Pathogenesis, Diagnosis and Treatment of Clostridium Welchii Infection

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In recent years considerable work has been done on the toxins of the various strains of *Cl. welchii* and the relation of these to pathological processes. In spite of this the treatment of clinical cases considered to be due to invasion by this organism is entirely unsatisfactory and there is no uniform agreement as to what constitutes a proper therapeutic program. It is proposed here to present certain considerations relative to pathogenesis and diagnosis which may stimulate a discussion to throw some light on the problem of treatment. No claim is made that a new theory is postulated concerning the modus operandi of such infection and no satisfactory method of treatment is presented. Rather, it is desired only to present certain facts which have recently been overlooked, or at least not given important consideration, with the view of stimulating inquiries along lines of endeavor which may lead to the development of a satisfactory treatment.

Pathogenesis

In 1892 Welch (46) described an organism which probably was identical with the one commonly bearing his name. The organism was isolated at autopsy eight hours after death from the blood of a patient who had died from tuberculosis and a syphilitic aneurysm. The original description was incomplete as far as present day bacteriology is concerned but many of the features of the organism indicate with a fair degree of certainty it was what would today be called Cl. welchii. It is to be noted that the organism was isolated from the blood after death and there was nothing in the clinical history to indicate it was related to the cause of death, directly or indirectly. Because of the lack of development of satisfactory bacteriological procedures, especially as regards anaerobes, Welch devised the following procedure as one for rapidly identifying the organism. A suspension of the culture in question was injected intravenously into a rabbit and the animal killed after circulation had fully distributed the organisms throughout the body. The carcass was then incubated overnight and the ballooned body was interpreted as indicating the presence of Cl. welchii. This mechanism is due to the formation of gas much as it is formed in milk where the reaction is called "stormy fermentation."

In the course of the next few years many reports appeared in the literature concerning the nature of the organism, its distribution in nature and its relationship to certain disease processes, especially to infections in and around wounds of the extremities. The procedures used by many of these authors were entirely inadequate to enable one to say definitely whether the organisms they were studying were identical with the Welch bacillus but there nevertheless gradually developed the idea

that certain types of tissue changes around wounds were associated with such organisms and it soon became generally accepted as a fact that the organism was the *cause* of the tissue changes. This concept was not without foundation for it was shown that injections of animals with pure cultures of the organism produced swelling of the extremity, with interstitial gas and edema rather suggestive of clinical gas gangrene. Since the organisms were found widely distributed in nature (including soil, sewage, water, fish, milk, cheese, a great variety of foods, various types of cartridges, feces and tissues of animals, skin of humans, mouths of infants, human salivary glands and their ducts, normal human bile, normal appendices and meconium of infants) (38), it was easy to understand how the infection would result from direct contamination of open wounds, particularly deep wounds with ragged margins and under such circumstances that the inoculum would likely be enormous. However, the condition of gas gangrene is rarely the site of a pure culture of the anaerobe but nearly always contains mixtures of organisms and this makes it difficult, if not impossible, to properly evaluate the relative importance of the various bacteria as possibly contributing to the infectious process. However, since experiments had shown pure cultures of the organism would produce fatal infections on the experimental animal (47), it soon became the procedure to look specifically for this organism in certain infections and to give little or no consideration to the associated bacterial flora.

During the first world war when better bacteriological procedures were available, data were collected by the military forces relative to the types of organisms present in various wounds and the incidence of gas gangrene. The data (3, 12, 19, 28, 36, 37, 39, 40, 41, 45, 48) show very clearly that rarely is there only one type of organism present. In fact, aerobes were so comonly present in cases of gas gangrene that various investigators have considered the process to be one of symbiosis. The line of reasoning in support of this is somewhat as follows: The aerobes proliferate and thereby use up sufficient oxygen to establish a satisfactory reduction potential to allow development of the anaerobes. The latter then liberate injurious agents which are absorbed by the blood circulation to produce the local and general reactions observed in patients.

