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**FOCAL INFECTION AND ELECTIVE LOCALIZATION IN RELATION TO SYSTEMIC  
DISEASE: A REVIEW AND RESULTS OF FURTHER STUDIES**

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It is the purpose of this paper to review the clinical and experimental studies which have been made on focal infection and elective localization in relation to systemic disease. The literature on this subject in the field of medicine and dentistry is so enormous that detailed descriptions of results and complete references are beyond the scope of this report. Only the more important recent clinical and experimental re-

sults of my own work and that of others with references to the original communications will be given. For a more complete bibliography the reader is referred to previously published articles by myself (1-3) and by others (4-8).

The deleterious effects of bacterial infection on the host wherever found are both general and specific in varying degrees. As a rule, the more virulent the infecting microorganism the

greater the general harmful effects, at the same time the greater the antibody response; and the more nonvirulent the infective agent, the less the general effects and antibody response and the more important the factors of specificity and focus. The former conditions usually prevail in acute diseases which often are self-limiting; the latter conditions usually prevail in chronic diseases which are often progressive.

#### CLINICAL CONSIDERATIONS

The importance of acute symptom-producing localized infections as a source of systemic disease has for years been generally recognized, but despite the large amount of evidence that has been adduced since Billings first showed that chronic, often symptomless, foci of infection may also be a source of disease in remote tissue this fact is still not sufficiently understood. The reasons for the lack of appreciation of the importance of this basic principle are manifold. The principle applies in a wide range of conditions and diseases. Its proper application is often difficult and calls for revision of well established procedures and the cooperation of the general practitioner, internist and widely different specialists including dentists and bacteriologists.

Symptomless foci are prone not to be suspected. They are not easily detected and may be situated in inaccessible regions. The resulting systemic diseases from such foci as a rule are mild in character and hence are usually not recognized in the early stages—the very time when elimination of foci does the most good.

Recurring inflammation in foci is still too often considered necessary to indicate causal relationship of focus to systemic disease. The bacteria isolated from symptomless foci, while having high specific virulence, usually have only a low general virulence and hence are incapable of causing acute symptoms at the primary focus. This is in accord with the fact that exacerbations of existing systemic disease or the first appearance of systemic disease following acute tonsillitis, pulpitis, prostatitis or respiratory infections usually occur not at the time of the acute attack but in from one to two or more weeks as the symptoms at the primary site subside or have disappeared.

Methods for elimination of foci by surgical or other means may be faulty. Removal of tonsils

in the presence of focal infection in and about teeth is illogical and may do more harm than good. Statistical studies on the remote effects of removal of foci made by some authors who have had little or no clinical experience in this field have usually erred in not considering sufficiently the question of faulty methods, the presence of other foci, and, most of all, the development of new foci following the removal of certain types of foci such as infected tonsils and infected teeth. Conditions following removal of tonsils, if improperly done, may be worse than before (8-10). Quantitative bacteriologic studies made by Caylor and Dick (11) have shown that remnants of tonsils are more heavily infected than tonsillar tissue removed the first time. Moreover they showed that tonsillar tissue with a high bacterial count was more often associated with arthritis, neuritis and heart disease than that with a low bacterial count. Tonsillar tags, scar tissue covering partially removed tonsils, residual regions of infection in the jaw, with or without root tips, following removal of infected teeth, especially those which contain large areas of rarefaction, have been shown to be infected (table 1) and to predispose to disease in contiguous structures, such as maxillary sinusitis, and to systemic disease, and to prevent recovery from systemic diseases present at the time the primary foci were dealt with. The proper elimination of these infected structures has frequently been followed by enduring improvement or recovery, especially if done early in the course of the systemic disease (7, 12-15).

Röntgenographically positive teeth are usually, but not always, infected teeth. Hence their removal should not always be expected to produce beneficial effects and roentgenographically negative teeth are still nearly always considered sterile and harmless and are allowed to remain despite the fact that they have been shown by special methods to be infected by streptococci having elective localizing power in most instances (table 1) in which patients are suffering from mild or severe systemic disease. One cannot see bacteria at the apexes of these teeth in the roentgenogram. The infection here may or may not cause absorption of bone. Streptococci isolated from roentgenographically negative pulpless teeth in my experience have

been more specifically virulent than those isolated from roentgenographically positive teeth.

Clinical studies on the effect of elimination of foci without regard to the organisms present in the focus or in the disease in question, as is commonly done, do not always suffice to establish cause and effect. Improvement, often permanent, following removal of foci from which the causative streptococci were isolated in my experiences has occurred with such regularity that I have come to consider lack of improvement as evidence that the removal was faulty, that the focus did not contain the causative micro-organism or that other foci were overlooked (11). Recurrence of the former symp-

tunity for the early application of a method such as this are especially great.

In general it may be said that the appreciation of the importance of the principle of focal infection by clinicians is in direct proportion to the thoroughness with which it has been applied. Purely theoretical considerations do not suffice. The lack of appreciation of this principle by some clinicians who admit that it applies in some instances and with whom I have had opportunity to examine patients is well illustrated by the conditions found in one large European clinic. The evidence of focal infection in relation to systemic disease had been entirely overlooked by its chief. Infection in foci was actually

TABLE I  
*Results of Cultures from Dental Foci of Infection Obtained by Different Investigators*

MATERIAL CULTURED	SPECIMENS CULTURED	POSITIVE IN LIQUID MEDIUMS, CHIEFLY DEXTROSE BRAIN BROTH		POSITIVE, 50 COLONIES OR MORE IN SOFT DEXTROSE BRAIN AGAR	
		Number	Per Cent	Number	Per Cent
Pulpless teeth:					
Apex, roentgenogram positive.....	728	600	82	290	40
Apex, roentgenogram negative.....	565	447	79	154	27
Root canal.....	80	67	75	—	—
Total.....	1382	1114	81	444	32
Vital teeth:					
Normal pulp; roentgenogram negative; no fillings or periodontoclasia.....	548	210	38	4	0.7
Normal pulp; roentgenogram negative, with or without degenerating pulp or periodontoclasia....	450	291	63		
Granulomas.....	80	78	91		
Residual regions following extraction of infected teeth.....	285	241	84	27 of 75	36
Root fragments.....	105	85	81	43 of 75	57

toms or the occurrence of new ones long after relief resulting from removal of a focus is taken to indicate the development of a new focus or activation of dormant foci.

The lack of striking clinical results from elimination of focal infection is often attributable to the fact that even now the attempts are too often made after the disease process has continued for a long time and secondary foci such as those in and about arthritic joints have become thoroughly established. It is a curious fact that the best clinical results usually are not obtained in large medical centers or hospitals, where advanced conditions are chiefly dealt with, but by physicians and dentists in out of the way places, where inclination, need and oppor-

demonstrated in five patients during my short visit. One of these had had recurring attacks of cholecystitis, two had suffered from rheumatic fever for about two months and two had had acute iritis. A history of an attack of acute tonsillitis shortly before the onset of systemic disease was elicited in each of these cases and large amounts of liquid pus were expressed from the tonsils of each patient by the method I use. Acute pulpitis with death of the pulp and draining dental sinuses occurred shortly before the attack in the two cases of acute iritis, and finally, the chief himself had been ill in bed suffering from an unexplained fever for some time prior to my visit. It was clearly evident that his condition was an example of the very problem

under discussion. His teeth were literally floating in pockets of pus arising from pyorrhea and his breath was malodorous. He died several years later, long before he should have died, from cardiac disease.

I recall other tragic occurrences which indicate the importance of unrecognized focal infections in men of note who had had little or no experience in this field, who refused to permit removal of symptomless, pulpless teeth which were normal in the roentgenogram and who died of cardiac disease or other diseases or in whom disabling systemic disease developed not long subsequently, long before it should have developed.

