every case in which we find extensive periodontoclasia our unit quantity of dental infection will always produce a large zone of rarefaction) are related through their causative factors, either directly or indirectly, with the forces of defense and resistance. This has led to an effort to analyze the involved forces and relate them to these phenomena.

HEREDITY

These studies have thrown an important light on some of the factors that are involved in the relation of heredity to the type of disturbance from which the patient suffers. In Table 2 I have arranged a group of the relatives of each of ten patients in such a way as to show the number of instances in all the members of the ten families (approximately sixteen relatives of each patient) in which there have appeared rheumatism and disturbances in the tonsils, heart, neck, nerves, internal organs, and special tissues. In all, forty patients were selected, ten of whom were suffering from rheumatism, ten from heart involvement, ten from nervous system disturbance, and ten from disturbance of internal organs. While the patient might be influenced by the health of the parents and grandparents, the latter, with the brothers and sisters of the father and mother and the brothers and sisters of the patient, could not be influenced by the patient.

In the section headed "Group," under rheumatism, it will be noticed that rheumatism was the most frequent lesion that was present. In the section headed "Number of Lesions in Families," it will be noticed that, in this group of ten patients with rheumatism, all the other members of all the ten families gave fifty-nine cases of

rheumatism, only eight instances of infected tonsils; seven of disease of the heart; nine of the neck; nineteen, of nerves; nineteen, of internal organs, and ten, of special tissues.

In the ten patients with heart involvement, the members of their families showed fifty-seven cases of heart disease, and only twelve cases of diseased tonsils; twenty-four cases of rheumatism; six of involvement of the neck, twenty-five, of nerves; thirteen, of internal organs, and nineteen, of special tissues.

In the ten patients suffering from involvement of the nervous system, all the other members of their families combined showed 142 instances of nervous affections; ten cases of diseased tonsils; fifteen instances of rheumatism; ten of affections of the neck; twenty-eight, of internal organs; and nineteen, of special tissues.

In the group of ten patients with involvements of internal organs, all the other members of their families showed ninety cases of involvements of internal organs; six cases of diseased tonsils; thirteen cases of rheumatism; nine of affections of the heart; ten, of the neck; thirty, of the nerves, and twelve, of special tissues.

This seems strongly to indicate not only a family characteristic, but also that it is a factor which relates to individual organs and tissues quite independently of other types of tissue.

When this problem is approached from another angle, it has given another type of data, which is also very suggestive. When we take the number of children affected in the case in which the patient being studied is the parent of the child, we find in the selected families in which both parents belong to the group that there is a marked increase in the prevalence of the total rheumatic group lesions in the group classed as having an inherited susceptibility, as compared with each of the two groups, absent susceptibility and acquired susceptibility.

This is shown in Table 3, in which *A* represents the patient with an absent susceptibility, *B* the patient with acquired susceptibility, and *C*, strongly inherited susceptibility. Eight families in which the patients have absent susceptibility are combined in a group with an average number of children of 7.3. The average number of children per family who were affected was 0.63, or 9

per cent. of the total number of children. In the group of families of patients classed as having acquired susceptibility, 17 per cent. of the children were recorded as having involvements; whereas, in the strongly inherited susceptibility group the percentage of children affected jumps to 44, or approximately five times as many as in the group with the absent susceptibility.

When we realize that so many of these degenerative diseases develop beyond the age of 40, and that most of the children being studied were well under that age, it appears that, if 44 per cent. were already affected at the time the record was made (for these were cases in which the parent involved was still living), a much higher percentage should be expected to present involvements later in life.

TABLE 3.—*Mendelian Factors*

Relative number of children affected in families when
A Patient has absent susceptibility
B Patient has acquired susceptibility
C Patient has strongly inherited susceptibility

	No. of Cases	Average No. of Children per Family	Average No. of Children per Family Affected	Percentage of Children Affected	Susceptibility
A.....	8	7.3	0.63	9	Absent
B.....	8	7.2	1.2	17	Acquired
C.....	8	9.0	4.0	44	Inherited

CHANGES IN THE BLOOD

We naturally look to the blood as being one of the earliest disturbed tissues, and as it is studied in large measure to determine the presence or absence of infection by its hematologic, serologic and bacteriologic changes, we have undertaken to compare these. In general, we find that chronic dental infections do not produce the blood picture of acute infections. Instead of there being a marked leukocytosis, there is frequently a marked leukopenia. The polymorphonuclears, instead of being increased, tend to be decreased in percentage, and the lymphocytes increased. When, however, a dental infection is producing an acute reaction, as an acute abscess, it then produces the marked leukocytosis and increase of polymorphonuclears. This is particularly true of the persons in Group 1, and these patients tend to develop a marked rise in temperature, and extensive swelling, severe pain and physical depression, usually

terminating in rupture of the abscess from its pressure, and rapid fall of fever and return to normal. In those with low defense, this process is much less acute, and most frequently absent. The condition tends to take on a chronic state with slight tenderness or no local tenderness, and a tendency to the development of subnormal temperature.