It should be remembered, however, that by definition symbiosis requires a mutual benefit to the organisms resulting from the biologic action and there is no indication in the above philosophy that the aerobes are benefitted in any way by the growth of the anaerobes. Therefore, if there be any truth in the mechanism postulated, the above outlined mechanism should more properly be considered as synergism rather than symbiosis. On the other hand, there is little or no evidence to indicate such synergistic action takes place in the clinical case and we have been unable to obtain evidence in the experimental animal to support this philosophy. We have incoulated mice, hamsters and guinea pigs with mixtures of *Cl. welchii* and various aerobes commonly found in wounds and have not been able to enhance the disease of gas gangrene by the addition of such aerobes. It is entirely possible however, that a proper strain endowed with special qualities on the part of the aerobe are

necessary for proper synergistic action and that it is purely a matter of chance that the proper combination is rarely obtained.

Another feature of wound infection which is commonly overlooked is that *Cl. welchii* capable of producing a true toxin are many times present in traumatic wounds and clinical symptoms of gas gangrene never develop (6, 7, 11, 24, 42). This could be easily explained on the grounds that such conditions represent antitoxin immunity on the part of the patient. There is little or no information in the literature to support such an hypothesis and the experiments dealing with naturally occurring *Cl. welchii* antitoxin in humans do not indicate that the level would likely be significantly high. Sir Almroth Wright in his investigations of wound healing during the first world war concluded that such resistance to infection was due to the substance which he called antitrypsin and that when *Cl. welchii* grew in a wound it reduced the antitryptic power of the tissue and elaborated acid (49). Wright also offered data supporting the view shared by other workers of the time that the presence of a foreign body was extremely important in the production of clinical symptoms. The exact mechanism of such bodies is rather vague but the interpretation revolves around the idea they serve as nidi to support growth. During growth the organisms liberate a variety of substances which tend to destroy more tissue which serves as a substratum for further growth. One factor which is known to enhance the development of gas gangrene is the presence of relatively large amounts of calcium ions (2, 5, 13, 14, 16, 27, 28, 30, 34). It was found from analyses of soil from various battle fronts in Europe during the first world war that the increased amount of calcium in certain areas probably accounted for the greater incidence and severity of infection in wounds received in those areas. In the experimental animal it has been repeatedly demonstrated that fewer organisms are necessary to initiate an infection when calcium ions are simultaneously inject than when organisms are injected alone.

Some of the products of growth of *Cl. welchii* many times may produce changes which indirectly accelerate the infection once it is started. In an extremity, for instance, the gas produced may be so great as to completely cut off the blood supply by compressing the artery. In the earlier stages the tissues may be so swollen as to produce serious interference with venous return and thereby materially handicap the normal metabolic changes which are necessary for the natural immunity, whatever is included in this concept. It might be the presence of some specific growth inhibitor or the absence of some nutritional substance necessary to stimulate bacterial multiplication but which substance develops as a result of poor circulation. Wright was of the opinion that the acid produced was picked up by the circulation and thereby caused a decrease in the antitryptic power of the serum. The acidity of the blood, as he measured it, however, became evident only late in the disease and could hardly account for the pathogenesis. In some of our preliminary experiments, by measuring the CO_2 combining power in place of titrating with alkali as Wright did, we have not been able to demonstrate a significant change in the acidity. The type of acid produced in tissues has not been

determined but in the test tube there is evidence that at least in some cases it is butyric. Some authors have even gone so far as to claim that butyric acid was the cause of death in this type of infection but our own experiments have not supported this point of view (43).

Other substances which are known to be produced by *Cl. welchii* in the test tube include many toxic agents and true exotoxins in the sense that they are poisonous, produce specific reactions and stimulate the production of specific neutralizing substances called antitoxins. During the early days of the first world war many investigators pointed out the symptoms of intoxication in human cases and in experimental animals but it remained for Bull and Pritchett (4) to demonstrate a poisonous filterable substance which could be specifically neutralized by an antitoxin. It should be pointed out, however, that the demonstration of antitoxin was from the standpoint of *protecting* guinea pigs and pigeons against a lethal infection and that their experiments relative to treatment during well advanced infections leave much to be desired. Since then most of the research concerning infection with *Cl. welchii* has been done on the toxins, a complete review of which has been given by Oakley (35). In spite of all the work which has been done on the toxins and the demonstration that certain of them will kill the experimental animals, two facts remain dominant: one is that the syndrome of clinical gas gangrene is not entirely reproduced by such materials and the other is that antitoxin therapy is still entirely inadequate in both the human and the experimental animal once the infection is well established (2, 13, 14, 16, 27, 28, 30, 34). It is theoretically possible that in an actual infection some different toxin is produced from that obtained by growing the organism in the test tube and that antitoxin therapy is on the wrong basis. It may be that the toxin produces an irreversible cardiac or cerebral damage, so that circulation eventually fails, even though the toxin is neutralized. Many of our experiments support this point of view (unpublished data).