These and many other examples which have come to my attention illustrate how far from accurate purely clinical observations may be concerning the etiologic importance of symptomless foci, especially pulpless teeth which are normal in the roentgenogram, most of them with fillings in the canals of the roots. The patient is not aware of their presence. Dentists and physicians generally consider such teeth to be sterile or harmless; roentgenograms are of little help even if they are repeatedly made, and the pathologist who performs the necropsy has not been schooled to consider them as in any way contributory to the cause of death. Experimental evidence that such foci are of importance is not lacking. Barnes and Giordano (16) have isolated from such foci, after death of the patients, streptococci with which they reproduced in animals the disease from which the patient died. I have had similar results. The findings in a most unusual type of case will serve to illustrate. A patient who had undergone an operation for congenital dislocation of the hip, although recovering satisfactorily, died suddenly from pulmonary embolism one month after the surgical procedure. Cultures by my methods from the embolus after surface sterilization yielded the usual green-producing *Streptococci* found constantly in instances of pulmonary embolism (17). A pulpless tooth normal in the roentgenogram was extracted after thorough disinfection of the site. Cultures from the apical end of this tooth yielded the same type of green-producing *Streptococci* as the streptococci obtained from the embolus. Pulmonary embolism was reproduced in rabbits and dogs following inoculation of the streptococcus from both the embolus and tooth, and the strepto-

coccus was demonstrated in and isolated from the experimentally produced thrombi and emboli.

Failures to achieve clinical results have repeatedly been traced to inadequate or improper application of this principle. Nickel and Huford (18), in a study of a series of patients in whom the symptoms of ulcer of the stomach or duodenum were not relieved following gastroenterostomy or other operative intervention and after it was thought that all foci had been removed and after some had received autogenous streptococcal vaccines without effect, found evident foci from which causative streptococci were isolated. These foci had been overlooked and after removal of them and further administration of vaccines, relief from symptoms and healing occurred. In my own experience it is still common to find one or more evident foci in patients who have had every attention known to medical science, including the removal of foci of infection without relief, and whose symptoms often disappear following removal, for example, of one or more pulpless teeth which in the roentgenogram appear to be normal, or tonsillar tags or tonsils that were considered to be normal but from the upper pole of which liquid pus was expressed, or an abscess ruptured by the method we use in examining tonsils and from which foci the causative streptococci were isolated.

Simple though the question of the relationship of focal infection to systemic disease seems, the proper application and interpretation of all the factors concerned require diagnostic skill of the highest order. The occasional occurrence of exacerbations or extension of systemic diseases following removal or attempts at removal of various foci, especially infected teeth, emphasized by Reimaun and Havens (6), deplorable as this is, should not prevent the application of this principle and should be interpreted as proof that a potential or active focus has been dealt with, but by inadequate methods. Such foci would with reasonable certainty do far more harm if retained indefinitely than is entailed occasionally by their removal even by the methods now employed.

In spite of the inherent difficulties which I have mentioned, favorable results from the application of this principle by critical clinical observers in the various branches of the healing art, including dentistry, have been reported in

such great numbers and in so many different diseases, that any impartial reviewer must admit that they lend the fullest support to this basic concept. In a critical review of the case of the oral focal infection idea, McCluskie (19) stated:

There are peculiar difficulties due to the limitations of almost every type of evidence and the varying reactions of the individual. But on considering the vast amount of clinical and experimental observations which have been accumulated in recent years, one is driven to conclude that oral focal sepsis is more than mere theory, and though imperfectly understood, is founded on fact. From the practical point of view the rational remedy is early recognition of oral sepsis, an appreciation of its importance, and closer coöperation in treatment between the doctor and dentist.

#### EXPERIMENTAL STUDIES

Results of experimental studies support the clinical evidence regarding the importance of this principle. Of the different foci, those in the tonsils and in or surrounding the apexes of pulpless teeth are perhaps the most important primary foci chiefly for mechanical reasons, as we shall see. The crypts of tonsils dilated by scar tissue formed as a result of attacks of tonsillitis or of other causes, teeming with microorganisms, in well or sick persons, may be considered as veritable test tubes with permeable walls and as an ideal experiment in focal infection. Atrophy of lymphoid tissue after middle life of the patient, when systemic disease most often occurs or tends to progress, and the almost constant presence of fibrosis and pus, in extirpated tonsils (20), and of erosion or ulceration of the epithelial lining in their crypts afford especially favorable conditions for ready entrance into lymph or blood channels of the bacteria and their toxic and sensitizing products and for maintenance or acquirement of peculiar virulence of the streptococci. The apical ends of pulpless teeth, from the microscopic and bacteriologic standpoint, represent a cancellous, cavernous structure especially favorable for localization and continued growth of bacteria, and for forming a nidus for the dissemination of bacteria and their toxic products. In this circumstance, as in chronic infections in ulcerated crypts of tonsils, healing of an infective process is for mechanical reasons almost impossible. The routine, complete filling of the foramina at

the apex with impervious material through the root canal or any other means is microscopically and mechanically well-nigh impossible. Antiseptic agents placed into the root canal, although they may sterilize the root, cannot always reach or prevent the recurrence of infection at the apex. The filling in of bone after the antiseptic treatment of the root canal of teeth which are not normal in the roentgenogram does not mean that infection has disappeared (4). Cultures by my methods from the apexes of such pulpless teeth, obtained in a sterile manner for me by Professor Hess of Zurich with a trephine, after he reflected the mucous membrane opposite the apex of the tooth and sterilized the field of operation, yielded the usual green-producing streptococci.

It is mainly for these mechanical reasons that these two types of foci are more or less continuously heavily infected and hence are especially prone to cause systemic disease. Absence of symptoms in these foci should not be interpreted as indicating freedom from infection, but rather as evidence of adequate drainage into the lymph or bloodstream of the bacteria and their toxic products. The bacteria contained in the granulation tissue at the apexes of pulpless teeth usually are not encapsulated by fibrous tissue, as is commonly taught; rather, since they are the incitants they are present in greatest numbers at the very periphery in which new blood vessels are being formed and in which inflammatory reaction is most in evidence, precisely where absorption channels are especially abundant. Mechanical removal, for the reasons mentioned, of such foci seems the only safe therapeutic method to employ. Experiments are not lacking which demonstrate why foci in tonsils or pulpless teeth are more important from the standpoint of systemic disease than infections in other tissues, such as those of lungs in bronchiectasis, cervix, prostate gland and the nonpocketed lymphoid tissue of nasopharynx and the normally functioning intestinal tract.

Injection of bacteria into soft tissues does not suffice to produce a chronic focus from which bacteria and their products are more or less continuously disseminated. Prompt healing with destruction of microorganisms, unless the microorganisms are highly virulent, usually occurs, whereas the implantation of infected nonabsorbable or porous material such as agar

(21-23), infected pieces of bone (24), suspensions or emulsions or aleuronat (25) and pledgets of cotton (26), does suffice to produce such a chronic focus. It has been shown that the infection in the nidus thus formed continues almost indefinitely, that it is associated with recurring cellular reactions (25), and that it is the cause of systemic effects, especially allergic states (21-23) similar to those attributable to foci, especially in tonsils and teeth. We have shown that it is usually impossible to desensitize or relieve symptoms of various diseases by means of specific vaccines in the face of active foci. Following removal of the responsible focus or foci, this often becomes possible.

The importance of chronic focal infection was well shown by Reith and Squier (27), who made blood cultures in large quantities of dextrose-brain broth in 293 apparently well persons. Positive cultures, chiefly streptococci, were obtained in fifty-three, or 27 per cent, of 194 persons who had chronic focal infection, whereas positive cultures were obtained from only 12 per cent of ninety-nine persons who had no demonstrable focus of infection. Of twenty-four persons harboring foci and having pain in joints or muscles, including chronic infectious arthritis, streptococci or diplococci were isolated from the blood of ten, or 42 per cent. Moreover, Reith and Squier found that the seasonal incidence of positive blood cultures in persons harboring foci of infection was consistently two to three times higher than it was in persons not harboring foci of infection, and in both groups the incidence of positive blood cultures was lowest during summer.