When nonvirulent green-producing streptococci, under which grouping approximately 99 per cent. of the strains taken from chronically infected teeeth will classify, generally spoken of as *Streptococcus viridans,* are inoculated into the marginal ear vein of rabbits, or when an infected tooth is placed beneath the skin of a rabbit, we frequently do not get the acute inflammatory reactions that we do from many other types, such as hemolyzing strains. There is often at first a slight rise in polymorphonuclears, and then a general depression of this cell, with a marked increase in both the actual number as well as the percentage of lymphocytes.

A typical group of such cases is shown in Table 4, in which will be seen the effect of tooth implantations in nine rabbits. From this it will be noted that there was a progressive decrease in the polymorphonuclears, with a progressive increase in small lymphocytes, which do not follow the changes in the total leukocytes. The decrease of polymorphonuclears for the nine rabbits is an average of 17 per cent., and the increase of small lymphocytes for the nine rabbits, an average of 17 per cent.

In our study of the chemical changes in the blood of rabbits and patients we have included sugar, nonprotein nitrogen, urid acid, urea, ionic calcium, pathologically combined calcium, ionic calcium plus pathologically combined calcium, total calcium of all forms, and alkalinity index. These have been run as a routine, and other elements have been made subject of special studies. Of these various factors, two that we have found to be of particular importance in connection with dental infections are the ionic calcium of the blood and the alkalinity index. Since the pathologically combined calcium plus the ionic frequently makes a total calcium up to or above normal, the determination of the total calcium is very inadequate and of much less value as an expression of the picture than is the ionic calcium.

TABLE 4.—*Effect of Tooth Implantations in Depressing Polymorphonuclears and Increasing Lymphocytes*

Case No.	Rabbit No.	Weight Loss		Hemoglobin	Erythrocytes	Leukocytes	Polymorphonuclears, per Cent.	Small, per Cent.	Eosinophils, per Cent.	Basophils, per Cent.	Mononuclears, per Cent.	Color Index
		Actual	Per Cent.									
	1055	163	12	B 85	5,500,000	7,000	55	30	1	...	4	0.7
				A 85	6,700,000	8,400	50	37		2	4	0.6
				A 80	7,950,000	18,000	38	49		1	3	0.5
				A 85	6,050,000	7,000	44	43		2	...	0.7
2..	1057	100	8	B 85	6,900,000	12,200	39	44		3	5	0.6
				A 85	5,800,000	12,800	32	52		4	4	0.7
3..	1097	211	19	B ..	.....	.....	60	23		2	4	...
				A 80	5,150,000	22,200	57	27	1	2	5	0.7
				A 80	4,600,000	8,600	39	51		1	1	0.8
	1123	114	10	B 85	5,200,000	12,600	42	43		1	6	0.8
				A 80	5,600,000	6,800	40	37		1	3	0.7
				A 80	4,300,000	7,200	26	58		...	2	0.9
	1125	263	17	B 85	5,800,000	10,200	63	22		1	4	0.7
				A 80	6,400,000	5,800	59	27		2	3	0.6
				A 80	7,200,000	5,800	43	43		...	5	0.5
	1126	519	30	B 85	7,400,000	15,600	60	29		2	1	0.6
				A 80	7,300,000	9,200	36	51		...	4	0.5
				A 80	6,900,000	5,600	38	51		1	1	0.6
				A 85	6,800,000	14,300	34	52		...	...	0.6
	1128	140	28	B 85	7,350,000	10,200	44	42		1	2	0.6
				A 85	7,100,000	9,600	46	34		6	4	0.6
				A 85	6,250,000	15,600	31	49		1	5	0.7
3..	1130	140	37	B 85	4,350,000	12,900	60	31		2	2	0.9
				A 80	5,050,000	7,800	29	58			2	0.7
				A 80	5,250,000	14,800	39	53			...	0.7
	1131	354	36	B 85	6,450,000	8,000	45	44			2	0.6
				A 80	6,000,000	6,800	43	47				0.6
				A 80	6,800,000	5,500	26	61				0.6

—. Before implantation.
—. After implantation.

Average percentage decrease of polymorphonuclears.....33
Average percentage increase of small lymphocytes.....58

When we relate ionic calcium to the three fundamental groups of patients, as I have classified them, we find a very striking difference which doubtless has great significance. In the group with an absent susceptibility, the ionic calcium is usually normal to high, with a range from 10.5 to 12 mg. per hundred cubic centimeters; in the group with an acquired susceptibility, usually from 9.5 to 11, and in the group with the strongly inherited susceptibility, already breaking, usually from 7 to 10.

In many instances, after the removal of dental infections, the ionic calcium of the patient rises from 10 to 15 per cent. in a few days or weeks, which is a great deal, since this difference makes a great change in the functioning of practically all the organs and tissues of the body. Normal circulating blood should contain from 10 to 11 mg. of calcium per hundred cubic centimeters. As it is in circulation, approximately 4 mg. is carried in combination with the thrombin, a little less than 1 mg. in the blood cells, and about 6 mg. as plasma ionic calcium. In the process of clotting, the 4 mg. in combination with fibrinogen will be released in the process of the formation of fibrin, and will appear as freshly released ionic calcium in the serum. When, therefore, there is a depression of say 2 mg. in the ionic calcium of the blood, it must largely be lost from the circulating plasma, since that, in combination with the thrombin, remains relatively constant; therefore, a loss of 2 mg., while it may mean a depression of only 20 per cent. of the total, may be one third of the plasma ionic calcium.

