EXAMINATION OF CULTURES FROM PERSONS SUSPECTED OF HAVING CHRONIC INFECTION

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EXAMINATION OF CULTURES FROM PERSONS SUSPECTED OF HAVING CHRONIC INFECTION*

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During 15 years investigation of the significance of immunobacteriologic reactions of streptococci, staphylococci, Micrococcus catarrhalis and colon bacilli isolated from persons suspected of having chronic infection, certain observations were made which resulted in better understanding of the pathological relationships of these organisms. A summary of these findings will be presented in this paper.

The difficulty of applying Koch's postulates has been a major problem in the bacteriological study of chronic infection. This has made it necessary to seek proof of etiologic relationships by indirect methods, such as attempts to show a higher frequency of some particular group of bacteria in "infected" persons than in "controls." Because of the difficulty of determining the presence or severity of infection in certain cases, it is likely that many persons with latent or hidden infection were used as "normal" controls. As a consequence, such experiments had less significance than similar tests in diseases in which infection and freedom from infection were rather sharply differentiated.

Another diagnostic difficulty was caused by the fact that certain "immune" bodies encountered in chronic infection studies are really response bodies, but are produced irregularly and have no constant relationship to infection, immunity or sensitization. They are further complicated by cross-reactions. Eastwood[1] called attention to the fallacy of considering that the characters

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of antibodies in vivo and in vitro are the same, and pointed out that active immunity could be acquired without the production of serological antibodies. Teale[2] showed that an immunized animal could clear streptococci, pneumococci, Friedlander bacilli and B. anthracis from the blood in the absence of agglutinins, bactericidins and protective antibodies for the invading micro-organisms. Gilbert and Dacey[3] reported the recovery of Brucella abortus from the blood clot of a patient whose serum did not agglutinate Br. abortus. These irregularities, together with the alteration of antigenic structure of the cultures as a result of dissociation, have prevented successful application of bacterio-immunologic reactions to the study of chronic infection.

A general relationship has been shown[4] between complement fixing properties of unheated blood serum and the electrophoretic migration velocities of B. coli isolated from the feces of the person from whom the blood was obtained. However, complement fixation reactions using a wide variety of bacterial antigens with active serum were not highly specific[5]. For example, there was only 65.3 per cent agreement between the presence of pathogenic type staphylococci in cultures from a person and the staphylococcal complement fixing power of his blood serum[5]. The results with other groups of bacteria appeared to be even less specific. The frequency of cross-fixation, the failure of usual methods for titrating antigens, the degeneration of antigens, the lack of complement fixing power in certain diseases, the presence of a non-specific anticomplementary property which existed in different strengths in different specimens of blood, and the difficulty of controlling the reactions prevented successful application of the method with active serum[5].

There was no relationship between agglutination reactions and certain in vitro tests which will be discussed later, except for Staphylococcus albus, in which there was agreement in 72.5 per cent of the cultures[6]. These in vitro tests had been shown to be parallel with certain pathogenic properties of the cultures and were used to study the relation between immunologic reactions and possible pathogenicity of the cultures.

There was agreement between intradermal tests and the in vitro tests in 83 per cent of cultures of Micrococcus catarrhalis,

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in 84 to 87 per cent of staphylococci, and in 70 per cent of gamma type streptococci, but there was no agreement in Streptococcus viridans, hemolytic streptococci or colon bacilli[7].

There was agreement between intradermal tests and agglutinability in 91 per cent of enterococci, in 100 per cent of Micrococcus catarrhalis, and in 70 per cent of staphylococci, but there was no relationship in other groups[7].

Based upon the bactericidal power of the blood, Solis-Cohen and his associates developed a technic[8] which they refer to as the "pathogen-selective" method. The assumption is made that the blood of a person with certain types of infection is able to kill organisms which have not invaded the tissues of his body, and that organisms which are able to survive are pathogenic for that individual. Although most of those who have used the method have accepted it without reservation, Solis-Cohen and Rubenstone[9] called attention to its limitations, pointing out that the reaction was to a certain extent quantitative and was affected by the proportion of blood and bacteria.

Short, Dienes and Bauer[10] discussed errors in the theoretical basis of such tests. Rawls and Chapman[11] reviewed the literature on the relation between resistance to the bactericidal power of the blood and certain pathogenic properties of the bacteria. Most of the evidence suggested that the "bactericidal" power of the blood was dependent upon a general antibacterial property which was closely related to complement activity.