We come now to a consideration of clinical gas gangrene as encountered in the human under natural conditions and in the experimental animal under artificial but controlled conditions. In either case a severe and fatal infection will give rise to many or most of the following conditions. Early in the course of the disease there is considerable pain. This is uniformly true in dogs, guinea pigs and mice, as well as humans. This appears to progress with the swelling which begins in the animals in one to three hours, depending on the dosage. As soon as swelling is definite, there usually develops a pitting edema which progresses rapidly, indicating some damage to the regional capillaries. In a short time (3-5 hours from time of infection in the experimental animal) the edema will be so extenesive as to produce a discoloration of the skin ranging from bright red to reddish-brown and later becoming bluish-red as indicative of definite necrosis. Concurrently with the onset of edema, the pulse accelerates, the blood pressure soon becomes lowered, the red and white count increase proportionately leading to the symptoms of shock as if resulting from hemorrhage or a burn. The animal loses interest in the surroundings, the respiration becomes rapid and shallow, the beast lies stretched out on the side and the conditions progress until death in-

tervenes at which time the animal gives a series of deep gasps as if being unable to keep up adequate circulation and aeration. At autopsy there is no significant involvement of the lung and the right heart is engorged. In the case of death within a few hours from the time of infection, there are seldom any demonstrable gross changes in the remaining viscera. At the site of infection there is extensive edema with a serosanguinous, gelatinous material which may extend in the subcutaneous tissue, far up on to the abdomen and chest and even across to the opposite side. Sometimes there will be extensive infiltration of such material into the abdominal cavity per se. If the infection is in the thigh and the weight of edematous tissue be compared with the normal tissue of the contralateral side it will be found that there has been much loss of fluid from the circulation as would be expected from the Hb. and R.B.C. determination. Considering that the symptoms of shock should be treated as such, we have given animals large doses of dog plasma and serum but without any satisfactory therapeutic results. Other animals we have treated with antitoxin after the disease is well developed and obtained only very irregular results; sometimes the animals survived a few days and died with mixed septicemia and other animals with larger doses of antitoxin died as if they had been untreated. Whether treated or untreated, many human and animal infections develop hematuria, hemaglobinuria and even jaundice. Whereas it is generally considered that dog tissues (esp. muscle and liver) contain many other organisms that are not toxin producers, we have been able to establish monovalent infections with *Cl. welchii* by injecting the thigh muscles through an area of skin cauterized by heat after infiltrating the overlying skin area with cocaine. It is known (35) that the so-called alpha toxin will produce hematuria in mice. In the human, hematuria and jaundice have occasionally been recognized but not as constant features and, of course, such conditions may conceivably be reflections of mixed infections.

It should be emphasized that in the human the clinical condition may progress rapidly and the patient be in extremis in a few hours only to recover spontaneously with only surgical treatment and sometimes not even that (6, 7, 11, 24, 26, 42). On the other hand symptoms may be relatively mild and the patient die in a few hours without developing recognizable general symptoms (1, 6, 7, 11, 17, 24, 42).

Diagnosis

In order properly to evaluate the clinical material relative to various therapeutic agents, it is desirable to review the various features commonly used to establish a diagnosis. In most cases the presence of swelling of a wound, especially if it develops rapidly and is associated with a pitting edema and crepitation, is considered sufficient by most physicians to suspect gas gangrene. These features, however, may be the result of activity of many bacteria and do not necessarily incriminate any anaerobe. It has been demonstrated (10) that many common aerobes may give rise to similar local reactions. X-ray examination is commonly used to determine the extent and progress of development of gas in the

tissue but this may be misleading in that many times little or no demonstrable gas is present or there may be so much air in the tissue one can not radiographically definitely demonstrate any small increase with progress of the disease. If one suspects the possibility of gas gangrene with an anaerobe as the causative agent, it is customary to ask the bacteriologist to demonstrate *Cl. welchii* or similar organism rather than to attempt a complete bacteriological evaluation of the condition. For such information it is a common procedure to inoculate boiled milk and look for stormy fermentation which will many times be interpreted as prima facia evidence of "gas gangrene *due to Cl. welchii.*" In those cases reported in the literature where careful bacteriological work has been done, it is evident that monovalent infections due to *Cl. welchii* alone are very uncommon.