Of several methods that we have used for studying the effect of the type of culture which we have found in infected teeth on experimental animals, one that has been very instructive has been the placing of freshly extracted infected teeth beneath the skins of animals for the study of the changes in the blood picture. Few, if any, of these changes have been more striking and regular than the depression of the ionic calcium in all cases in which the animal was being seriously affected by the presence of the tooth. In practically every instance, when the infected tooth is so placed under the skin of an animal, if the animal does not become seriously injured by the presence of the tooth, it builds about it a fibrous capsule, highly vascularized, which for a time at least apparently quite successfully protects

TABLE 5.—*Comparison of Changes in Ionic Calcium and Blood Morphology Due to Culture Inoculations*

Date, 1923	Hemoglobin	Erythrocytes	Leukocytes	Polymorphonuclears	Lymphocytes		Basophils	Arneth Index	Calcium and Thrombin	Calcium Ionic	Calcium, Ionic and Combined	Calcium in Combination
					Large	Small						
6/1*	85	6,900,000	15,000	57.0	7.0	34.0	2.0	83	15.20	11.53	13.00	1.47
6/2	85	6,150,000	27,700	70.1	14.4	15.4	...	48	17.20	11.80	13.22	1.42
6/4	80	5,750,000	19,800	35.5	8.8	53.3	2.4		15.00	9.45	13.66	4.21
6/5	80	5,800,000	16,600	64.7	16.8	17.9			17.00	8.46	8.71	0.25
6/6	85	5,100,000	14,800	31.2	6.4	62.4			17.40	8.05	9.80	1.75

* Before inoculation.

TABLE 6.- *Chemical Changes in the Blood, Produced by Implanting Infected Teeth Subdermally, and the Relation of the Changes of Ionic Calcium and Body Weight*

Rabbit No.	Date	Weight, Gm.	Weight Loss		Calcium plus Thrombin	Calcium Ionic	Calcium Ionic plus Combined	Calcium in Combination	Calcium Ionic Loss	
			Actual	Per Cent.					Actual	Per Cent.
1106	A. 2/16/23	1,141	...	..	14.78	10.88	11.78	0.90		
	B. 2/20/23	.....	...	..	11.27	7.00	7.00	0.0	....	..
	C. 2/20/23	942	199	17	9.80	5.41	6.09	0.68	5.47	50
1145	A. 3/27/23	1,381			14.50	10.13	10.13	0.00		
	B. 3/28/23				13.88	8.89	11.67	1.77	...	..
	B. 3/30/23	.....	...	..	16.80	8.95	11.23	2.28	.18	12
	C. 4/13/23	910	471	14	.....	.....				
1099	A. 2/13/23	1,822			14.80	11.00				
	B. 2/14/23	1,483	...	..	13.2	9.92	10.36	0.44		
	B. 2/14/23	1,385	137	24	18.5	11.22	10.82	0.40	....	..
	B. 2/16/23	.....	...		10.19	7.91	9.00	1.99	3.09	28
1108	A. 2/20/23	1,265	...	.	17.00	10.59	12.61	2.02	....	..
	B. 2/22/23	1,185	80	6	18.40	8.84	13.00	4.16	1.75	17
1109	A. 2/20/23	1,375	..	.	17.20	9.88	10.37	0.49	....	..
	B. 2/22/23	1,256	19	1	17.80	7.82	9.80	1.98	2.06	21
1080	A. 1/27/23	1,478	...		16.50	8.90	8.90	0.00	....	
	B. 1/29/23	1,360			10.17	7.12	7.12	0.00		
	B. 1/31/23	1,321			7.74	7.25	8.69	1.44	....	
	B. 2/ 1/23	.....	...	..	11.80	7.99	8.56	0.57	0.91	10
	B. 2/ 3/23	1,210	268	19	19.00		12.74			

A—Readings before tooth implantations.
B—Readings after tooth implantations and before death.
C—Readings after death.

the animal from the toxic products of the bacteria and from the invasion of the animal by the organisms of the tooth.

In every instance in which an animal does not build such a membrane, and that promptly, it tends to lose in weight, there is a formation of an abscess, more or less pronounced, and there are very important and quite uniform changes in the blood picture, followed by death. One of the most important of these is the progressive depression of the polymorphonuclears and progressive increase of the small lymphocytes, which process is quite regularly paralleled and accompanied by a depression of the ionic calcium of the blood.