The parallel between the power of streptococci to survive exposure to fresh blood and exposure to certain chemicals suggests that the ability of certain bacteria to overcome the bactericidal power of the blood may depend upon the greater resistance of pathogenic strains to unfavorable environmental conditions and not upon a specific differential property of the blood. Thus, tests based upon the bactericidal power of the blood should determine pathogenicity of the micro-organism for the general population rather than for the particular person from whom the blood was obtained. Hare[12] tested organisms against normal blood and the blood of the patient and concluded that in general there was no difference. Fleming and Petrie[13] were of the same opinion.

A further difficulty with the method lies in the high proportion

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of non-pathogens which are capable of growing in the patient's own blood. Boerner and Solis-Cohen[14] reported that 35.1 per cent of Staphylococcus albus, 42.8 per cent of diphtheroids, 33.3 per cent of unidentified micrococci, and 100 per cent of Proteus vulgaris grew in the patient's blood. They stated also that the method is not applicable to spore-forming organisms, to those producing exotoxins (although they used it for Staphylococcus aureus and hemolytic streptococci, both of which may produce exotoxins), or to those difficult to cultivate.

Results with mixed cultures may not be as specific as those with pure cultures, as suggested by experiments with streptococci[15]. Finally, because a different technic is required for each group of bacteria, it is impossible to select a technic or a dilution of blood which will be suitable for all groups.

The foregoing observations illustrate the difficulty of establishing the identity of the infectious agent in chronic infection studies. A new approach to the problem appears to lie in the study of the pathogenicity of the suspected bacteria. Micro-organisms with pathogenic properties would more probably cause chronic infection than would organisms with non-pathogenic properties, which are more likely to be degenerate daughter races, contaminants or secondary invaders. While individual differences in resistance may account for differences in susceptibility to infection, such differences should not make a person more susceptible to non-pathogens than to pathogens. It was pointed out by Chapman et al.[16] that, in staphylococcal infections of the skin, the degree of pathogenicity of the invading micro-organisms, as indicated by in vitro tests, was parallel to the severity of the infection.

The problem of dissociation and its effect upon antigenic properties is a difficult one. Streptococci and staphylococci are easily dissociated, even in the tissues of the body. In many cases, the dissociation is accompanied by antigenic changes, with the result that the antigenic properties of the dissociated daughter races may be quite different from those of the parent strain and, unless the dissociants are separated, serologic and immunologic tests may give erroneous results. Saelhof[17] isolated a streptococcus in two forms from the urine of a patient with pyelocystitis.

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The diphtheroid phase was non-pathogenic for rabbits but the streptococcal phase produced pyelocystitis in rabbits. It was shown[16,18] that many strains of staphylococci from pathologic sources are mixtures of dissociants, some of which are highly pathogenic, while others are non-pathogenic. McGaughey[19] isolated two variants from a toxigenic culture of Clostridium Welchii. The first produced small amounts of toxin after prolonged cultivation, while the second produced 3 to 6 times as much toxin as the parent culture. Pathological differences associated with smoothness and roughness are well known.

In view of these observations, a more critical analysis of cultures from the standpoint of possible differences in antigenic structure within a culture should assist in understanding the bacterio-immunologic relationships in chronic infection.

In attempting to develop simple methods for estimating probable pathogenicity, comparison was made of certain in vitro tests and animal inoculation tests of streptococci, staphylococci and colon bacilli[20]. It was argued that, if these in vitro tests gave results reasonably parallel with animal inoculation tests, if they were subject to similar or smaller errors, if they were simpler and more easily made in duplicate, then for practical purposes, such in vitro methods should be more practicable for studying large numbers of cultures.

The animal inoculation tests had several disadvantages: They required from 2 to 5 days; several animals were necessary to test each culture; it was difficult to measure accurately the amount of culture injected; 14.7 per cent of the animals died from intercurrent infection, shock, emboli, etc.; and animals (e.g. rabbits) available from supply houses did not have the resistance possessed by those especially bred for such purposes.

In contrast, the in vitro tests had several advantages. They were easily reproducible within a small margin of error, a "loopful" was a sufficiently precise unit for measurement, and the results were obtainable within about 18 hours. For these reasons, they offered hope of being useful as substitutes for animal inoculation tests, *when the latter were impracticable.*

Because animal inoculation tests were used to appraise the

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accuracy of the in vitro tests, any error in the animal tests reflected itself as an apparent error in the in vitro tests. However when the irregular results of animal inoculation experiments were taken into consideration, the in vitro and animal inoculation tests gave similar results. While the error of the in vitro tests differed with the particular tests, and while the precision of the results depended upon technical skill and experience, these tests were subject to fewer irregular results than animal inoculation tests and, hence, were considered more satisfactory, particularly when only one test was made on each culture. The use of two or more independent in vitro tests increased the accuracy of the tests.