For this reason it is a question whether cases of gas gangrene reported as due to *Cl. welchii* actually represent simple infections. It is therefore logical to suspect that the treatment of the condition with any agent is likely to result in failure or at least be unsatisfactory unless due consideration is given to the effect of the associated organisms. In most cases this is not done. On the other hand, the aerobes commonly present in wounds the site of gas gangrene are staphylococci and/or streptococci, most of which respond well to treatment with sulfonamides or penicillin. These products are used extensively in the various war theaters in addition to antitoxin without greatly reducing the mortality rate. This suggests the clinical symptoms may not be due entirely to either the associated aerobes or the known toxins of the anaerobe but may be due to some other substance not produced in artificial culture medium.

Treatment

In order to indicate the need for further work on this problem it will be well to review briefly a few of the various procedures which have been advocated for the treatment of this condition.

Since the *Cl. welchii* is an anaerobe various oxidizing agents have been employed. These include hydrogen peroxide, potassium permanganate and more recently, zince peroxide. There is some experimental work indicating the latter might be valuable but the problem of having satisfactory zinc peroxide and the problem of obtaining adequate contact with the organisms finally makes the procedure unsatisfactory and the mass results are disappointing (8, 15, 20, 31). Sulfonamides of various types have been tried in the experimental animal with widely varying results but the entire data, pooled together, do not offer much encouragement although selected experiments have yielded brilliant results (9, 16, 21, 32). Tyrothricin is very toxic when administered subcutaneously or intravenously and the conditions in the wounds make it almost impossible to obtain satisfactory contact with the organism. Our own experiments are in accord withe this conclusion. Penicillin has been tried clinically and experimentally and the results in the available literature indicate it is not satisfactory (10, 22, 23, 29). The clinical cases reported where it has been used are rather too few to permit drawing sweeping con-

clusions as to its therapeutic value. X-ray has been used by many workers and its use widely advocated by Kelly and others (25, 33). However, the more recent experimental work as concerns the value of x-ray in the treatment of these infections does not support the earlier hopes which, in fact, had no experimental basis. If it should eventually be shown that x-ray is of statistical value in such treatment, then additional work will be necessary to determine the mechanism of such results because experiments have already clearly demonstrated that in maximum doses tolerated by humans, x-rays will not kill the organisms, retard their rate of growth, destroy the lethal, hemolytic or dermonecrotic toxin as tested in vitro or in vivo (44). The clinician is inclined to reassess the experimental data obtained on laboratory animals on the grounds that the human is an entirely different type of animal and the results are therefore not directly transferable to clinical cases. It is to be noted, however, that many of the experimental data have been obtained on dogs and the veterinarian is just as enthusiastic about the value of x-ray therapy of infections as the medical man and in his work, the experimental animal *is* the clinical case.

The therapeutic value of *Cl. welchii* antitoxin has been a puzzle since its early inception late in World War I, where it scarcely had opportunity to be properly evaluated. The limited data available on its use, however, were favorably interpreted and it was soon considered as a routine part of the surgeon's armamentarium for human cases. Around 1930 enough civilian cases of *Cl welchii* infection had been seen and treated in the routine fashion with such disappointing results that there was a real interest in the development of something more certain of saving life.

By the time the present war was well under way, it was fairly well agreed that antitoxin was not the real answer to treatment and the data available from the military sources confirm this view. It is evident therefore, that the problem is open to a more thorough study in order to develop a proper understanding of the disease process and thereby develop suitable methods of prophylaxis and therapy. It is true many cases appear to have been cured or prevented independently by sulfonamides, Zn_2O_2, penicillin, x-ray and antitoxin. But the results are very irregular and unreliable. In this disease, time is measured in hours and minutes when therapy is considered. Therefore, one cannot vacillate and change from one method to another, hoping to select the proper procedure for a given case. In addition to this, many cases which appear to be moribund, recover spontaneously and dramatically with no more treatment than surgery and sometimes this is withheld. It is therefore quite evident we do not as yet fully understand the mechanism of death in this disease and do not have satisfactory prophylactic or therapeutic procedures to cope with it.

