by the Nuffield Trust (the other based on Glasgow) for the collection and analysis of morbidity statistics; that it is sponsoring some studies of endemic goitre in rural England; and that its director and his colleagues have recently initiated regular socio-medical teaching and demonstrations (with the help of the hospital staff and social workers) for students in their clinical years at the Radcliffe Infirmary. Close co-operation with the Institute has been generously offered by the public health authorities of the city of Oxford and of the county. For our team of graduate assistants we shall have to wait until demobilization provides them with their opportunity for new service and us with a new stimulus.

To those in our universities or health departments, in practice, or serving with the armed Forces who are interested in these things and in the needs of the future it seems that the ideas and tasks of social medicine may be justly regarded as essential contributions (perhaps the most essential and practical of any at present within our range) to the developing philosophy of scientific humanism. The potentialities of this philosophy are very great. Wherever our science, our faith, and unpredictable chance may lead us it can now scarcely be doubted—even while the present mad epoch of destruction continues—that we are moving upon the borders of new and possible worlds. To the rational and humane enrichment of these worlds the profession and the sciences which have the most intimate concern with man himself—a very social animal—have surely much to offer. To envisage and design a close equality of opportunity for health in the coming generations is no longer an extravagant fancy. Whether at home, in India or the colonies, or in the broader international field, it may shortly become our most urgent common interest. Nor should we forget that in our Dominions and other countries, and notably in the land of our most virile and victorious ally, there have been important experiments in social medicine and hygiene from which we have much to learn.

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THE THERAPEUTIC VALUE OF GAS-GANGRENE ANTITOXIN*

BY

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Gas gangrene is characteristically a disease due to the invasion of tissues and the production of toxins by anaerobic bacteria of the *Clostridium* group present in infected wounds, particularly in wounds involving muscle. The most rational treatment appears to be a combination of measures—the use of surgery and bacteriostatic drugs to control the infection, and the use of antitoxin to alleviate the toxæmia. The War Wounds Committee of the Medical Research Council accordingly recommended (*M.R.C. War Memorandum No. 2*, 1940) that antitoxin should be used in conjunction with surgery and chemotherapy in the treatment of gas gangrene, the procedure then advised being the intravenous injection of 13,500 units† of polyvalent antitoxin as soon as possible after diagnosis, repeated according to the signs. In order that the value of this and other lines of treatment could be assessed, surgeons were asked to make detailed returns of all cases of gas gangrene and of lesser anaerobic wound infections on the forms issued (Army Form I 1241 and its supplement I 1241A). Through the courtesy of the Medical Directors-General of the three fighting Services and the E.M.S. the

returned forms have been made available for study, and enough data have now accumulated for a preliminary analysis of the therapeutic value of antitoxin.

Evidence of the value of the specific antitoxins in the treatment of gas gangrene developing in wounded men was brought forward by Weinberg and Séguin (1918); promising results were also obtained in 1918 by British workers (Medical Research Committee, 1919). MacLennan (1943a, 1943b) has recently made a detailed report on the clinical and bacteriological features of the anaerobic wound infections encountered in the Middle East Forces, in which he discussed the value of the various lines of prophylaxis and treatment. His demonstration that in a group of patients which comprised 70% of all the cases of true gas gangrene reported in these Forces the fatality rate was significantly lower among those who had received antitoxin provides further evidence of the therapeutic value of polyvalent antitoxin in field conditions. The present survey is based primarily on all the reports (259) of anaerobic wound infections received by the Medical Research Council up to June, 1943, excluding those from the Middle East Forces, and is concerned only with the value of antitoxin in the treatment of established cases of gas gangrene. The question of its prophylactic value will not here be discussed; it will only be repeated, as MacLennan has already pointed out, that the prophylactic value cannot at present be determined, as the necessary information on the number of casualties that have received this prophylaxis and have not developed gas gangrene is not yet available. The occurrence of gas gangrene in a patient who has received antitoxin soon after wounding is an individual failure of prophylaxis which is without significance, in a statistical sense, until the total number receiving this prophylaxis is known.