The test for coagulase production, supplemented by tests for pigment and hemolysin, was used for staphylococci[16]. Resistance to injurious agents was used for streptococci[14, 21]. Electrophoresis was used for colon bacilli[4]. Crystal violet agar was used for the Micrococcus catarrhalis group[22].

These in vitro tests were applied to cultures obtained from a large series of patients. In most cases, one or more serological or immunological methods was used also. In some patients, there was a high degree of correlation between different tests. In others, the results were difficult to interpret.

For example, in M. E. C. (table 1) there was agreement between intradermal tests, agglutinability and in vitro tests of the different groups. Hemolytic streptococci and Staphylococcus aureus gave positive results with all three methods, while Streptococcus viridans gave essentially negative results with all three. In Streptococcus viridans #1353 it was impossible to make agglutination tests because of autoagglutination, but it was possible to carry out resistance tests and intradermal tests.

R. K. (table 2), who had evidence of infection with several groups of bacteria, affords an example of the uses and limitation of certain tests. The positive complement fixation reactions (active serum) to certain groups were not constant, which suggests that the results may have been influenced by the antigens used at different times. However, Staphylococcus albus and aureus gave strongly positive complement fixation every time. This patient had ethmoiditis, and a strain of Staphylococcus

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aureus which reacted positively to all 6 in vitro tests was isolated from the ethmoid secretion. At first, the electrophoretic mobility of one of the B. coli strains was P.D. 48, which was considered characteristic of a pathogenic culture, and the complement fixation reaction with B. coli antigen was strongly positive.

TABLE 1
Correlation of Different Tests Made on M. E. C.

Organism	Source				Culture number	Agglutination titer	In vitro tests of pathogenicity	Intradermal tests	
	Feces	Throat	Left nose	Right nose				Immediate	24 hr.
B. coli	150*					0	0		
Strep. alpha	1000*				1348				
		Few			1350	0	0	0	+
		Mod.			1353	Rough	0	0	++
		Mod.			1354	0	0	++	+
			Few		1403	0	±	0	++++
		Mod.			1612	0	0		
		Mod.			1613	0	0		
		Few			1614	0	0		
		Few			1616	0	0		
Strep. beta		Few			1615	1:10,240	+	+	++++
			Few		1609	1:10,240	±	+	+++
				Mod.	1608	1:10,240	+	++	++++
Staph. aureus	800*				6305	1:640	+	++++	++++
		Few			6309	1:1280	+	++++	++++
			Many		6307	1:2560	+	++++	+++
				Many	6308	1:2560	+	++++	++

* Millions per 100 grams dry feces.

Twenty months later the P.D. had changed through 53 and 56 to 58, considered in the non-pathogenic range, and the complement fixation reactions with B. coli antigens were negative. Hemolytic colon bacilli were isolated in January 1930 and complement fixation with this group was positive in December of that year. Friedlander bacilli were recovered from the sinus secre-

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TABLE 2

COMPARISON OF TESTS ON R. K.

COMPLEMENT FIXATION	7/11/29	1/7/30	3/25/30	12/11/30	4/7/31	11/5/31	5/8/32	4/5/38
B. coli	+++	++++		++++	++++	0	0	
A. aerogenes	++	++			++	0	0	
Citrate neg. inter.	0	++++		0	++++	++	0	
Sl. hem. coli	0	++++		++	++	0	0	
Hemolytic coli	0	0		+++	0	++	0	
Salmonella	0	0						
Typhoid	++++	0		++++	++++	++++	0	
Dysentery	0	0		0	0	0	0	
Pseudomonas	0	0		0	0	0	0	
Proteus	0	0		++	0	0	0	
Alcaligenes	0	0		0	0	0	0	
Friedlander	0	0		++++	++			
Diphtheroids	0	0		0	0	++	0	
Monilia	0	0		0	0	0	0	
Cl. Welchii	0	+++		0	0	0	0	
Other anaerobes	0	0		0	0	0		
Strep. viridans	++	0		0	0	++	0	
Strep. gamma	++	+++		0	0	0	0	
Hem. strep.	0	0		0	0	0	0	
Enterococcus, gamma	0	0		0	++++	0	0	
Enterococcus, alpha	0	0		0	0	0	0	
Enterococcus, beta	0	0		0	0	0	0	
Staph. albus	++++	++++		++++	++++	++++	++++	
Staph. aureus	++++	++++		++++	++++	++++	++++	
Gonococcus	0	0		0	0			
Other Neisseria	0	++++		0	0	++++	++++	
Monilia	0	0		0	0	0	0	
Hemophilus	0	++++		0	0	0	0	
B. Morgani I				++++	++++	++++	0	
Br. Abortus				0	0	0	0	
Feces:								
Cl. Welchii	40,000	4,800	600	200	3,500	(mill. per 100 gms. dry)		
B. coli (P.D.)	48	48, 69	53, 73	56, 72	58			
Hem. coli (P.D.)		50						
Aerog. (P.D.)		48						
B. Morgani I (P.D.)			55					
Sinus secretion:								
Friedlander (P.D.)					49			Present
B. coli (P.D.)					59			
Staph. (pathogenic type)			Present					Present
Pseudomonas					Present			Present
Strep. (path. type)								Present
Bile:								
Hem. coli (P.D.)			55					
Non-hem. coli (P.D.)			55					
Eberthella (P.D.)			56					
Staph.			Present					