#### BACTERIOLOGIC ASPECTS OF FOCI OF INFECTION

Ordinary cultural methods usually do not suffice for the isolation of causative streptococci from dental and other foci of infection, or for the demonstration of specific virulence, elective localizing power and other specific properties. It was found very early in my work that micro-organisms, especially streptococci in foci and systemic lesions, are highly sensitive to oxygen and other requirements for growth. The addition of pieces of brain to 0.2 per cent dextrose broth and to soft dextrose-brain agar made these mediums highly favorable for the isolation and maintenance of specific properties and of streptococci from the blood, from foci of infection

(especially those at the apexes of pulpless teeth), from prostatic fluid in prostatitis, from the exudate from the cervix in cases of endocervicitis and from metastatic or systemic lesions. The successful use of these or similar methods by others no longer leaves any doubt of their value.

Slight contamination of teeth may occur during extraction, despite every precaution which may in part be the source of the higher incidence of isolations of bacteria in liquid mediums than in the soft agar. Cultures made from apexes of pulpless teeth resected under sterile precautions have been shown by Precht, Rickert (28) and others to be infected. The much higher incidence of isolations from pulpless than from vital teeth simply cannot be referable to the aforementioned source of contamination. The chances for contamination are precisely the same in the removal of the two types of teeth. Moreover, we have found in our studies that the streptococci obtained from saliva and from pyorrheal pockets and gingiva grow readily on the surface of blood agar plates, whereas those obtained from apexes of pulpless teeth are highly sensitive to oxygen and usually do not grow on blood agar plates. We have used this fact to control our cultures, in addition to the swabbing of the gingivae just before extraction of teeth. Heavy growth in our mediums (dextrose-brain broth and dextrose-brain agar, which afford a gradient of oxygen tension and other favorable conditions) and no growth on blood agar, and a negative control swab culture, are considered proof that the organisms which grew were from the apex of the tooth and were not contaminants.

Austin and Cook (29) found by the use of these methods that anterior pulpless teeth quite without regard as to whether they were normal or abnormal in the roentgenogram, were not only more often infected but were also more heavily infected than vital teeth. Thus, 89 per cent of 100 pulpless teeth and 4 per cent of 100 vital teeth yielded streptococci in dextrose-brain broth; 75 per cent of 100 pulpless teeth yielded a heavy growth in dextrose-brain broth and none of the vital teeth yielded a growth. Differential quantitative cultures were also made by Rhoads and Dick (30) who found that the number of colonies obtained from the apexes of pulpless teeth was from 700 to 1000 times greater than the number obtained from vital teeth drawn and cultured in identical manner. Swanson and

Van Kirk (31) cultured the midportion and the apical ends of roots of extracted teeth after surface sterilization with alcohol and burning. Ninety-six per cent of 1220 root-filled pulpless teeth and 98 per cent of 582 non root-filled pulpless teeth yielded a growth, chiefly green-producing streptococci.

By means of a serial dilution method utilizing soft dextrose-brain agar, we have found that the number of viable streptococci at the apexes of pulpless teeth of persons having systemic

reported on the use of this method in culturing pulpless teeth with similar results.

In order that the reader may visualize the bacteriologic aspects, as now recorded in the literature, of infected teeth, granulomas, residual portions and root tips, I have summarized the results of cultures which have been made by different investigators by what we considered as adequate methods. The results of eight different studies made by fourteen different investigators (4, 33-41) are summarized in

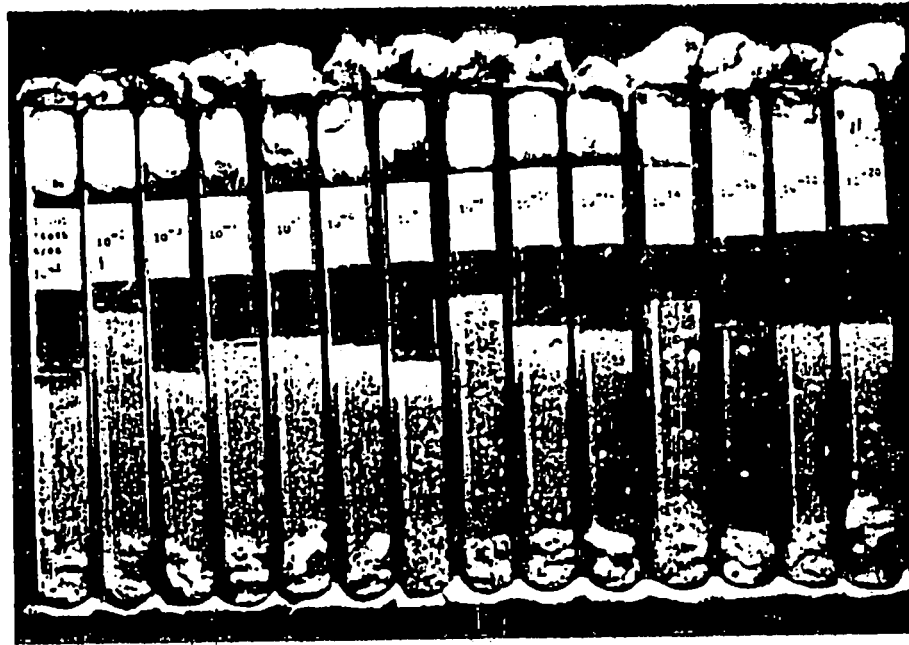


FIG. 1. Serial dilution culture of the washings of the apex of an extracted tooth appearing normal in the roentgenogram, in soft (0.2 per cent) dextrose brain agar. Note the diffuse growth in the first two dilutions, innumerable colonies in the next two dilutions and a progressive diminution in the number of colonies of streptococci, with six colonies in the  $10^{-10}$  dilution ( $\times \frac{1}{2}$ ).

disease, or the ability of these viable streptococci to grow as dilutions are being made, is far greater than the number or ability to grow of viable streptococci at the apexes of vital teeth. The results of growth obtained from pulpless teeth are well shown in figure 1. Washings obtained from the apex of the pulpless tooth yielded six colonies of streptococci at  $10^{-10}$  or a dilution of one billion trillions of the material inoculated, whereas those from nonvirulent streptococci, such as isolated from vital teeth, yielded growth only to a dilution of  $10^{-4}$  or, one hundred thousand. Thomas and Hubbell (32) have

table 1. It will be seen that there was a much higher incidence of growth of chiefly green-producing streptococci in cultures obtained from pulpless teeth, quite irrespective of whether the teeth were normal or abnormal in the roentgenogram, than in cultures obtained from vital teeth. The number of viable streptococci as indicated by the number of colonies that grew was from fifty to seventy times higher in the case of washings from the apexes of pulpless teeth than from the apexes of normal vital teeth without fillings or periodontoclasia. Nearly all granulomas, residual regions following ex-

tractions of infected teeth and root tips were found to be infected, and many were heavily infected.

The question of the value of different methods used in the filling of root canals calculated to prevent pulpless teeth from becoming infected has been studied in patients by myself and by Meisser and Brock (42) in dogs. At one time I, with many others, felt that if fillings of the canals of roots of teeth were made first after the material scraped from the canals had been proved to be sterile or in sterile teeth at the time the pulp was removed, then subsequently the infection from blood stream or otherwise might be prevented. The results in one case will serve to illustrate.

After cultures in dextrose-brain broth of scrapings of the root canals of two teeth had remained sterile on two separate occasions after root canal therapy, a dentist highly skilled in this work filled the canals of the roots in a sterile manner, controlling the placement of the fillings in the canals of the roots with the roentgenogram. The patient, of middle age, was well at the time. The teeth remained symptomless and normal in the roentgenogram, but the subject several years later began to suffer from severe progressive myositis and arthritis associated with exhaustion. Rest, fresh air and the best of care proved of no avail. The tonsils had been cleanly removed some years before. No foci were found other than the two teeth whose root canals had been filled, and the only pulpless teeth the patient had. These were drawn in a sterile manner. Cultures from the apexes yielded innumerable colonies of streptococci in dextrose-brain agar and a heavy growth in pure culture of short-chained streptococci in dextrose-brain broth. Intravenous injection in rabbits of the streptococci isolated was followed by extreme myositis and arthritis. The streptococcus was isolated from the experimentally induced lesions in muscles and joints. The patient made a prompt, complete and permanent recovery.