Object of the Present Analysis

It is not to be expected that gas-gangrene antitoxin will be of value in the treatment of anaerobic cellulitis and lesser clostridial infections without toxæmia. In order to provide an adequate and reasonably uniform test of efficiency, only those cases (treated or untreated) have been included in this analysis in which the presence of *marked toxæmia*, accompanying other signs and symptoms of gas gangrene, was recorded by the clinician. Since bacteriological confirmation of the diagnosis was, for obvious reasons, not always attainable, the possibility that some cases were due to streptococcal infections (MacLennan, 1943a) is not excluded. The figures in the ensuing paragraphs refer to the toxic cases on which the analysis was finally made.

The evaluation of a single therapeutic measure in gas gangrene is complicated by many variables, particularly in field conditions. First, there are the factors which may determine whether treatment as a whole is effective: these include the interval between the onset of the disease and treatment, in relation to the rate of development after onset; the site of the wound and the general condition of the patient; the nature of the pathogenic clostridia present, and of concomitant infections; the facilities for surgery and nursing. So far as is possible with the data available, these factors will be taken into account by grouping similar cases together and analysing the groups separately. Secondly, since the treatment advised consists of two measures—the use of surgery, to which the employment of drugs is ancillary, and the use of antitoxin—it is necessary to evaluate both measures. Thirdly, it is necessary to know whether there has been any selection of cases for treatment.

It may be useful to discuss here the general aspects of the probabilities with regard to the effectiveness and the practice of the two main lines of treatment. The necessity for speedy and adequate surgical treatment of patients with established gas gangrene is well recognized and has been repeatedly urged. The patients in whom gas gangrene developed formed a very small proportion of the total number of wounded, and were under the care of surgical specialists; the high general level of skill and care afforded can be gauged from the very low general fatality rate of patients with limb injuries—that is, with wounds of a type prone to develop gas gangrene (Pulvertaft, 1943). As might be expected, appropriate surgical measures were recorded in the majority (86%) of the reports

* A report to the War Wounds Committee of the Medical Research Council.

† Therapeutic dose: 7,500 i.u. *Cl. welchii* antitoxin; 3,750 i.u. *Cl. septicum* antitoxin; 2,500 i.u. *Cl. oedematiens* antitoxin; 20% in excess in each ampoule = 16,500 units polyvalent antitoxin.

here analysed; the only reasons given for the omission of such measures were that the patient was too ill for operation and that gas gangrene was not diagnosed before death. For the present object it is not necessary—and certainly not within my competence—to criticize the surgical treatment in an individual patient; but the time of intervention and its effectiveness as judged by the recurrence or otherwise of infection after amputation have been considered.

The position with regard to the use of antitoxin was different, since its therapeutic value was not fully established. It might be suspected that its early and energetic use would be prompted largely by personal faith, and that its use at a later stage would often be due to a last hope of saving life. It has been realized that many were unfamiliar with the theory and practice of antitoxin therapy. It is a recognized principle that if antitoxin is given at an early stage of an infection by toxigenic bacteria it will be more effective in saving life than if it is given later, and that the amount of antitoxin needed for an individual patient cannot be arbitrarily prescribed. Though antitoxin was given to the majority (82%) of the patients, little more than half of them received it promptly or by intravenous injection, and frequently the dose was not repeated. The time of administration of gas-gangrene antitoxin is indeed a factor in determining its effectiveness; it is therefore very important to know whether the patients treated promptly with antitoxin were selected because they were less severe cases, since these might respond better to any form of treatment. The total amount of antitoxin given is also a factor, but a statistical analysis of the relative effect of different amounts of polyvalent antitoxin would require full bacteriological data, which are not yet available. It should therefore be emphasized that the main object of the present analysis was to find out whether antitoxin was of any value in treatment, by comparison of the fatality rates of the treated and untreated cases; the extent of this value is dependent on a number of factors, including, no doubt, the size of the dose of antitoxin.

Throughout this report a difference is regarded as significant if it exceeds twice its standard error, in which case it would occur by chance less than 5 times in 100 trials. If two groups differently treated show a "significant" difference of fatality the result does not *prove*, in the colloquial sense of the word, that the difference was due to the method of treatment, but it is reasonable to suppose so unless it can be shown that the groups were differentiated also in some other way.

Reports on Anaerobic Wound Infection

The reports received on cases of anaerobic wound infection fell into three series, excluding 6 in which the necessary data for tabulation were lacking:

Series I.—88 reports on casualties in the B.E.F. in May and June, 1940, returned on Army Form I 1241 (Dunkirk cases). In many of these reports the data recorded were not sufficient for the differentiation of toxic and mild cases, nor was it possible to distinguish casualties wounded in battle in Flanders from those wounded on the beaches. The entire series has been omitted from the analysis because the criterion for inclusion could not be applied; from other information available it seems probable that many of these cases were not examples of true gas gangrene, but rather of lesser forms of anaerobic wound infection.