tion and from the feces. The electrophoretic potential of the strain from feces was P.D. 50 and of that from the sinus P.D. 49.

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Because of other similarities, this suggests that the two strains were related. The complement fixation reaction with typhoid antigen was positive on most occasions and a strain of Eberthella which, however, did not give specific agglutination, was recovered from the bile. Since the electrophoretic mobility of the strain was P.D. 56, which is considered to be in the borderline range of pathogenicity, it is possible that it was a degenerate typhoid bacillus. A culture of B. Morgani I was isolated from the feces in 1930 and the complement fixation reaction to this group was strongly positive on three subsequent occasions. The presence of Clostridium Welchii in large numbers was explained by the fact that there were numerous domestic animals on the patient's estate. However, complement fixation reactions with Cl. Welchii antigens were negative, except on one occasion. The agglutination reaction with Brucella abortus was positive in a dilution of 1:50 but complement fixation reactions with this group were negative. Complement fixation reactions with streptococcus antigens were negative almost every time but strains reacting 8+ to the resistance tests were isolated on several occasions from the nose and throat. Since many patients with evidence of streptococcal infection gave negative complement fixation reactions with streptococcal antigens, it is possible that the negative results in this case were caused by failure of the invading organism to stimulate the production of complement fixing antibodies.

While the difficulty of establishing the presence or absence of infection in most cases of chronic disease makes it impossible to determine the specificity of the different reactions, it is possible from the experience gained from this investigation to draw certain general conclusions.

Each of the tests discussed has certain disadvantages. The serologic and immunologic reactions appear to depend largely upon certain pathogenic properties of the cultures. The irregular production of antibodies in many persons with chronic infection and the apparent dissimilarity between the presence of serologic antibodies and immunity to the invading micro-organisms would leave the pathogenic properties of the micro-organisms as the common denominator of the host-parasite relation

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ship. Therefore, better understanding of bacterio-immunologic reactions would seem to lie in better knowledge of the pathogenic properties of the bacteria.

A priori, this would be taken to mean that the presence of a pathogenic micro-organism in a culture from the body always indicates an infection by that organism. Obviously, such an assumption is contrary to common knowledge. However, the presence of a pathogenic micro-organism in increased numbers would have more significance than when the organisms are non-pathogenic. A number of such relationships have been shown in the monographs discussed in this paper.

The serologic and immunologic reactions discussed in this paper appear to be more useful for certain groups of bacteria, and for this reason may be of lesser value than simple tests which may be more closely related to the pathogenic properties of the cultures. In the two patients just cited, the in vitro tests which had been shown to give results parallel with certain pathogenic properties appeared to give as much information as was obtained by serologic and immunologic tests and, consequently, would be preferable on the basis of simplicity.

The evidence obtained in this investigation suggested that certain in vitro positive bacteria are capable of implanting themselves in the respiratory and gastrointestinal membranes at an early age, and that these organisms may remain constantly, although the number may vary from time to time. On several occasions in vitro positive bacteria were isolated from apparently normal areas which further investigation proved to be chronically diseased.

Progress depends upon more accurate knowledge of dissociative or degenerative tendencies and their effects upon serologic and immunologic reactions. When these have been accomplished, it should be possible to obtain better results with the different tests of bacteria isolated from possible foci of infection.

SUMMARY

An analysis of the theoretical basis for, and practical tests of, serologic and immunologic reactions which have been proposed

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for determining which organisms have invaded the tissues of a particular person suspected of having chronic infection indicates that each method is subject to error. In certain instances, the tests apparently resolve themselves into crude tests of pathogenicity of the suspected bacteria.