A typical illustration is shown in Table 5, in which it will be seen that the polymorphonuclears, starting at 57 at first, increased to 70 and then decreased to 31 (26 per cent.), while the small lymphocytes, starting at 34, increased to 62 (28 per cent.). Parallel with these changes, the ionic calcium decreased from 11.53 to 8.05, or 3.5 per cent., which was about half of the plasma ionic calcium. The depression in ionic calcium is practically always accompanied by a loss in weight of the animal. These two factors are shown in comparison in a group of animals in Table 6. In the first of these rabbits, it will be noted that the ionic calcium was reduced 50 per cent., while the actual body weight was reduced 17 per cent. In the next, the weight reduction was 34 per cent., the ionic calcium loss 12 per cent.; the next, weight loss, 24 per cent., calcium loss, 28 per cent.; next, weight loss, 6 per cent., calcium loss, 17 per cent.; next, weight loss, 9 per cent., calcium loss, 21 per cent.; and the last, weight loss, 19 per cent., calcium loss, 10 per cent.

Another very striking phenomenon is the effect of placing some pieces of patients' infected teeth into some of the serum of that patient's blood for from twenty minutes to a half hour. This often produces a very marked reduction in the ionic calcium of that blood serum, with a marked increase of the pathologically combined calcium. In Table 7, a group of blood samples from patients so tested with their own teeth are shown, in which the total decrease in ionic calcium has been from 10 to 76 per cent., and the total increase in pathologically combined calcium from 15 to 83 per cent.

TABLE 7.—*Blood Calcium Changes Produced by Infected Teeth*

Case No.	Calcium			Tooth Placed in Serum			Decrease in Ionic		Total in Pathologic Combination	
	Ionic	Ionic and Combined	Pathologically Combined	Ionic	Ionic and Combined	Pathologically Combined	Actual	Per Cent.	Actual	Per Cent.
10	9.86	10.58	0.72	8.95	9.38	0.43	—0.91	—10	—1.63	15
11	9.89	10.13	0.24	8.66	.....	....	—1.23	—13	1.47	15
9	11.904	15.40	3.496	12.732	13.44	0.708	+0.828	+ 7	+2.66	17
7	11.920	11.920	....	8.51	9.16	....	—3.41	—29	—3.41	28
12	9.06	9.66	0.60	8.54	12.58	4.04	—0.52	— 6	—1.12	12
13	11.802	13.334	1.532	7.258	11.802	4.544	—4.544	—38	—5.076	38
14	8.10	9.53	1.43	6.05	8.13	2.08	—2.05	—25	—3.51	37
15	5.25	7.50	2.25	1.25	....	....	—4.00	—76	—6.25	83

The methods used for making our calcium determinations have been chiefly those suggested by West [4] and Vines.[5]

EFFECT OF CALCIUM LACTATE

In many instances we have found it very helpful, in addition to the removal of the dental focal infection, to administer to the patient calcium lactate, from 10 to 15 grains (0.65 to 1 gm.), with each meal, which may be kept up for several weeks without any unfavorable effects, and in cases of marked pathologically combined calcium to administer parathyroid extract, one-tenth grain (0.006 gm.) daily, usually for only a few days. In some cases, we have found additional assistance in the use of thyroid extract, particularly in patients suffering from marked depression, for whom the administration of from one-eighth to one-fourth grain (0.008 to 0.016 gm.) daily for a few days is very helpful.

TABLE 8.—*Effect of Treatment on Ionic Calcium of Blood*

Date	Hour A. M.	Treatment for Ionic Calcium	Ionic Calcium	Pathologically Combined Calcium	Ionic plus Combined
8/31/22	9:00	Began.....	7.5	2.2	9.7
9/ 6/22	10:00	Continued.....	7.9	1.9	9.9
9/13/22	11:00	Continued.....	8.1	1.4	9.5
9/26/22	11:00	Continued.....	8.2	1.2	9.4
1/24/23	11:00	Discontinued....	10.6	0.3	11.0
2/16/23		Resumed.....	9.2	1.8	11.1
4/25/23		Continued.....	9.4	0.5	9.9

An illustration of the change in ionic calcium with the administration of calcium lactate and parathyroid is shown in Table 8, which represents the changes in the patient from one of complete incapacity for work, extreme lassitude and persistent discharge from surgically drained glands of the neck, which had become involved following the extraction of a tooth some months previously, accompanied by a general cellulitis, all of which latter promptly disappeared with the change of ionic calcium content of the blood from 7.5 to 10.6 mg. For approximately one and one-half years this patient has carried on his work very efficiently at the

4. West, Fred: A New Method for the Determination of Calcium and Thrombin in Serum, J. A. M. A. **78**: 1042 (April 8) 1922.

5. Vines, H. W. C.: Coagulation of Blood, I, Rôle of Calcium, J. Physiol. **55**: 86 (May) 1921; II, Clotting Complex, ibid. **55**: 287 (Aug.) 1921.

age of 65, when previously he had been an invalid for two or three years. It will be noted that, Jan. 24, 1923, when the ionic calcium was up to 10.6, the calcium lactate and parathyroid were discontinued; in about three weeks the ionic calcium dropped back to 9.2, at which time treatment was resumed, and by its resumption from time to time this man has kept in working condition. He had had several extensive zones of dental infection removed, which apparently had been largely contributary to bringing about his serious condition.