Series II.—85 reports on casualties in the M.E.F. from 1940 to 1943. Most of these reports were considered by MacLennan (1943b) together with information on additional cases which had not been reported on Army Form I 1241. To avoid confusion this series has been omitted from the analysis, but the data obtained by MacLennan are quoted. The outstanding features of this series of cases were wounding in the desert, delay in treatment, with a high proportion of cases established on admission, and the frequent incidence of *Cl. oedematiens* infection.

Series III.—165 reports of anaerobic wound infections from other theatres of war, returned on Army Form I 1241 and its supplement between Aug., 1940, and June, 1943. In the supplement clinicians were asked to report the presence and degree of general toxæmia. The criterion of gas gangrene taken for inclusion of a case in this analysis—the presence of marked toxæmia—was noted in 139 cases (85%). Three others were reported as "anaerobic wound infection without gas gangrene." Of the remaining 23 patients, 5 received prophylactic and therapeutic doses of antitoxin, 10 received a therapeutic dose, and 8 received no antitoxin; all these 23 subjects made satisfactory progress with, in general, the minimum of operative intervention, and in the absence (or non-recording) of marked

toxæmia it was doubtful if they could be included as "survivors from gas gangrene," either in the treated or in the untreated group.

The patients in Series III were grouped first according to Service, etc., and to the circumstances of wounding:

- 38 civilian air-raid casualties.
- 42 Army casualties treated in this country. In most of these patients the wounds were similar to battle wounds—i.e., caused by trench mortars, splinters, and bullets—and appear to have been sustained in accidents.
- 11 R.A.F. casualties treated in this country. There is no evidence that any of these patients was wounded during an operational flight.
- 17 casualties from the Royal and Allied Navies and Merchant Navies. These were scattered cases treated variously in this country, in hospital ships, and in medical units of the M.E.F. and B.N.A.F.
- 52 casualties from British, Allied, and enemy land and air Forces, treated in medical units of the B.N.A.F. between Oct., 1942, and May, 1943.
- 5 casualties in the Army over-seas.

Some particulars of the groups in Series III are shown in Tables I and II.

TABLE I

Group of Series III	Total Cases	Toxic Cases	Dths.	Fatality (% of Total Cases)	Amputations (% of Total Cases)	Transfusions or/and Infusions (% of Total Cases)
Civilian	38	32	20	52.6	50.0	58.0
Army U.K. .. .	42	34	17	40.4	54.8	54.7
R.A.F. U.K. .. .	11	11	7	63.6	36.4	54.5
Naval and seamen ..	17	16	9	52.9	29.4	68.8
B.N.A.F. .. .	52	43	25	48.1	50.0	63.5
Army over-seas ..	5	3	1	20.0	20.0	80.0
Total	165	139	79	47.9	47.3	60.0

TABLE II

Group of Series III	Toxic Cases	Estab. on Admission	No Antitoxin		With Antitoxin		
			Cases	Dths.	Cases	% of Total	Dths.
Civilian	32	6	5	5	27	84.5	15
Army U.K. .. .	34	4	3	3	31	91.5	14
R.A.F. U.K. .. .	11	0	2	2	9	81.8	5
Naval and seamen ..	16	7	4	3	12	75.0	6
B.N.A.F. .. .	43	21	11	8	32	74.5	17
Army over-seas ..	3	1	0	0	3	100.0	1
Total	139	39	25	21	114	82.0	58
Mean fatality rate			84.0%		59.9%		
			Difference = 33.1 ± 10.9				
			Diff. S.E. = 3.3				

As might be expected from the difficulties of collection and transport, the proportion of the cases of gas gangrene in which the disease was already established on admission to hospital is much higher among the casualties wounded in battle—and in the few cases among those wounded at sea—than among those wounded in this country. The proportions of toxic cases, amputations, transfusions, and deaths, and the proportions of the total number of toxic cases treated with antitoxin, are not, however, significantly different in the different groups. It will be seen from Table II that the mean fatality rate for all the patients who received antitoxin is significantly less than for those who did not receive it. Moreover, the fatality rate of the treated patients is lower in each of the constituent groups, in spite of gross differences between these various groups in the circumstances of wounding—such as the nature of the soil and climate, the cause of injury, and the physique of the patients—and in the general facilities for treatment of casualties. It has been considered permissible, therefore, since the numbers in each group are too small for further subdivision, to take the series as a whole and regroup the cases according to the time and nature of treatment and the nature of the wound.