The experiments of Meisser (42) performed on dogs on the question of resistance to infection of teeth from which pulps were amputated or removed in a sterile manner and of which the root canals were filled by methods then in common use in human beings showed (1) that that amputated pulps invariably degenerated, (2) that all teeth from which the pulps were removed and in which the canal had been filled

in a sterile manner became infected in from two to eighteen months, (3) that staphylococci and streptococci having elective localizing power injected intravenously could be isolated more often and in larger numbers and for a much longer time from the pulpless teeth with fillings of the canals of the roots than from vital teeth and (4) that the pulps of vital teeth either remained sterile or rapidly became sterile at about the same time as the kidney, liver and blood, following these intravenous injections of bacteria. It is suggested on the basis of these experiments and many other facts that methods calculated to render pulpless teeth sterile and to prevent their becoming infected be proved efficacious in dogs before being used in human beings. It is of course taken for granted that any method that fails to prevent localization and growth of bacteria at the apexes of such teeth falls short of a basic requirement and should not be used.

#### THE INFECTING POWER OR VIRULENCE OF STREPTOCOCCI ISOLATED FROM FOCI

The reproduction or simulation of a disease in experimental animals is still the best evidence we have to show the etiologic relationship of an inciting agent to a particular disease entity. The results from intravenous injection of streptococci isolated from foci in a large number of diseases have been reported previously (1-3). I have summarized the results of experiments of my own in seven diseases also studied with my or similar methods by my co-workers and by others. The incidence of localization in the different organs obtained by the different investigators is summarized in tables 2 (1-3), 3 (43-51), and 4 (52-65). In each of the seven diseases, namely, ulcer of the stomach or duodenum, arthritis, iritis and other diseases of the eye, myocarditis, myositis, pyelonephritis and ulcerative colitis, the incidence of grossly visible lesions was consistently higher and usually much higher in each of the three series of experiments in the very organs or tissues affected in the patient from whom the respective strains were isolated (elective localization). Aside from a relatively high incidence of lesions of joints, greatest in the series studied by other investigators, there was no high point of lesions in the different organs following injection alike of nonspecific strains and strains from patients not suffering from systemic disease, a point overlooked by Valentine and Van



Meter (61). The incidence of specific lesions, although it is striking, does not adequately express how very specific these strains usually are on isolation as observed at necropsy.

The technic used by me in experiments on animals is described in detail in the original communications. Although in most instances the

in dextrose-brain broth were made in previously warmed dextrose-brain broth in rapid succession (four to six or eight times a day), and single colonies from young (usually six to eighteen-hour) dilution cultures in dextrose-brain agar were transferred to dextrose-brain broth for injection. It is a curious fact that the streptococci from foci

TABLE 2

*Elective Localization of Streptococci Obtained in Experiments by Rosenow in Diseases Also Studied by Other Investigators*

SOURCE OF STREPTOCOCCI: DENTAL AND OTHER FOCI OF INFECTION IN PERSONS HAVING:	CASES OR STRAINS	ANIMALS THAT RECEIVED INTRA-VENOUS INJECTIONS	PER CENT OF ANIMALS SHOWING LESIONS IN:								
			Stomach or Duodenum	Joints	Eyes	Myocardium	Muscles	Kidneys	Colon	Endocardium	Gallbladder
Ulcer of stomach or duodenum.....	354	1539	66	9	1	1	2	5	3	5	7
Arthritis.....	723	1447	8	63	0	1	12	8	1	6	2
Iritis or other diseases of the eye.....	87	272	2	5	42	0	3	3	0	3	1
Myocarditis.....	7	36	6	0	0	61	19	3	0	50	0
Myositis.....	192	391	14	30	1	15	72	0	1	10	2
Pyelonephritis.....	50	168	7	12	0	4	10	73	3	5	2
Ulcerative colitis.....	200	527	1	1	0	0	1	1	68	1	1
No systemic disease (control group).....	534	1329	14	18	8	0	3	9	5	11	5

TABLE 3

*Elective Localization of Streptococci Obtained in Experiments by Co-workers of Rosenow*

SOURCE OF STREPTOCOCCI: DENTAL AND OTHER FOCI OF INFECTION IN PERSONS HAVING:	NUMBER OF INVESTIGATIONS	CASES OR STRAINS	ANIMALS THAT RECEIVED INTRA-VENOUS INJECTIONS	PER CENT OF ANIMALS SHOWING LESIONS IN:								
				Stomach or Duodenum	Joints	Eye	Myocardium	Muscles	Kidneys	Colon	Endocardium	Gallbladder
Ulcer of stomach or duodenum.....	6	439	1231	52	6	1	13	16	3	0	2	1
Arthritis.....	8	511	1225	7	58	1	3	11	6	0	0	2
Iritis or other diseases of the eye.....	2	107	323	1	4	43	2	2	3	0	0	1
Myocarditis.....	1	11	39	0	18	3	38	5	5	0	0	3
Myositis.....	2	19	50	4	22	0	6	58	4	0	2	4
Pyelonephritis.....	3	21	96	5	17	0	6	12	83	0	6	8
Ulcerative colitis.....	1	15	60	7	5	0	0	8	3	60	0	0
No systemic disease (control group).....	8	278	665	7	11	0	3	7	7	0	0	3

primary cultures (usually pure or nearly pure streptococci) were injected, it must not be supposed that elective localization following intravenous injection was not also obtained following injection of pure single-colony cultures or of pure cultures otherwise far removed from their original source. In order to not destroy the property on which elective localization depends, subcultures

at the end point of growth in the serial dilution method in dextrose-brain agar and dextrose-brain broth, often representing an almost unbelievably high dilution, have especially high elective localizing power and other specific properties. One or two platings on the surface of blood agar usually sufficed to destroy this property.

The inoculated streptococci were isolated

routinely from, and often demonstrated in, the experimentally produced lesions and proved to be absent in healthy tissues. On reinjection they again caused the lesions characteristic of the disease in question. Reinjections in dosages small enough for the animals to live for a long time commonly produced a disease picture and microscopic lesions resembling those at hand in patients.

The inability of Lehmann (66) to obtain evidence of elective localization is clearly referable to variation from our technic. He injected from

Nickel and Judd (49) not only produced acute but also chronic cholecystitis and gallstones with streptococci obtained from patients who had cholecystitis. Nickel and Stuhler (67) produced chronic villous and deforming arthritis in rabbits with streptococci obtained from the prostate gland of patients who had rheumatoid arthritis.

The results of experiments by Illingsworth (68) and A. L. Wilkie (69) were particularly striking. D. P. D. Wilkie (70) stated that Illingsworth, working in his clinic, was able to show that, using Rosenow's special medium, streptococci could be

TABLE 4  
*Elective Localization of Streptococci Obtained in Experiments by Other Investigators*

SOURCE OF STREPTOCOCCI: DENTAL AND OTHER FOCI OF INFECTION IN PERSONS HAVING:	NUMBER OF INVESTI- GATIONS	CASES OR STRAINS	ANIMALS THAT RECEIVED INTRA- VENOUS INJECTIONS	PER CENT OF ANIMALS SHOWING LESIONS IN:								
				Stomach or Duodenum	Joints	Eye	Myocardium	Muscles	Kidneys	Colon	Endocardium	Gallbladder
Ulcer of stomach or duodenum.....	2	101	280	60	39	2	5	13	6		5	2
Arthritis.....	7	More than 75	415		69	0	13	9	13	0	12	0
Iritis or other lesions of eye.....	3	67	186	5	45	63	11	17	34	1	11	3
Myocarditis.....	3	More than 27	94	9	43	3	69	21	32	0	38	2
Myositis.....	1	14	86	10	44	1	13	56	18	0	13	4
Pyelonephritis.....	2	More than 10	96	3	45	2	13	16	58		7	
Ulcerative colitis.....	3	More than 20	119		20		13	3	8	42	12	
No systemic disease (control group).....	7	141	300	7	31	2	17	13	19	0	1	6