DEFENSE AGAINST BACTERIAL INFECTION

I have referred to the fact that, when an infected tooth is planted beneath the skin of a rabbit, one of two things will generally, if not always happen: either the animal will build about the tooth an encapsulating, highly vascularized structure, which protects it from the toxic and bacterial elements of the tooth, and the animal lives with very little change in weight, blood chemistry, or general health, or else there is formed about the tooth a local abscess which may or may not be accompanied by a considerable exudate or pus, without the formation of the closely adapted encapsulation tissue, and the animal loses in weight, suffers a reduction in ionic calcium of blood, and ultimately dies, frequently without much local destruction of tissue, all of which may occur in from two days to a few weeks. (We have had one tooth transferred to a series of thirty rabbits in succession, which killed all but one in from two to six days, one living ten days.)

Rats have a relatively high defense for streptococcal infections such as occur in teeth, and not only build the capsule quickly, but, when on a normal diet, exfoliate the tooth in an average time of nine days; on a deficiency diet, it may take over forty days. This quality of high defense is not found in rabbits, which in this regard behave more nearly like human beings. However, many, if not most, human beings have a higher defense for this type of infection than do rabbits that have not had their resistance raised and their immunity established by previous inoculations.

Human beings, as they come under observation, have very great difference with regard to the capacity of their blood, both plasma and whole blood, to destroy serophytic micro-organisms, which are chiefly streptococci and

staphylococci. This is well illustrated by the method of Wright [6] for testing the bactericidal property of the blood. In Figure 2 will be seen tests made from the bloods of two patients seen within an hour of each other, one with an exceedingly high defense, the other with a very low defense. *A* shows control cultures, approximately 1,000 streptococci placed in Petri dishes, and their profuse growth is noted. *B* shows the result of taking a similar quantity—namely, 1,000—of this strain of streptococci, and placing them for ten minutes in 0.3 c.c. of the patient's blood, after which they were transferred to similar Petri dishes, and except for the

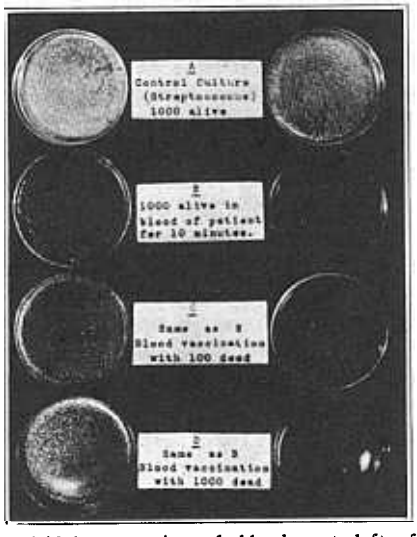

Fig. 2.—Bactericidal properties of bloods: at left, from girl with low defense with heart involvement; at right, from man with high defense, physically excellent.

effect of the blood, should show the same growth as in *A*. The cultures on the left are from a girl, aged 15 years, suffering from a partial nervous breakdown and heart involvement, probably contributed to by the overload of strenuous college. The cultures on the right are from a man, aged 56, with extensive periodontoclasia (pyorrhea) with much suppuration, never sick a day in his life. It will be noted that with this test, as shown in *B*, this man killed off a very large proportion of the streptococci, and the girl a little more than half.

6. Wright, A. E.; Colebrook, L., and Storer, E. J.: Therapeutic Inoculation, Lancet **1**: 365-373 (Feb. 24), 417-420 (March 3), 473-478 (March 10) 1923; Ann. de l'Inst. Pasteur **37**: 107-182 (Feb.) 1923.

But the plasma of the circulating blood does not contain all the available defensive properties that it may, if the individual is suffering from an invasion. Therefore, the placing of some dead organisms in the blood (in this case 100 for twenty minutes), to call out from the leukocytes additional defensive factors, resulted in inducing the blood of the man to kill off practically all the organisms, whereas, when this was done with the blood of the girl, the defensive mechanism not only did not kill off as many as before the dead organisms were introduced, as shown in *B*, but the blood was very much less efficient, suggesting that an additional overload had been provided. Similarly, when 1,000 dead organisms were added to this quantity of blood (0.3 c.c.) for twenty minutes, prior to the adding of 100 live organisms, the blood of the man, with its high defense, was not only able to devitalize practically all the live organisms in ten minutes, but could do that in the presence of so large a quantity of toxic material as was added with the 1,000 dead organisms. The blood of the girl, however, was not so efficient as with either 100 dead organisms or with no dead organisms. For her blood, it seems that there had been simply the addition of supplemental toxic material. She, apparently, was already utilizing all her available reserve forces for fighting this infection. With the removal of the dental infections, one of which was a badly infected first permanent molar, which, incidentally, showed very little rarefaction roentgenographically and had not been in the least tender, she gained 15 pounds (7 kg.). The acute heart irritation disappeared, as did also the nervous symptoms, and she returned to practically normal health. By inheritance she had a marked susceptibility for heart and nervous system.