The cases have been graded according to the time of administration of antitoxin as follows: (a) initial dose given within 6 hours of diagnosis; (b) initial dose from 6 to 24 hours after diagnosis; (c) initial dose more than 24 hours after diagnosis. Owing to lack of detail in some reports it is not possible to distinguish between intravenous and intramuscular injection, but at least 40% of the cases in the first category received the initial dose intravenously: the initial doses ranged from 4,000

units intravenously at the time of diagnosis to 40,000 units intramuscularly. The time of administration was not always given explicitly: in the few instances in which it was not clear from the context that the dose had been given within 6 hours the case was placed in the 6-24 hour category.

Effect of Delay in Treatment

Treatment should properly be judged in relation to the time of onset of the disease, but in practice this is impossible, as the time of onset even in cases developing in hospital was often not known within several hours; generally the time noted was the time of diagnosis. When the patient was admitted with established gas gangrene, only the maximum possible interval between onset and diagnosis could be gauged from the time of wounding.

TABLE III

Antitoxin Therapy	Onset in Hospital			Established on Admission		
	Cases	Dths.	Fatality %	Cases	Dths.	Fatality %
Nil	19	17	89.5	6	4	66.7
24 hours after diagnosis ..	8	5	62.5	1	1	100.0
6 to 24 hrs. " " ..	22	19	86.4	7	4	57.2
0 to 6 " " " " ..	51	22	43.0	25	7	28.0
Total	100	63	63.0	39	16	41.0

It might well be expected that the interval between onset and treatment would be so much longer in the cases already established on admission to hospital that treatment with antitoxin would be too late to be effective, and the fatality rate therefore higher than that of comparable cases developing in hospital. In Table III, however, no significant difference can be demonstrated between the fatality rates for the corresponding category of antitoxin therapy in the two groups. It could no doubt easily happen that the disease might develop in some patients during evacuation, only an hour or so before their arrival and examination at the hospital, so that they received treatment more promptly than others, already in hospital, in whom the disease developed more insidiously. Be that as it may, it appears probable that there was no material difference between these two groups in the range of time between onset and diagnosis, and that there is therefore no necessity to analyse the groups separately with respect to other factors. It will be realized that this is a finding particular to this series of cases, in which the majority of the gas-gangrene infections established on admission occurred in a single campaign; in different circumstances the patients in whom the disease developed during evacuation might be received too late for treatment to be effective.

Selection of Cases for Treatment

It was previously mentioned that it was necessary to know if the patients treated early with antitoxin were selected because they were less severe cases who would have responded better to any treatment. One test of the relative severity of the cases in the treated and untreated groups at the time of diagnosis is to ascertain the proportion of rapidly fatal cases in each group. Table IV shows the numbers and proportions of the patients in each group dying at different intervals after diagnosis.

TABLE IV

Time of Death after Diagnosis	No Antitoxin		Antitoxin after 24 hrs.		Antitoxin 6 to 24 hrs.		Antitoxin 0 to 6 hrs.	
	Deaths		Deaths		Deaths		Deaths	
	Not	%	No.	%	No.	%	No.	%
0 to 6 hrs. ..	2	8.0	0	0	0	0	1	1.3
6 to 12 hrs. ..	5	20.0	0	0	5	17.2	8	10.5
12 to 24 hrs. ..	5	20.0	0	0	7	24.1	5	6.6
24 to 48 hrs. ..	3	12.0	0	0	5	17.2	6	7.9
2 to 4 days ..	4	16.0	4	44.4	5	17.2	6	7.9
Over 4 days ..	2	8.0	2	22.2	1	4.5	3	4.0
Total deaths	21	84.0	6	66.7	23	80.2	29	38.2
Total cases ..	25		9		29		76	