1 to 2 cc. of broth cultures of streptococci obtained from single colonies, presumably from blood agar, and he killed surviving animals one week or longer after injection. We injected from 5 to 10 cc. of the primary culture of streptococci in dextrose-brain broth and killed animals to search for lesions one to three days following injection. Despite Lehmann's different technic, he did produce endocarditis with *Streptococcus viridans* in sixteen animals, and by the use of dextrose-brain broth, succeeded in isolating streptococci from 164 or 167 granulomas, results which are in accord with our results and with those of others.

grown from the wall of the gallbladder in quite a large number of cases in which the bile was sterile. He further showed that organisms of the *coli* group are relatively infrequent except in acute suppurative cases. This work has been carried a step further by A. L. Wilkie (69), who has shown that cholecystitis is almost invariably an intramural streptococcal infection, and Rosenow's contention of a selective affinity of this organism for the gallbladder in experimental animals is strikingly true. A. L. Wilkie concluded, after his experimental studies, that (a) cholecystitis would appear to be a blood-borne streptococcal intramural infection; (b) late changes in-

cluding formation of gallstones following repeated injection of the streptococcus emphasized the intramural path; (c) the intramural pathologic changes produced experimentally resemble in every detail the changes seen in the human gall-bladder in cholecystitis.

Jarlov and Brinch (8) produced chronic arthritis, and concluded from their long series of experiments that certain strains of streptococci especially those from arthritis produced arthritis more often than others. Cecil and Angevine (71) produced in rabbits, with small doses of streptococci obtained from foci of infection and blood and joint tissues in arthritis, pathologic lesions very similar to those of rheumatoid arthritis in man.

In addition to these aforementioned highly specific effects, there is a close parallelism between the incidence of involvement of various tissues or organs as observed clinically and the incidence of lesions as found in experiments in animals after the intravenous inoculation of organisms recovered from dental and other foci of infection. The lesions most frequently seen in patients referable to focal infection are those of the locomotor system, joints, muscles, tendon sheaths and ligaments. The kidney, skin, heart, stomach, duodenum and eyes are often affected. Less commonly, other organs such as those of the nervous system and blood-building tissues may be involved. Rarely, very unusual localizations of streptococci from dental and other foci of infection such as onychia occurred as shown by Haden and Jordan (72), thyroid disease (especially thyroiditis) as shown by Cantero (73) and lesions of the gasserian ganglion produced electively in experiments of my own in cases of trigeminal neuralgia. The removal of foci in instances of trigeminal neuralgia (and in my experience their presence is constant in this condition) obviously should be done as a preventive measure before central irreversible lesions have occurred, rather than as a curative measure long after the disease has existed. Van Kirk and Swanson (74) produced encephalitis in rabbits by the intravenous injection of streptococci obtained from the pulpless teeth from patients who had encephalitis, an observation corroborative of our own studies.

Nickel and Mussey (75), Fasting (76), Curtis (77) and Reith (78) have shown that streptococci, isolated from foci of infection in women who had spontaneous abortion not caused by syphilis, had predilection for the uterus and

caused abortion in rabbits. Following removal of such foci, pregnancies went to full term. Horton and Dorsey (79) produced vascular lesions with gangrene of the toes in rabbits with material containing streptococci from patients who had thrombo-angiitis obliterans. The intravenous injection of relatively small numbers of streptococci grown not in the test tube but in various foci such as pyorrheal pockets, apexes of pulpless teeth and tonsils, often sufficed to cause lesions referable to streptococci electively in various diseases.

#### ELECTIVE LOCALIZATION OF STREPTOCOCCI OBTAINED FROM EXPERIMENTALLY INDUCED DENTAL FOCI

Methods other than the intravenous inoculation of freshly isolated living cultures of streptococci have sufficed to show the existence of the property of elective localization. Marked ulceration of the stomach in guinea pigs occurred following the intraperitoneal injection of the streptococcus from a sinus draining an infected tooth of a patient who had acute ulcer of the stomach and recurrent hemorrhage. Cure was prompt and permanent following removal of the infected tooth from which the sinus issued. Suppurative pulpitis and hemorrhagic edema of the peritoneum opposite the roots of the teeth of animals followed the intraperitoneal injection of the streptococcus from the pulp of a tooth of a patient who had recurring attacks of pulpitis, dental neuritis and myositis. Squier and Bach (80) produced hypotension in rabbits by injecting the streptococcus isolated from dental and other foci of infection in patients having hypotension into the joints (foci) of rabbits. Moreover, streptococci that manifest elective localizing power have been shown to produce within themselves, and to free in dextrose-brain broth cultures, poisons or toxic products which specifically localize and produce lesions in the same tissues as do the living microorganisms. Specific effects have been produced by the intravenous or intracerebral injection, respectively, of the living streptococci, the dead bacteria or filtrates of active cultures obtained from patients suffering from pyelonephritis, myositis, endocarditis, myocarditis, arthritis, dental neuritis and pulpitis, ulcer of the stomach or duodenum and myasthenia gravis.

Thus, the induction by Meisser and me (81) of

chronic foci in the teeth of dogs with streptococci and staphylococci shown to have elective localizing power was followed by a high incidence of specific localization in the case of strains of streptococci obtained from patients who had nephrolithiasis (7), alkaline phosphatic cystitis, ulcer of the stomach and ulcerative colitis, chorea, encephalitis and epidemic hiccups; and the aforementioned induction was followed by a high incidence of localization in the kidney of staphylococci obtained from the maxillary sinus of a patient who had nephritis.

Jones and Newson (82), following the production of similar foci in the teeth of dogs with streptococci having affinity for the vascular system, produced symptoms and lesions of the myocardium and endocardium resembling those characteristic of chronic heart disease in human beings. The conditions in the experiments in which elective localization through foci was produced simulated in important respects those at hand in patients. The teeth from which the pulps were removed became discolored. They remained free from pain or tenderness, and at the apexes absorption of bone with formation of granulation tissue in varying degree occurred similar to that observed at the apexes of pulpless teeth in human beings, and as this occurred, specific systemic disease developed in addition to an increased susceptibility to intercurrent infections. At the end of the experiments the streptococci having elective localizing power were isolated from pulp canal and from the granuloma, and were demonstrated microscopically in large numbers in sections. The intravenous inoculation in rabbits of the strains thus isolated revealed the fact that they had retained their elective localizing power for months in the experimentally induced dental foci. The results of these basic experiments were not considered by Holman (83), and Reimann and Havens (6) in their critical reviews. Holman concluded: "However, what Rosenow and his followers particularly showed and what all the other investigators of the problem have definitely demonstrated is that streptococci do localize in various organs and tissues and can produce lesions at least sufficiently suggestive of those found in man so that their potential danger in infected foci cannot be neglected." Reimann and Havens and other critics conceded that the principle of focal infection applies in some cases.

I wish now to discuss other observations which indicate that the streptococci commonly isolated from foci, that is, streptococci that have elective localizing power, have etiologic significance.

#### RELATIONSHIP OF FOCI OF INFECTION TO HYPERSENSITIVENESS AND ALLERGY

Although I have studied chiefly the specific localizing and necrotizing power of the bacteria isolated from foci and their products, the question of the effect of these and of the focus on the host, aside from the induction of specific disease, has also been considered. Symptoms resembling those of anaphylaxis were produced in guinea pigs, rabbits and dogs by primary intravenous injections of autolysates and of leukocytic digests of pneumococci, streptococci and other bacteria. The appearance, and later disappearance, of these highly toxic properties were associated with proteolysis. Hypersensitiveness to extracts and autolysates of pneumococci and streptococci was also obtained, a point reported on more recently, and with similar results, by Zinsser and Grinnell (84). Leukocytosis and destruction of organisms following the intraperitoneal injection of the corresponding antigen or bacteria in the hypersensitive animals were greater and more rapid than in normal animals. The hypersensitive animals exhibited decreased resistance to the intraperitoneal injection of large numbers of virulent pneumococci, but exhibited increased resistance or immunity following the inoculation of small numbers. The induced hypersensitiveness or allergy in guinea pigs to pneumococcal extracts disappeared on repeated inoculations of dead pneumococci or pneumococcal extracts and autolysates and after recovery of the animals from pneumococcal infections.