Since the pathogenicity of the micro-organisms may be a factor in their ability to implant themselves in susceptible tissues, it is suggested that tests of pathogenicity may be of value in chronic infection studies. Because of the difficulties involved in applying animal inoculation tests, in vitro tests which give results parallel with pathogenic properties should prove useful when it is necessary to study large numbers of cultures.

Discussion of the relationships of the results of these in vitro tests suggests that further study, with particular reference to antigenic differences in dissociants, should throw light on the problem of the sero-bacteriology of chronic infection.

CONCLUSIONS

Each of the serologic, immunologic and bacteriologic methods proposed for the differentiation of bacteria thought to be the cause of certain chronic infections is subject to considerable error.

Because of the possibility that pathogenicity of the invading micro-organisms may play a major rôle in the host-parasite relationship, it is suggested that further study of the pathogenic properties of bacteria isolated from persons suspected of having chronic infection may be of value in better understanding of bacterio-immunologic reactions of such persons.

Certain in vitro tests have been shown to have been useful in appraising the significance of these organisms.

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CLINICAL RESEARCH LABORATORY

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GRAPHIC REPRESENTATION OF FINDINGS IN SUSPECTED CHRONIC INFECTION – AN ATTEMPT AT BETTER UNDERSTANDING

Lab. no.
Date begun
Patient
Physician

COL.		COL.	
2	mm in 1 hour (Westergren)	15,16	Percentage of eosinophiles
6,8,10,12,14,16	Inhibition of leukopoiesis	17	Pathogenic staphylococci in the nose
5,7,9,11,13,15	Stimulation of leukopoiesis	18	Pathogenic staphylococci in the throat
7,8	Total mature leukocytes	19	Pathogenic staphylococci in the feces
9,10	Percentage of polymorphonuclear neutrophiles	23	Total number of streptococci in the throat, in millions
11,12	Percentage of mature (filamented) polymorphonuclears	25,27,28	In millions per 100 grams of dry feces
13,14	Percentage of monocytes	27	Counts above 1,000,000 are characteristic of achlorhydria

SEVERITY OF BACTERIAL INTOXICATION	SED. RATE	URINE TITER (UNITS)	NONFIL-FIL. RATIO %	W. B. C.		MATURE LEUK.		POLYS. %		MAT. POLYS. %		MONOS.		EOS.		STAPHYLOCOCCI				STREPTOCOCCI						FECES			
																				NOSE		THROAT		FECES					
				+	−	+	−	+	−	+	−	+	−	+	−	N	T	F	OTHER	NO.	%	NO.	%	NO.	%	COLI	PARA-COLI		
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
MARKED (++++)													0		0	VERY LARGE NUMBER				V.L.N	100		100		100	ABOVE 1,000,000 ACHLORHYDRIA			
	36	41	136	14,050	5,000	5,010	1,500	81	39.5	60.5	24.5	8.5	0.5	9.0		LARGE NUMBER				LG. NO.	90	21	90	1,010	90	990	10,100		
	35	40	135	14,000	5,050	5,000	1,550	80	40	60	25	8.0		8.5							85	20	85	1,000	85	1,000	10,000		
CONSIDERABLE (+++)													1.0		0.5	MANY				MANY									
	21	28	101	12,050	6,000	4,510	2,000	75	47.5	58.5	29.5	7.0		7.0						—	75	5.1	75	101	75	8,990	1,010		
	20	25	100	12,000	6,050	4,500	2,050	74	48	58	30	6.5		6.5							70	5.0	70	100	70	9,000	1,000		
MODERATE (++)													1.5		1.0	MODERATE NUMBER				MOD. NUMBER									
	13	16	76	10,000	7,000	4,200	2,800	70	54.5	55.5	39.5	6.0		5.0							55	1.0	55	11	55	24,900	101		
	12	15	75	9,950	7,050	4,190	2,850	69.5	55	55	40	5.5	2.0	4.5	1.5	F	E	W		FEW	50	0.95	50	10	50	25,000	100		
SLIGHT (+)																													
	5	11	51	9,000	7,850	3,900	3,500	65.5	61	50.5	44.5	4.5	2.5	3.5	2.0	OCCASIONAL				OCCAS.	25	0.25	25	1	25	74,000	1		
	4	10	50	8,950	7,900	3,700	3,550	65	61.5	50	45	4	3	3.0	2.5	N	O	N	E	NONE	20	0.2	20	0	20	75,000	0		
NONE	0	0	RIGHT SHIFT																		0	0	0		0				

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