IMMUNITY VERSUS SUSCEPTIBILITY

One of the most important values of these new data is the light they throw on some of those fundamental forces which are at work in determining not only the local and systemic expressions of disease but also the nature of some of the factors involved in immunity and defense, in contrast with susceptibility. I have previously shown data demonstrating that individuals with a tendency to tearing down of bone, whether at the necks

of teeth or at the apexes, tend as a group to have a high defense against systemic involvements of streptococcal origin; in other words, they tend to be quite free from so-called rheumatic group, degenerative diseases. I have also stated that these individuals tend to have a higher ionic calcium content of the blood than do persons with a mild or marked susceptibility to rheumatic group disturbances, where they are suffering from such; and these factors obtain in the presence of even considerable dental infection, and that dental infection tends in all individuals to depress the ionic calcium, but in proportion to the factor of lack of ability to maintain the body without systemic involvements. When, therefore, individuals are studied on the basis of the significance of the type of reaction in bone about such infections as dental infections, very important light is thrown on the types of disease which tend to develop in individuals in accordance with this factor of the development of rarefaction on the one hand, or its absence, and a tendency to condensation of involved calcified structures. This is graphically brought out in Table 9, in which are arranged the various disturbances and types of disease on the basis of the factor of whether bone will go into solution or be deposited.

Under the caption, Type of Local Reaction in Bone, I refer to the structural change in the alveolar bone about infected pulpless teeth and teeth with periodontoclasia or pyorrhea. I have divided these changes into three groups: first, rarefying osteitis with extensive decalcification; second, condensing osteitis about extensive rarefying osteitis; and third, condensing osteitis, or very slight rarefying osteitis, or both; and have related each of the following factors to these groupings: namely, susceptibility group (absent, acquired or inherited), blood ionic calcium (serum calcium), bactericidal efficiency of the blood for streptococci; and, finally, to all these I have related certain of the systemic disturbances or involvements, both streptococcal and nonstreptococcal.

There is doubtless a great significance in these associations of data, which, so far as I am aware, are largely new. Clinicians, particularly dental, have long observed that the mouths with active pyorrhea have little or no caries. We have not, however, associated these with particular types of systemic susceptibility. Patients with periodontoclasia or pyorrhea in an active stage seem always to develop large areas of cavitation and

TABLE 9.—*Relation of Calcification and Decalcification to Type of Systemic Disease*

Type of Local Reaction in Bone	Susceptibility Group	Blood Ionic Calcium	Bactericidal Efficiency of Blood for Streptococci	Systemic Disturbances, Streptococcal and Nonstreptococcal																		
				Heart	Proliferative Arthritis	Acute Rheumatism	Caries	Kidneys	Stroke	Nervous Breakdown	Degenerative Arthritis	Neuritis	Skin Sensitizations	Hypertrophic Rhinitis Sensitization	Asthma Sensitization	Periodontoclasia (Pyorrhea)	Hay-Fever	Extensive Salivary Calculus	Diabetes	Tuberculosis	Cancer
Rarefying osteitis, with extensive decalcification	Absent	Normal or high	High	..	..	..	..	..	..	..	..	..	..	..	..	*	*	*	*	*	*	*
Condensing osteitis about extensive rarefying osteitis	Acquired	High or subnormal for individual	Subnormal	..	..	..	*	*	*	*	*	*	*	*	*	*	*	*	*	..	..	..
Condensing osteitis, or very slight rarefying osteitis, or both	Inherited	Subnormal or low	Low																			

radiolucence about the apexes of infected pulpless teeth, typifying a good reaction to an irritant. These individuals tend to keep themselves free from rheumatic group disease involvements, such as arthritis, and hence class as absent susceptibility, have a normal or high ionic blood calcium, and have a high bactericidal efficiency of the blood for streptococci, as well as for most other organisms. They do not develop the rheumatic group, degenerative diseases while in this state, but the persons who develop progressively fatal miliary pulmonary tuberculosis are largely in this group, as are also those who develop cancer. This is easily verified in many ways. For example, how often have any of us seen patients with deforming proliferative arthritis develop either tuberculosis or cancer? It should also be noted how constantly cancer patients are free from the recurring rheumatic group symptoms and how frequently, if not almost constantly, they report that they have never been sick a day before in their lives.

In the second general grouping, namely, condensing osteitis about extensive rarefying osteitis, we find the persons who formerly had a high defense but have lost it as the result of infection and physical overloads. They are therefore in the acquired susceptibility group. Their blood calcium is usually below their normal, as is also the bactericidal efficiency of their blood. Previously, while in the preceding group, they had little or no caries, but now they have it in active form. Their systemic breaks tend to appear in the nervous system. One type of arthritis, the degenerative, which is associated with a normal or above normal ionic calcium content of the blood, may develop, but not the proliferative type. Since they tend to return to their normal, which is high, the prognosis for recovery from systemic involvements arising in streptococcal focal infections is good. This is the group which, according to our tabulation, we find developing the sensitizations, such as skin irritations, asthma, hypertrophic rhinitis, and hay-fever, all but the last coming frequently from the antigen of dental infections. The development of these phenomena seems to be related to the long continued presence of the antigen in an individual with normally a high defense or a high capacity for developing antibodies. The sensitizations frequently completely disappear with the elimination of the dental focal infection. There is evidence that many disturbances are fundamentally

related to, or have involved in them, antigen-antibody reactions.