The difference in the behavior of normal and sensitized guinea pigs toward unautolyzed and autolyzed extracts of pneumococci was especially illuminating in these early studies. The unautolyzed extracts were nontoxic to normal animals and very toxic to the sensitized animals. Partially autolyzed extracts were very toxic to normal animals, and only slightly toxic, or not at all, to sensitized animals, whereas more completely autolyzed extracts were nontoxic to both. These results and those of Zinsser and Grinnell (84) indicate that a parenteral digestion of bacteria and bacterial antigens into highly toxic cleavage products occurs more rapidly, and, it would seem,

in greater amount, in experimental or spontaneous hypersensitiveness, or in the presence of allergy, than in normal animals. Zinsser and Grinnell (84) assert that in the autolysis of various bacteria there are set free substances which stimulate the allergic state and that such autolysates are the best reagents with which to test hypersensitiveness.

Patients who have foci of infection, especially those who have chronic infectious arthritis or myositis and neuromyositis, often were found to be exceedingly sensitive to streptococcal vaccines. The dogs in which we successfully produced chronic foci about the teeth, in addition to exhibiting lesions specific for the strains of streptococci inoculated, lost weight and hair, and became more susceptible to intercurrent infection. A diet sufficient to keep the control animals well was inadequate for the dogs who had chronic foci of infection.

Derick, Hitchcock and Swift (85), and Clawson (22) have shown that focal infection resulting from the inoculation of nonhemolytic streptococci may be followed by a state of hypersensitiveness and they have emphasized the relationship of allergy to streptococci in rheumatic fever. Swift, Derick and Hitchcock (21) induced a hyperergic state in rabbits by the production of focal lesions; this state was maintained for months by making an agar focus infected with allergizing green-producing streptococci. Clawson (22) and Birkhaug (23) obtained similar results. Moon and Stewart (86) produced lesions in rabbits and dogs essentially like those of rheumatic fever by establishing foci of infection in the subcutaneous tissues with pledgets of cotton soaked in cultures of streptococcus viridans obtained from persons who had rheumatic fever. Harkary (87), in a memorial volume to Dr. Emanuel Libman, stressed the importance of focal infection in bacterial allergy in asthma and arthritis. Cook, in his paper at the Dental Centenary Celebration at Baltimore stressed the importance of focal infection in relation to allergic states. Weisberger (88) showed that dissemination of bacteria from foci established at the apexes of teeth in rabbits was far greater following injection of horse serum into sensitized animals than it was following injection of the same serum into non-sensitized animals.

Patients whom I have found to be extremely

sensitive and whose condition improved following removal of foci and guarded use of vaccines became less sensitive to the vaccine as improvement occurred. The mechanism of bacterial and protein hypersensitiveness has been shown to be the same. Hence, a focus, in addition to affording conditions favorable for the production of specific systemic disease, may have more general deleterious effects, the nature of which may be determined in part by the bacterial antigens absorbed from chronic bacterial foci, and in part by the peculiar reactivity of the host.

Streptococci which had specific elective localizing power and characteristic cataphoretic velocity repeatedly have been demonstrated to be present in various foci of infection and elsewhere (carrier state) for a period of years, and long after the onset of symptoms among patients suffering from certain chronic diseases, such as arthritis and encephalitis. This is believed to be of fundamental significance, for it indicates that the patient's tissues or tissue juices afford the conditions favorable for streptococci to acquire and maintain particular elective localizing power and cataphoretic velocity, peculiar to the disease from which the patient is suffering.

May not this be a reason why so many chronic diseases tend to persist, recur and run a progressive course with so few localizations elsewhere, and why they are so difficult to cure? Might not the inherited rheumatic diathesis, the neuropathic or the allergic constitution and other "diatheses" and "constitutional predispositions" be expressions in part of a peculiar interaction between host and invading organism, and not expressions merely of an inherited "weakness" of joint, brain or other organ, as is usually assumed? The focus furnishes a ready source of infecting organisms and bacterial antigens to which the host reacts variously, depending, among other factors, on inherited or acquired constitutional peculiarities. If of allergic tendency, local and general hypersensitiveness are prone to develop; if of normal constitution, increased resistance or immunity is probable. The particular tissue in which local hypersensitiveness develops and in which allergic manifestations are especially marked is determined, it would seem, by the specific or elective localizing power of either or both the bacteria and their antigens or toxins.

# ELECTROPHORETIC MOBILITY OR VELOCITY AND ELECTIVE LOCALIZATION OF STREPTOCOCCI

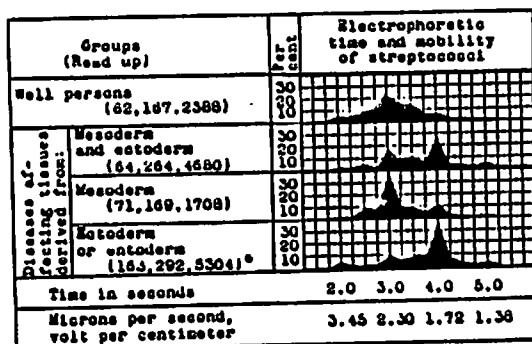
To obviate the use of animals and to determine, if possible, more precisely wherein lie the reasons for elective localization, Jensen and I (89) have studied cataphoretically streptococci that have elective localizing power, and Sheard, Pratt and I (90) have studied the effects of exposing streptococci having elective localizing power and characteristic cataphoretic time and velocity to the high frequency field. Among other interesting facts, it has been discovered that there is a close parallelism between elective localization and cataphoretic time and velocity of streptococci. The details of the technic are described in pub-

and which tend to localize electively, have a cataphoretic time and velocity of chiefly 4.0 seconds and 1.07 microns per second, volt per centimeter.

In figure 2 are given the average distribution curves of cataphoretic time and velocity of streptococci isolated from infected teeth and other foci of infection of persons having streptococcic diseases affecting tissues derived from ectoderm or endoderm, mesoderm, and mesoderm and ectoderm and of well persons. The higher the column at a given time or velocity, the larger the number of streptococci that traversed the unit distance (50 microns) at that particular time or velocity. The cataphoretic time and velocity of streptococci isolated from the depths of the jaws and from apexes of pulpless teeth of persons having various diseases during epidemics of influenza, although characteristic of each disease when influenza was not at hand, were, as in the case of streptococci isolated from the nasopharynx, also more like those of streptococci from influenza.

Exposure to the high-frequency field caused marked changes in the cataphoretic time and velocity of streptococci and, concomitantly, in their elective localizing power. Thus, in a series of experiments in which animals were injected with unknown cultures of streptococci, it was found that when the cataphoretic time and velocity of streptococci isolated from instances of chronic infectious arthritis (which streptococci, when untreated, manifested marked affinity for joints) had become cataphoretically like those of streptococci isolated from instances of encephalitis, the streptococci had lost affinity for joints, and concomitantly, had acquired affinity for the nervous system. Conversely, when streptococci isolated from instances of encephalitis (which streptococci on isolation had marked affinity for the nervous system) had become cataphoretically like those isolated from instances of arthritis, they had lost affinity for the nervous system and had acquired affinity for joints of animals that had received intravenous injections.

The work on cataphoresis has proved of importance in still other respects. I could often predict before injection of a given culture whether or not localization would be specific by determining the distribution curve of cataphoretic time and velocity of the streptococci. This has made clear an otherwise puzzling fact, often observed in elective localization work; namely, the sudden disap-



\*The figures in parenthesis indicate, respectively, the number of strains, cultures and streptococci timed in each group studied.