Of 34 patients who did not receive antitoxin within 24 hours, 7 (20%) died within 12 hours of diagnosis, while of 76 who received antitoxin within 6 hours, 9 (11.8%) died within 12 hours. The proportions are not significantly different, and

it is assumed that antitoxin has not already affected the fatality rate. Moreover, of the group who received no antitoxin within 24 hours more than half lived for more than 24 hours. It may be noted also that there was ample time for treatment to be given, whether or not it was effective: only 3 patients died within 6 hours of diagnosis. The group given antitoxin between 6 and 24 hours after diagnosis has not been taken into consideration, as times of administration and death were not noted exactly enough. It appears that the group treated early with antitoxin contained a fair proportion of rapidly fatal cases, and that the group not treated contained a high proportion of cases which were comparatively slowly fatal. There is therefore no evidence of a selection of the less severe cases for early treatment with antitoxin.

Fatality Rate in Various Categories

The time of diagnosis in the hospital at which treatment was carried out has been taken as the base-line in grading the time of the initial dose of antitoxin and the time of surgical intervention. Table V shows the data relevant to the effects of surgical treatment and antitoxin on the fatality rates of all the toxic cases and of two categories separated approximately according to the site of the gas gangrene as "thigh" cases (thigh, buttock, and abdomen) and other cases (leg, arm, and other sites).

TABLE V

Therapy	"Thigh" Cases			Other Cases			All Cases		
	Cases	Deaths		Cases	Deaths		Cases	Deaths	
		No.	%		No.	%		No.	%
Surgery nil; antitoxin nil	6	6	100.0	1	1	100.0	7	7	100.0
Surgery nil; antitoxin plus	11	10	91.0	2	2	100.0	13	12	92.4
Surgery plus; antitoxin nil	12	8	66.7	6	6	100.0	18	14	77.8
antitoxin after 24 hrs.	2	1	50.0	4	2	50.0	6	3	50.0
antitoxin 6 to 24 hrs.	11	11	100.0	13	7	53.7	24	18	75.0
antitoxin 0 to 6 hrs.	29	16	55.0	42	9	21.4	71	25	35.2
Total ..	71	52	72.2	68	27	39.7	139	79	56.8

Table VI shows the fatality rates, according to the time of amputation and the time of the initial dose of antitoxin, in the 69 patients who underwent amputation for the treatment of gas gangrene.

TABLE VI

Antitoxin Therapy	Amputation 0 to 6 hrs.			Amputation after 6 hrs.			All Cases		
	Cases	Deaths		Cases	Deaths		Cases	Deaths	
		No.	%		No.	%		No.	%
None ..	4	3	75.0	8	7	87.5	12	10	83.4
After 24 hrs.	0	0	0	4	1	25.0	4	1	25.0
6 to 24 hrs.	5	5	100.0	7	3	42.8	12	8	63.7
0 to 6 hrs. ..	28	10	35.8	13	4	30.8	41	14	34.2
Total ..	37	18	48.6	32	15	47.0	69	33	47.6

Amputation was the first major surgical measure recorded in 64 of these cases; in 5 patients it was carried out after excision had failed to control the infection. Recurrence of gas gangrene in the stump was noted in only two patients, so that this group is substantially one in which the infection was eliminated at a definite time.

From the data in Tables V and VI the following points emerge:

Fatality Rate of Untreated Cases

There are three groups of patients who did not receive the composite treatment recommended—namely, those who had no surgical treatment and no antitoxin, those who had antitoxin but no surgical treatment, and those who had surgical treatment but no antitoxin; the fatality rate is not significantly different in the three groups. These groups comprise 29 cases, with 24 deaths, in which the site of gas gangrene involved the thigh, buttock, or abdomen; and 9 fatal cases in which the gangrene involved the leg, arm, or other sites. The mean fatality rate (87%) emphasizes the remorseless nature of the disease, and

the data—so far as they go—suggest that when treatment is lacking or inadequate the site of the infection makes no difference to the issue.

Effect of Antitoxin in Patients receiving Surgical Treatment

The mean fatality rate of all the patients who received both antitoxin and surgical treatment (Table V, last column) is 45.5%. This rate is significantly lower (41.3 ± 9.4) than that of the mean rate of those who did not receive the combined treatment. This result would probably occur by chance less than once in 1,000 trials. A similar effect of antitoxin is seen in the group of patients in whom the spread of infection was controlled by amputation (Table VI, last column), the mean fatality rate of the treated group (40.4%) being again significantly lower than that of the group who did not receive antitoxin. It seems clear that the combined use of surgery and antitoxin was a more effective method of treatment than either of those measures alone.