In the third group, we have as the typical local bone reaction about dental infections or irritations, apical or gingival, condensing osteitis or very slight rarefying osteitis. Since there is generally a familial phase, they are grouped as inherited susceptibility. The blood ionic calcium tends to have a low normal for the group, and when involved with some rheumatic group disturbances, to which such patients are easily subject, the blood calcium is often much reduced. The bactericidal efficiency of blood is low in such patients, and, when involved, often relatively very low. Their affections are very frequently of the streptococcal or so-called rheumatic group degenerative diseases, as diseases of the heart, kidney, or digestive tract, proliferative arthritis, acute rheumatism, and tonsillitis. They very seldom develop cancer or tuberculosis, and if they do develop the latter, prove to be the group in which is found the tendency to recover. In them, lung tubercles and glands tend to calcify; and, so far as this disease is concerned, this seems to suggest why so many persons who have tuberculosis recover, as shown by the results of postmortems. I have visited several sanatoriums for tuberculosis patients, looking for (among other data) cases of multiple deforming proliferative arthritis and tuberculosis associated, and have not yet found it. I will be glad to be informed of such cases. We might expect to find the other type—namely, the degenerative—which has a higher than normal ionic calcium, though it also is apparently a very rare association.

These new data have suggested the desirability of studying the effect of producing an arthritis or an associated streptococcal lesion in rabbits, and then submitting them to comparison with controls inoculated with tuberculosis only. These studies are in progress, and while deductions are not yet justifiable, the results are strongly suggestive, as indicated by the lung picture shown in Figure 3, in which zones of calcification are seen in tubercles of a rabbit that was inoculated with streptococci some weeks before receiving the culture of tubercle bacilli, both intravenously. We have not found such calcifications in lungs of rabbits receiving only the tubercle bacillus. There has also been an apparent lengthening of life for these rabbits.

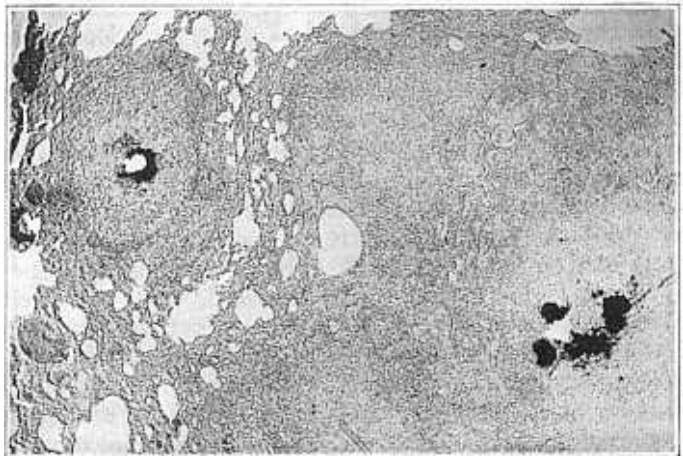

Fig. 3.—Zones of calcification in lung of treated tuberculous rabbit.

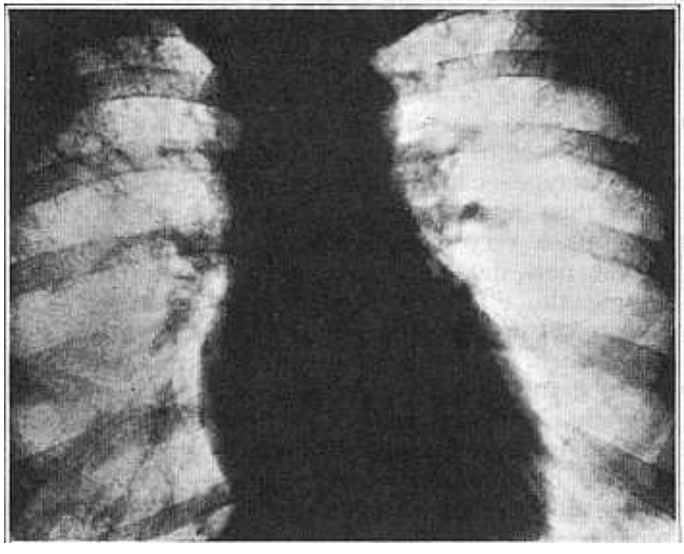

Fig. 4.—Fibrosis and calcifications in lungs of patient with quiescent pulmonary tuberculosis.