FIG. 2. Distribution curves of cataphoretic time and velocity of streptococci isolated from dental and other foci of infection, according to the embryologic origin of the tissues chiefly affected.

lished reports. It is sufficient to state herein that the migration rate, under constant voltage in an electrical field, of the different streptococci is determined in the cataphoretic cell of the Northrop-Kunitz-Mudd apparatus. Since under these conditions migration rate is directly proportional to surface charge, it follows that the greater the charge, the faster the streptococci move. For example, streptococci from atria of infection of patients who have chronic infectious arthritis and other diseases involving tissues derived from the mesoderm and which have respective elective localizing power, have, by our measurements, chiefly a cataphoretic time of 3.0 seconds and velocity of 2.22 microns per second, volt per centimeter, whereas streptococci from similar sources, among patients who have encephalitis and certain other diseases of the nervous system

pearance of elective or all localizing power, or the appearance of new affinities following successive animal passage and repeated transfers in cultures. It has yielded information which makes more explicable certain discrepancies of some workers in this field, for consideration of the inherent property of changeability of streptococci, is basic in studies on focal infection and elective localization. A lack of appreciation of this fact and lack of sufficient attention to technical details have led to misinterpretations and failures to repeat some of these results.

Of great importance is the fact that the medium dextrose-brain broth with which I have obtained the best results in experiments on elective localization, is by far the best medium for preserving characteristic cataphoretic time and velocity of streptococci of any mediums that we have tested. Several transplants in other mediums, such as plain broth, dextrose-beef broth, veal infusion broth, heart muscle infusion broth, yeast broth and even the same dextrose-brain broth minus the brain, often sufficed to convert a strain in which originally most organisms had characteristic cataphoretic velocity and which had elective localizing power, into one of very different velocity with changed localizing power or without this faculty.

As has been pointed out, the antibody content of the serum of patients suffering from the different diseases studied was not uniformly high enough to obtain consistent results by the usual methods of agglutination and precipitation to prove causal relationship. The work on cataphoresis has furnished a method whereby consistent results have been obtained. The serum obtained from patients suffering from various diseases in which elective localization has been demonstrated has specific slowing (charge-reducing) action on the respective streptococci having characteristic distribution curves of cataphoretic time and velocity and elective localizing power. Among the diseases in which this has been demonstrated are acute and chronic arthritis and encephalitis, epidemic hiccup, persistent postoperative hiccup, epidemic vertigo, acute and chronic poliomyelitis, and multiple sclerosis and chorea.

#### SEROLOGIC PROOF OF SPECIFICITY OF STREPTOCOCCI

Because of the great variability of streptococci as isolated from infected teeth and other foci

of infection in various diseases, the prompt loss of specific properties on artificial cultivation, their tendency to agglutinate spontaneously as grown on the usual mediums, and the use of inadequate methods of agglutination with the serums of patients, little evidence has been obtained with which to indicate the causal relationship of streptococci to chronic disease. In a large measure, these difficulties have been overcome by the use of dextrose-brain broth for the primary isolation, by growing the streptococci for purposes of agglutination in this medium or in dextrose broth for one culture generation and by preserving the centrifuged streptococci in dense suspension in glycerol (two parts) and 25 per cent solution of sodium chloride (one part). One cubic centimeter of this menstruum was made to contain the growth of from 50 to 500 cc. of the culture. The antigens for agglutination were prepared by diluting the suspension in glycerol-sodium chloride solution to the density of a broth culture with salt solution to which 0.2 per cent phenol had been added. The patient's serum was likewise diluted in sodium chloride solution to which 0.2 per cent phenol had been added, to one-half the desired dilution and then 0.2 per cent of suspension and serum dilutions were mixed and placed at 50°C. (122°F.) for from eighteen to twenty-four hours, at the end of which time readings were made. Highly specific results were obtained with many, but not all, of the serums obtained from patients who had chronic disease.

The streptococci isolated, grown and preserved in the manner indicated were found to be highly satisfactory also for the preparation of hyperimmune serums in horses and for agglutination experiments with these antisera. Moreover, the antisera prepared in this way caused precipitation (antibody-antigen reaction), often specific, when overlaid in small precipitation tubes with cleared washings in sodium chloride solution of nasopharyngeal swabbings or with the serum of patients. The results summarized in table 5 show how very specific this reaction was with the serums obtained from the respective patients. The demonstration by the precipitation test of the common presence of streptococcal antigen in the serums of patients who had chronic disease that was antigenically related to the streptococcus with which the reacting serum was prepared is new, and, from the

TABLE 5  
Precipitation Reaction with the Serum of Patients and the Serum of Horses Hyperimmunized with Streptococci

SOURCE OF SERUMS (ANTIGENS)	CASES STUDIED	PERCENTAGE OF POSITIVE REACTIONS WITH						
		Antiserums Prepared with Streptococci from:					Control Serums	
		Enceph- alitis	Polio- myelitis	Chronic Ulcer- ative Colitis	Myas- thenia Gravis	Chronic infect- ious Arthritis	Pneumo- coccus I, II, III	Normal Horse
Encephalitis.....	55	78	31	40	45	64	0	0
Spasmodic torticollis.....	12	75	41	41	25	58	0	13
Chronic poliomyelitis.....	20	50	60	30	25	35	0	5
Acute poliomyelitis:								
Human beings.....	28	40	64	4	17	18	0	7
Monkeys.....	9	55	89	44	33	33	0	0
Neuritis, herpes, hiccup.....	12	92	8	33	17	42	0	0
Epidemic gastro-enteritis.....	51	67	33	90	60	45	0	0
Myasthenia gravis.....	8	63	25	38	88	75	0	13
Neurofibromyositis.....	24	63	29	41	33	83	0	13
Asthmatic bronchitis.....	16	68	25	37	31	37	0	0
Chronic infectious arthritis.....	12	50	8	8	8	67	0	0
Iritis.....	11	27	9	9	0	45	0	0
Normal controls.....	48	8	0	6	2	10	0	0

TABLE 6  
Erythematous Reactions to Intradermal Injection of the Euglobulin Fraction of Antistreptococcal Serums

SOURCE OF SERUMS (ANTIGENS)	PERSONS TESTED	AVERAGE REACTIONS (NO. CM.) TO:									
		Euglobulins Prepared with Streptococci from:								Control Serums	
		Enceph- alitis	Polio- myelitis	Chronic Ulcer- ative Colitis	Ulcer of Stomach or Duodenum	Myasthenia Gravis	Chronic Infectious Arthritis	Iritis	Pyelonephritis	Pneumococcus I, II, III	Normal Horse
Encephalitis.....	92	6	5	3	3	2	3		0	1	0
Spasmodic torticollis.....	30	6	4	4	1	4	6			1	1
Hiccup.....	10	10	8	4	1	1	2			1	1
Amyotrophic lateral sclerosis.....	19	4	5	5	8	5	1			1	0
Chronic poliomyelitis.....	27	3	2	8	6	3	2			1	0
Optic or peripheral neuritis.....	17	8	7	7		3	4			1	0
Chronic ulcerative colitis.....	13	5		3	10	4	5		2	1	1
Epidemic gastro-enteritis.....	69	3		12	3	2	5		1	2	1
Ulcer of stomach.....	39	5	3	4	5	10	4		2	0	0
Neuromyositis and fibrositis.....	35	5	5	6	5	4	9	3	3	0	0
Rheumatic arthritis, neuromyositis and carditis.....	28	5	5	5	4		9	1		2	0
Myasthenia gravis.....	19	4	2	2	1	11	3			1	1
Chronic infectious arthritis.....	42	3	3	0	3	3	1	8	2	2	0
Osteitis deformans.....	10	3	2		1		1	8			0
Iritis.....	12	6		1	5		14	11		4	1
Pyelonephritis.....	19	1	8	1	5	2	3		9	3	0
Diseases not due to streptococci.....	33	0	0	1	1	0	0		1	0	0
Well persons.....	32	1		1	1	1	0			1	1

\* St. Louis type.



standpoint of pathogenesis and specific therapy, is considered to be of great importance.