Time of Administration of Antitoxin

Considering the fatality rates for all types of cases (Table V, last column), it will be seen that the decrease on treatment with antitoxin is due almost entirely to the decrease in the group treated within 6 hours of diagnosis, as the rates for patients treated later are not significantly different from those for the untreated group. In a comparison of the fatality rates of different groups of patients who all received antitoxin, the total amount of antitoxin given and the identity of the infecting organism should be taken into account, and not merely the time of the initial dose. The distribution of the total dosage given to those patients who also received surgical treatment is shown in Table VII, the patients being grouped according to the site of the infection and the time of the initial dose of antitoxin.

TABLE VII

Time of initial dose:	Group A				Group B			
	0 to 6 hours				6 to 24 hours			
Subgroup:	1		2		1		2	
Site of infection:	"Thigh" Cases		Other Cases		"Thigh" Cases		Other Cases	
Total Dose of Poly-valent Antitoxin	No.	Dths.	No.	Dths.	No.	Dths.	No.	Dths.
Units:								
Up to 20,000 ..	6	2	18	6	3	3	8	5
20,000 to 50,000 ..	12	8	12	2	6	6	4	1
50,000 to 100,000 ..	5	3	7	1	0	0	1	1
Over 100,000 ..	6	3	5	0	2	2	0	0
Total ..	29	16	42	9	11	11	13	7
Fatality rates ..	35.2%				75.0%			

It is not possible to draw any definite conclusion from the figures in Table VII, since, apart from the fact that the numbers are small, the necessary bacteriological data are not available. Nevertheless there are some tendencies which are of interest.

First, with an early initial dose and the same total dose of antitoxin, the fatality rate of the "thigh" cases tends to be higher than that of the other cases; if the patients are grouped as receiving up to or over 50,000 units of antitoxin the difference between the two types of case is quite significant arithmetically. MacLennan (1943b), in noting the distribution of the different sites of infection in his series of cases, gives figures which show that the mean fatality rate of all the thigh, buttock, and abdominal cases was 68%, and of all those involving the arm or leg 37.6%; these figures are closely similar to those given in Table V for the present series of cases (72.2 and 39.7%). The poorer response to treatment when the gas gangrene involves the thigh and buttock region appears to be a general experience, and it is probably attributable to the difficulties of surgical excision and to the anatomical factors affecting the blood supply of these sites.

Secondly, Table VII shows that there is a tendency for the fatality rate to be higher when a dose of a certain size—e.g., 20,000 units—was given late than when it was given early. This, of course, is consistent with both the theory and the results of experimental work—that an amount of antitoxin sufficient to neutralize all the toxin present will be effective in saving life if given at an early stage, when the damage done by the toxin is minimal, and ineffective if given later, when the damage is irreparable.

Thirdly, it will be seen that in the subgroup A2, in which all the patients received the initial dose of antitoxin within 6 hours, the fatality rate tends to fall as the total dose rises from 20,000 to 50,000 units or more. Moreover, of all the patients receiving antitoxin early (Group A), 32.4% received a total dose of more than 50,000 units of antitoxin, compared with only 12.5% of those (Group B) who received the initial dose late; it appears probable that the striking difference in the fatality rates is due not only to the fact that the one group received antitoxin more promptly than the other, but also to the fact that this group received larger doses, though, as has been said, the data are not sufficient for statistical treatment. That there is a possible fallacy in this tentative conclusion has been pointed out by Prof. M. Greenwood: thus, one cannot be certain that the fatality was lower because the larger dosage of antitoxin was given and not that the larger dosage was given because the fatality was lower—i.e., the patients in this group lived long enough to receive the larger dosage. For that reason any conclusion from these data as to the value of the high doses of antitoxin can only be provisional.

Time of Surgical Intervention

Surgical operations of a major nature were carried out within 6 hours of diagnosis in 68 of the 120 patients treated, within 12 hours in 81, and within 24 hours in 98 (81.6%). It seems clear, however, that even rapid elimination of the whole site of infection is not by itself a sufficient treatment in a toxic case; the fatality rate for patients who underwent amputation within 6 hours of diagnosis without having received antitoxin (Table VI) is not significantly different from 100%, while for those who received antitoxin within this time the rate is significantly less. Most of the patients who were treated early with antitoxin received the dose pre-operatively or at the time of operation; this is perhaps worthy of consideration, since in 11 of the 60 fatal cases in which surgical treatment was carried out death took place during or within two hours of operation.