By the application of these principles to clinical observation, some interesting and instructive data have been accumulated, and there is evidence that a proper application of this newly observed principle and its relationship may have important prognostic value in the study of cases of tuberculosis, for it seems demonstrated that those patients who produce a calcification process as a reaction about their zone of rarefaction at the apex of an infected root are the same individuals who experience a remission and healing process in the course of an active tuberculous infection, presumably because of the presence of calcification in the fibrosis about the zones of pulmonary tuberculous infection. This is also a condition reported by pathologists to be present in the lungs of those individuals who have apparently had no history of tuberculosis, but, from the presence of calcified tubercles, have apparently had the infection and have recovered from it by maintaining a zone of calcification, or as a process that is incidentally accompanying the spontaneous recovery. The roentgenogram of the teeth, illustrating the type of local dental pathologic change presented by the patient marked *B* in Figure 1, is of a woman, aged 32, who has had pulmonary tuberculosis from which she had an elevation of temperature for about a year and recovered. Figure 4 shows the appearance of the lung, which the roentgenologic diagnostician thus interpreted and diagnosed:

Trachea in midline. Heart and aorta normal. Right chest smaller than left. Diaphragm adherent at costophrenic angle. Hilium normal. Intercostal spaces narrower than on left side. Apex lagging. Definite infiltration with moderate fibrosis in the upper lobe and apex. Left chest: Diaphragm and costophrenic angle clear. Hilium contains several calcified glands and moderate infiltration in the upper lobe and apex. Diagnosis: Tuberculosis with fibrosis both upper chests.

On studying the bone about the apexes of the two roots of this molar in *B*, Figure 1, there will be observed in the mesial root the distinct outlining of the zone of condensation about the zone of rarefaction. This tooth is normally thin mesiodistally and broad buccolingually, which produces an egg-shaped chamber at the apex, and the roentgenogram is accordingly showing this oval shell in its long diameter. The distal root being normally more nearly round in shape, the buccolingual

diameter of the zone of rarefaction is less and the relation of the thickness of the zone of condensed bone to that of the diameter of the chamber of rarefaction in this plane is relatively less, and accounts largely for the difference in the appearance of the zone about the distal root from that of the mesial root. The local structural condition—namely, the zone of condensation about the zone of rarefaction—I take it, indicates that during the period that this was taking place, this patient was in a condition in which calcifications occur in the presence of all irritants such as that which obtains here.

When *B* of Figure 1 is compared with *A* of Figure 1, a distinct difference in these two types of reaction will be seen. The patient shown in *A* has had a high capacity for reaction, has never had systemic involvements, has the type of bone structure and type of reaction that we would consider to be like that of the group in which the patients, when they have tuberculosis, do not make a successful fight. A study of this girl's family history shows that her father died at 34 of tuberculosis, and her brother at 15. If space permitted, I could present other interesting and typical illustrations of this condition.

SUMMARY

I might briefly summarize here my interpretation of these local phenomena and their relation to the systemic defense. When a person has a normally high defense, as expressed by absence of recurring rheumatic group lesions, he or she tends to make the warfare against the organisms and toxic materials coming from the openings at the apexes of the involved teeth as close to the source of that infection as possible. This seems to be a principal reason why these patients have the large zones of rarefaction. This large zone of radiolucence is generally occupied in these individuals by a highly vascularized, defensive tissue, whose function appears to be chiefly that of a local quarantine station. When it is adequate and efficient, the balance of the body is protected. The production of the local warfare expresses itself as pus, which is eliminated usually through a fistula and contains exceedingly few, and often no, living organisms. It is apparently largely because these individuals can make a fight to a finish close by the source that the balance of the body is safe from injury from these disturbances. When, however,

that patient with a normally high defense has an overload, such as influenza, pregnancy, grief, exposure or poor nutrition, he is unable to continue the maintenance of the adequate quarantine, the warfare is no longer a fight to a finish immediately about the tooth, and the organisms and their toxic products pass into the body, and that warfare, which should have been made in special tissues close to the source of the infection, must now be made in the various organs and tissues of the body. The local dental involvement now ceases to be uncomfortable because of the absence of a local warfare. The accumulating toxic and bacterial material produces general changes in the blood and in the defensive forces, and the final warfare may have to be made in various organs and tissues far from the source of invasion. Since the blood stream rapidly distributes these materials to these various structures, the final warfare must be made there, and that organ or tissue tends to break which has been most weakened by some of the overloads mentioned above, or by that other noncontrollable factor (so far as the individual is concerned), namely, his or her inherited susceptibility, which now proves to be a factor which relates to individual organs and tissues, and which apparently is the reason why heart disease, etc., runs in families.

In those persons with a high defensive mechanism, the long continued presence of the antigenic substances of focal infections, such as chronically infected teeth, the evidence suggests, causes zones of irritation to develop as sensitization reactions, which are completely relieved by the removal of the focal infection when it is the source of the antigen, as it frequently is. There is much more than a suspicion that these factors have more than an association relation in the grouping of cancer development cases in that group with the high streptococcal defense.

Tuberculosis tends to be associated with decalcifying processes about dental infections and in patients without a previous tendency to dental caries. The prognosis in a cases of tuberculosis is suggested by the presence of a zone of condensing osteitis about a zone (previously developed) of rarefaction.

May we not have here a new approach to the study of both the streptococcal, rheumatic group, degenerative

diseases and the nonstreptococcal diseases, such as tuberculosis and cancer?

These new data furnish important suggestions, if not a preliminary basis, for diagnosis, prognosis and treatment, particularly for dental focal infections, and indicate the necessity for a greatly enlarged program of research on these fundamentals.

Calcium metabolism seems to play a most important rôle in both health and disease.

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