It was also found that intradermal injections of the euglobulin fraction of the antiserum prepared in horses, in the manner indicated, elicited an immediate (ten minutes) erythematous-edematous reaction in patients suffering from a streptococcic disease identical to, or closely related to, the one in studies of which the immunizing strain of streptococcus was isolated. This test is an application to streptococcic diseases of the Foshay antigen-antibody reaction, first noted in relation to tularemia. It serves to determine whether or not a patient is suffering from a streptococcic infection, and if so, of what particular type and what antiserum or stock vaccine had best be used therapeutically. The results recorded in table 6 well illustrate how specific the test is as applied to patients having different diseases.

#### COMMENT AND SUMMARY

A review and results of further studies of clinical, bacteriologic and experimental observations on focal infection and elective localization are reported.

Despite the lack of clinical improvement or cure following the elimination of foci of infection in many cases and in certain diseases, alleviation of symptoms occurs so often and in so many diseases that this principle should be applied not so much as a form of therapy unrelated to other conditions but as one of other well-established procedures in diagnosis, prognosis and treatment.

Bacteriologic studies conducted by adequate methods no longer leave any doubt that chronic, often symptomless, foci, especially those of tonsils and teeth, are infected, usually heavily infected, and chiefly by green-producing streptococci. The results of earlier experimental studies have been corroborated sufficiently often by myself, my co-workers and other investigators to indicate conclusively that the bacteria (especially the green-producing streptococci found in the presence of chronic focal infection) are not only virulent but are usually specifically virulent. Their probable or undoubted causal relationship to a number of diseases has been shown by intravenous and other methods of injection in animals, by the induction with streptococci of chronic foci especially at the

apexes of teeth in dogs, by cataphoretic studies, by diagnostic cutaneous tests made with the euglobulin fraction of the serum of horses hyperimmunized with the respective freshly isolated strains, by the precipitation reaction with the respective undiluted antistreptococcic serums of horses and the blood serum of patients and by agglutination tests made by special methods.

The property or tendency of these streptococci to localize and to produce lesions electively has been shown to be referable to a toxic substance or substances elaborated by the organisms within themselves and free in the medium in which they grow. Filtrates of actively growing cultures of the respective streptococci, the dead bacteria and the live culture, all tend to localize and produce symptoms and lesions specifically or electively in the tissues or organs characteristic of the disease the patient had and from whose foci the streptococci were isolated. The specificity of the streptococcus on isolation from dental and other foci is often so marked that the clinical and pathologic pictures of certain diseases have been reproduced by the induction of chronic foci of infection at the apexes of pulpless teeth in dogs, and these pictures simulate in all essential respects those commonly at hand in human beings. The streptococci in chronic foci maintain their specific infecting and other properties for many months, whereas artificial cultivation (especially on aerobic mediums) destroys specificity promptly, especially the property on which elective localization depends.

The focus affords ready entrance of bacteria and their toxic products which may, depending on inherited or acquired predispositions or other factors, cause infection in remote tissues, general ill effects, hypersensitiveness or allergy or a combination of some or all of these in the same persons, or perhaps at times increased resistance and immunity.

The localizing and necrotizing power peculiar to these organisms (usually streptococci) determines largely the site or tissues to be affected. The sooner foci are eliminated, after the onset of a disease, or preferably even before systemic symptoms have occurred, the better should be the immediate and end results. The common practice of waiting until the disease is far advanced or until a serious condition, such as a hemorrhage in ulcer or a cardiac attack in heart disease, has developed, or until advanced age has occurred,

before evident foci, especially pulpless teeth, are removed, is most deplorable.

Since streptococci appear to be a cause of so many diseases, since immunity is of short duration, and since mechanical factors play so large a part in maintaining infection in structures so commonly the seat of foci, mechanical correction or removal, so far as possible, probably always will be necessary, even if highly effective specific or other remedial agents are discovered. Recurrence of the previous condition or new localization is prone to occur unless the predisposing cause, the focus, is eliminated. Likewise, operation probably always will be indicated in many of the chronic systemic lesions, such as chronic indurated ulcer, cholecystitis with gallstones and appendicitis with fecal stones or a constricted lumen resulting from previous attacks.

The removal of pulps of teeth and the filling of the roots of teeth calculated to prevent subsequent infection and root canal therapy are so difficult, so expensive and the results so uncertain, as to preclude their routine adoption. Many who formerly skillfully practiced the art find it no longer necessary, and consider it safer to remove pulpless teeth and to attach restorations in a way harmless to vital teeth. It is to be hoped that efficient methods may be found that will not only sterilize pulpless teeth and periapical tissues that have become infected, but will also prevent subsequent infection, especially of the periapical tissues. Considering the mechanical difficulties, the fulfillment of the latter requirement seems almost unattainable, and until this has been accomplished, it would seem wiser to remove teeth that have become infected or that require extirpation of the pulp, rather than to retain them at the risk of having them become the source of an insidious, incapacitating and perhaps fatal infection. Vital teeth free from pyorrhea and fillings should never be extracted except as it becomes necessary for restorative work, but the extraction of pulpless teeth seems to me to be indicated, wholly regardless of the appearance of the roentgenograms. Not too much should be expected or promised from the removal of a given focus, especially in chronic conditions, because a similar condition may be present in inaccessible foci and in foci too small to be detected. The source may not be a focus at all. Moreover, recovery may be

made difficult by local tissue sensitivity or unusual mechanical conditions, and living bacteria in a metastatic lesion may continue the process independently of the focal source.

Elective localization of streptococci isolated from pyorrheal pockets occurred commonly following intravenous injection, emphasizing the importance of recognizing periodontoclasia as a focus of infection. Steps to prevent and correct this most common of evils should continue.

Teeth, especially multicrooked teeth, with deep fillings or caries, which manifest evidence of infection of the pulp, with or without pulp stones, and even symptomless teeth which react positively to vitality tests and that have deep fillings, may be the source of systemic effects and may need to be removed. However, this should be done only after due consideration has been given to other sources of infection. I have repeatedly seen marked benefit following the removal of such teeth when all other efforts had failed, especially teeth in which pulps had died and were found to be heavily infected. Direct injection of the material containing the bacteria in such teeth often was followed by extremely specific effects.

The importance of good hygiene, proper living and inheritance as factors in preventing infective diseases from any source is granted. But why jeopardize or break down these barriers of nature through foci of infection, provided the latter can be prevented or eliminated? The fact that some persons may harbor foci of infection for a long time without apparent harm or systemic disease should not be interpreted as proof of the harmlessness of such foci, any more than polluted water was considered blameless in the days of water-borne typhoid because only a few of the many who drank the contaminated water contracted typhoid fever.

It must not be supposed that other regions, not foci in a mechanical sense, may not also harbor the streptococcus or other bacteria with which the disease from which the patient is suffering may be reproduced. I have isolated streptococci in some instances, not only from foci, but also from the more nearly normal mucous membrane of the upper part of the respiratory tract and from the stool. This may be a reason why the condition of some patients does not improve following removal of one focus or more. It also

serves to show that the concept of the principles embodied in focal infection must not place too much emphasis on mechanical factors. The bacteria that gain entrance through foci must overcome the same inherent resistance of the host to produce diseases as those that gain entrance elsewhere. The factors determining localization are the same in both instances.

The clinical, bacteriologic and experimental studies now extant no longer leave any doubt of the basic fact that localized or pocketed infections or foci in the dental and other regions predispose to systemic disease, that prevention and removal of foci at the proper time and by proper methods are indicated and that mere elimination of foci does not always suffice to cope successfully with the many diseases which still beset human beings. More than removal of foci is necessary; this much seems established; these are matters on which all can agree. How often foci are responsible for the occurrence and for the progressive course of systemic diseases and how often preventive and curative effects may be expected from the elimination of primary or secondary foci in different diseases are still unsettled questions and call for further study.

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