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Table I. Symbiosis of *Cl. welchii* (SR12) and Aerobes in Hamsters

Vol. SR12	Broth Control	Aerobe		
		Strep. hemolyticus	*Staph. aureus*	*E. coli*
0.2 cc.	2/2	2/2	2/2	2/2
0.1	2/2	2/2	2/2	2/2
0.07	2/2	2/2	2/2	2/2
0.04	2/2	2/2	2/2	2/2
0.02	2/2	0/2	2/2	2/2
0.01	0/2	0/2	2/2	2/2
0.005	0/2	0/2	0/2	0/2
0.002	0/2	0/2	0/2	0/2
0.001	0/2	0/2	0/2	0/2

Fractions give ratio of dead to total number of animals used.

Table II. Symbiosis of *Cl. welchii* (Gerbig strain) with Aerobes in Mice

Dilution of welchii culture	Welch Control	Aerobe		
		Staph. aureus	*Strep. hemol.*	*E. coli*
1:2	3/4	0/4	1/4	1/4
1:5	0/4	1/4	0/4	0/4
1:10	1/4	1/4	0/4	0/4
1:50	0/4	0/4	0/4	0/4

Table III. Symbiosis of *Cl welchii* with Stock Aerobes in Rats

Dilution of welchii culture	Welch Control	Aerobe			
		Staph. aureus	*Strep. hemol.*	*E. coli*	*Proteus vulgaris*
1:1	3/4	0/4	1/4	1/4	2/4
1:2	1/4	1/4	0/4	0/4	0/4
1:5	0/4	0/4	0/4	0/4	0/4
1:10	0/4	0/4	0/4	0/4	0/4
1:50	0/4	0/4	0/4	0/4	0/4

Table IV. Physiological Reactions of Dogs to Infection with *Cl. welchii*

Dog No.	Weight Lbs.	Blood Pressure (mm. Hg.)		Pulse (per min.)		Respirations (per min.)		Hemoglobin (gm%)		Red Blood Count (millions/cu. mm.)		Increase in weight of infected leg (gms.)
		N	T	N	T	N	T	N	T	N	T	
45	31	115–120	63	50–95	195	25–30	47	12	17	6	9	1100
65	33	125–130	35–40	50–60	180	20	50	12.5	11	6.5	5	700
67	40	130–150	46	70–80	200	20–30	.....	15.3	19	8	13	1100
70	45	120–150	too low to read	75–80	150–160	hot weather, panting	.....	13.5	19	5.5	10.8	1200
71	47	170–180	too low to read	90–100		60	no record	14	19.5	7	13	1600

N—normal value before infecting the animal.
T—terminal values obtained near the time of death.

Table V. Treatment of Gas Gangrene with Plasma and Serum

Dog No.	Weight (lbs.)	Treated with Dog Plasma: Hr. and min. after infection	Treated with Dog Plasma: cc. given	Results
Animals Treated with Dog Plasma				
68	38	6:50	225	Well developed symptoms
		7:35	200	
		27:00	150	
		46:30		Died
69	39	6:50	500	Well developed symptoms
		10:00		Died
72	55	5:15	400	At 7:55 and 9:15
		7:15	300	1 cc. 10% Ca Gluconate
		10:00	400	At 10:05 1 gm. $CaCl_2$ 10 cc. H_2O
		11:15	300	With $CaCl_2$ as above
		11:55		Died
Animals Treated with Dog Serum				
78	32	8:30	Untreated control	Died
79	32	2:30	350	At crisis—before first transfusion. Hb 18 gm.%
		5:00	350	RBC 9,700,000 After 1800 cc. serum
		7:30	400	Hb 15.1 gm. RBC 6,000,000 Normal Hb 18.5 gm.
		9:30	800	Normal RBC 8,500,000
		13:00		Dead

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