Effect of Sulphonamide Drugs

MacLennan (1943b) showed that in his series of cases in the M.E.F. the striking reduction in the fatality rate of the group treated with antitoxin was independent of treatment with sulphonamide drugs; his figures are reproduced in Table VIII.

TABLE VIII (From MacLennan, 1943b)

Drug Therapy	No Antitoxin		With Antitoxin		Difference
	Cases	Deaths	Cases	Deaths	
With sulphonamides ..	28	22 (78.6%)	58	19 (32.8%)	35.8 ± 11.5
No sulphonamides ..	19	15 (78.9%)	8	2 (25.0%)	53.9 ± 20.3

In the present series more than 90% of the patients had received sulphonamide drugs, and the numbers untreated with drugs were so small that it was not possible to find out from the records whether the combined use of surgery, sulphonamide drugs, and antitoxin was more effective than surgery and antitoxin by themselves. It should be emphasized that several varieties of sulphonamide drugs and regimes were employed, and this necessarily complicates any attempt to assess the results. All that can be said under this heading is that the relevant data (Table IX) are not sufficient to provide significant statistical evidence of a beneficial effect of the drugs.

TABLE IX

Therapy	"Thigh" Cases		Other Cases	
	No.	Deaths	No.	Deaths
Surgery; antitoxin 0-6 hrs.:				
With sulphonamides ..	28	15 (53.6%)	41	8 (19.5%)
No sulphonamides ..	1	1 (100.0%)	1	1 (100.0%)
Surgery; antitoxin late or nil:				
With sulphonamides ..	23	18 (68.3%)	22	14 (63.6%)
No sulphonamides ..	2	2 (100.0%)	1	1 (100.0%)
No surgery; antitoxin 0-6 hrs.:				
With sulphonamides ..	3	2 (66.7%)	1	1 (100.0%)
No sulphonamides ..	1	1 (100.0%)	0	—

Effect of Complications; Serum Reactions

The opinion was recorded by the clinician in 14 reports that death was due not solely to gas gangrene but to complicating factors. After making an initial recovery, 2 patients died from secondary haemorrhage and 1 from pulmonary embolism. The

omission of these 17 cases from the appropriate categories makes no difference to the general trend of the results.

Serum reactions were noted in only 3 of the 114 patients in the series treated with antitoxin; these occurred after some hours or days in the form of a rash or pyrexia, and apparently gave no cause for anxiety.

General Remarks

The reduction of the fatality rate in the group receiving both surgical treatment and antitoxin can be reasonably held to establish the value of antitoxin in the treatment of gas gangrene. It is to be hoped that with a more effective use of antitoxin the fatality rate of 45% for treated cases will fall considerably. Speed in the administration of antitoxin is clearly essential for good results, but it is no less important that the amount of antitoxin given should be adequate for the individual case, since the neutralization of toxin by antitoxin is a quantitative reaction. It has been recently recommended (*M.R.C. War Memorandum No. 2*, revised second edition, 1943) that the initial therapeutic dose of polyvalent antitoxin should be not less than 50,000 units; the figures in Table VII indicate that, though often enough such a dose may be more than ample, it is not excessive as a routine.

The clinician still has the onus of judging quickly whether the dose given has been sufficient to neutralize all the toxin—that is to say, whether a previously rapidly progressive toxæmia has been arrested—or whether the dose of antitoxin has been insufficient and the progress of toxæmia is still acute. Delay in the neutralization of the toxin present cannot be compensated by giving an excess of antitoxin at a late stage; on the other hand, since the individual capacity to recover from the effects of toxæmia is incalculable, there is no justification for withholding an adequate dose of antitoxin from a patient received late for treatment, however small the chance of recovery may be. In the treatment of gas gangrene the probability should be borne in mind that the amount of toxin present in the body is increasing so long as the infection is spreading in the affected tissue. A patient received late for treatment, or one in whom surgical and chemotherapeutic measures have not been completely effective in eradicating the infection, may therefore need heroic or repeated doses of antitoxin, not because an excess has at any time a beneficial effect, but because an amount equivalent to the toxin present is the dose justifying a hope of recovery. This is entirely different from deprecating the continued administration of large doses of antitoxin to a patient in whom the infection has been controlled and the effects of the toxæmia are already vanishing.

Patients in whom the site of gas gangrene involved the thigh, buttock, or abdomen showed a poorer response to doses of antitoxin of the order recommended than those in whom the site was more favourable to the elimination of the infection both by the surgeon and by Nature. These findings support the recommendation that surgical treatment should be supplemented by chemotherapeutic measures as well as by antitoxin therapy, and point to the need for local chemotherapeutic agents more effective against clostridia than the sulphonamide drugs alone.

Summary

The value of antitoxin in the treatment of established gas gangrene has been examined in a series of 139 cases in which the patients were suffering from toxæmia to a marked degree. The fatality rate was significantly lower among the patients who received antitoxin, and this difference between treated and untreated cases persisted in those who received major surgical treatment, including a group in whom the site of primary infection was rapidly extirpated by amputation. The combined use of surgery and antitoxin was therefore more effective than that of surgery alone.

The effect of antitoxin was more pronounced in those who received the initial therapeutic dose soon after diagnosis, but this difference was probably due not only to the speed of administration but also to the fact that a greater proportion of the patients in this group received a large total dosage (50,000 units or more) of antitoxin.

The fatality rate of the patients who received no major surgical treatment was nearly 100%, and in the cases reported here the rate in this group was not reduced by antitoxin therapy. Patients in whom the site of the gas gangrene involved the thigh, buttock, or abdomen showed a poorer response to doses of antitoxin of the

order recommended than those in whom the site was more favourable to the elimination of the infection.

These results emphasize the necessity for the early and combined use of surgery, effective chemotherapy, and antitoxin in the treatment of gas gangrene.

This evaluation of antitoxin in the treatment of gas gangrene has been made possible by the work of the medical officers who reported their cases, often in difficult conditions. Thanks are due to the Medical Directors-General of the three fighting Services and the E.M.S. for making the case records available for analysis. I am greatly indebted to Prof. M. Greenwood and Dr. E. Lewis-Faning for their constructive criticism and for the verification of the significance of the data; to Mr. C. H. S. Frankau for his advice on the clinical aspects; to Dr. F. H. K. Green for his help in preparing this report; and to Lieut.-Col. H. J. Bensted for much useful information. It is a pleasure also to thank Major-Gen. L. T. Poole and the members of the Anaerobic Wound Infection Subcommittee for their criticism and many illuminating discussions.

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DYSPEPSIA: AN INVESTIGATION

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The enrolment into the Forces of most of the young manhood of the country has presented us with an opportunity for statistical investigation of some of the commoner ailments. The immediate demands of warfare are so far uppermost that the clerical assistance necessary for statistical research cannot be spared. Thus little can be done towards elucidating the medical problems which in civilian life were so urgent and which we shall have to face again in the years of peace. One of the most important of these problems from a sociological and industrial standpoint is dyspepsia. In the years preceding the war the project of a research centre for gastric disorders was very much before the mind—a centre whose sole object was research into the causation of these disorders. The clinical, radiological, biochemical, and sociological data were to be collected and collated, and submitted to statistical analysis.

An opportunity of doing something along such lines presented itself at a military hospital. A scheme was devised and put into practice which had a twofold object: (1) to make some contribution to the immediate problem of dyspepsia among the troops the hospital served; (2) to furnish data for statistical research. A "gastric board" was formed consisting of the officers in charge of the medical and surgical divisions, the medical specialist, the radiologist, the pathologist, the psychiatrist, and a general-duty officer.

All dyspeptics were admitted into a 30-bed ward for investigation. None was treated there—an important point, and a partial answer to the criticism levelled against the segregation of dyspeptics. The general-duty officer examined each patient on admission, and took the history according to an agreed schedule. The whole worth of the scheme depends upon the way this part of the work is done, and it requires for its performance a medical officer of ability who is really interested in the problem. In the present instance we were fortunate in having the services of Capt. (Miss) Phoebe Charlton, who, except during brief periods of leave, was responsible for all the histories taken. Within five days of admission each patient was x-rayed (Major Baird; later Major Wearing), and test-meal and occult-blood examinations were done (Major Roper; later Major Stewart). The board met weekly, and saw and discussed each case, and decided upon disposal. If indicated gastroscopy was performed. Cases in