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TETANUS PROPHYLAXIS AND CIRCULATING ANTITOXIN IN MEN AND WOMEN

BY

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In the summer of 1939 it was decided to offer active immunization against tetanus to all members of the staff of these laboratories and, as facilities offered, to estimate the titres of circulating antitoxin induced by the injections. We were naturally anxious to satisfy ourselves from the results of the titrations that the procedure we were adopting was sound. Unfortunately we could not arrange a systematic investigation under wartime conditions, and injections had to be given and blood samples taken and examined at somewhat irregular intervals. Nevertheless our results appear worthy of publication, for they confirm the observations of Boyd (1938) on antitoxic titres, and thus bring forward additional evidence that the general immunological principles primarily established in experiments on animals and summarized by Glenny (1925) are applicable to tetanus prophylaxis in man.

Preparation and Potency of Toxoid

The toxoids used in our investigation were in most instances derived from toxins produced in a beef infusion broth with 1% Witte peptone (Campbell, 1938). Owing to a shortage of supplies of Witte peptone we have more recently used toxoids produced from a peptic digest of beef broth introduced by our colleagues C. G. Pope and F. V. Linggood (unpublished). A further reason for the change of medium was that mild allergic symptoms have been reported in a few persons, mainly after second injections of toxoids prepared from broth containing Witte peptone (Whittingham, 1940; Parish and Oakley, 1940; Cooke, Hampton, Sherman and Stull, 1940; Cunningham, 1940); these manifestations are apparently due to the peptone. We do not claim that the substitution of a medium which does not contain Witte peptone will obviate all allergic symptoms, although so far none has been reported to us. Unfortunately it has not hitherto been possible to obtain potent tetanus toxin except on media containing early cleavage products of peptic digestion, and these are present in the new medium as in the old and may therefore induce some sensitization.

Altogether we used six batches of toxoid, four of which had been produced from media containing Witte peptone and two from Pope and Linggood's medium. The toxic filtrates before formalinization contained an average of 14 Lf doses per c.cm. with an average L+ dose of 0.008 c.cm. All *in vivo* tests were done in mice, and the combining powers determined against 2 international units (1 U.S.A. unit) averaged 0.0155 c.cm. From the Lf values of each individual batch there appeared to be little loss on conversion into toxoid. All the batches of toxoid passed the usual laboratory tests for sterility, absence of toxicity, and for antigenicity in guinea-pigs (Glenny and Stevens, 1938). The individual toxoids did not vary widely in immunizing potency in guinea-pigs, the geometric mean of all antigenic values being 0.2239. This figure is the

geometric mean of the antitoxic values of the serum of at least eight guinea-pigs per batch bled six weeks after one injection of 5 c.cm. of toxoid.

Active Immunization in Man

The method most used in this country is to inject two doses of 1 c.cm. deeply into the subcutaneous tissues of the left arm at a time interval of six weeks. Boyd has stated that, while a longer period than six weeks might give better immunity with higher antitoxic values, the interval recommended induces useful titres and does not entail the practical disadvantages of too wide a gap. Following the publication of Colonel Boyd's preliminary investigation on volunteers of the R.A.M.C., tetanus prophylaxis has been offered to all troops in the British Army and Royal Air Force.

Different schemes of dosage have been adopted in various countries over-seas. Thus, in France, Ramon (1939) has recommended a course of three injections of 1, 2, and 2 c.cm. of tetanus toxoid at intervals of two, or preferably three, weeks, followed by a single injection of 2 c.cm. one year later. For the purposes of this paper it is unnecessary to review the mass of recent work on tetanus immunization, as useful editorials on this subject have appeared from time to time in a number of medical journals.

Route of Injection

It has been our practice to give 1-c.cm. doses of toxoid *intramuscularly* into the left deltoid or triceps, instead of subcutaneously as carried out by Boyd. We used the intramuscular route originally in preference to the subcutaneous, because in previous work with diphtheria prophylactic, A.P.T., less obvious local reactions were observed after injection into the deeper tissues and immunization appeared to be equally effective. Moreover, if the Schick type of needle is used one can insert it to the full extent into the arm at an angle of about 45 degrees, which is a very simple technique. It will be seen presently that the method works well for tetanus prophylaxis in man. Further, Montgomerie (1940) has obtained better antitoxic values when horses are injected intramuscularly rather than subcutaneously.

Reactions

These have been much less than after diphtheria or staphylococcus toxoids. They have in fact been negligible, apart from the rare allergic type of reaction, already referred to in this paper, which occurs within half an hour

of injection and is readily controlled by adrenaline. It is advisable to keep persons under observation for a short time after injection as a precautionary measure. The possibility of anaphylaxis need not be regarded as a contra-indication to the use of toxoid; allergic symptoms are infrequent by comparison with the large numbers of doses now administered, and their incidence may be still further reduced as Pope and Linggood's peptic digest of beef medium is substituted for broth containing Witte peptone.

Response to Injections of Toxoid

Lahiri (1939) and others could bring forward no evidence of the presence of natural antibody to tetanus toxin in man, and it is therefore to be expected that individuals will possess no basal or potential immunity and will give a primary stimulus response to a first injection of toxoid. In our investigation titres after a single dose of toxoid were generally very low. Of four persons bled six weeks to five months after one injection, three had titres of 0.005 international unit,* while one had a titre of 0.01 unit after two months, which was still maintained at this level six months later.

Two Doses

Much higher titres of circulating antitoxin were observed after two injections of 1 c.cm. than after a single dose. The doses were in almost all cases widely spaced on the assumption that the second injection was then of the nature of a "secondary stimulus." In accordance with immunological principles and findings a rise in antitoxic titre might then be expected to occur after a latent period of about four days, attaining its peak in ten to twelve days, and followed by a fall to a level which would be maintained for a considerable period. The intervals between doses in our series varied from 13 days to 9 months, and blood samples were taken, as facilities offered, at irregular intervals after the second injection and tested by one of us (D. M. M.) by the method described by Glenny and Stevens (1938). A detailed analysis of all our data showed that there was no significant difference between the results obtained with the two types of prophylactic produced with the Witte peptone and Pope and Linggood media respectively; the combined figures for these types are therefore shown in the tables selected for publication.

The largest group comprised 187 blood samples from 116 persons (male and female) injected with two doses of 1 c.cm. of tetanus toxoid at an interval of approximately six weeks (thirty-nine to forty-five days). Fifty-two of the 116 persons were bled once, fifty-seven twice, and seven on three occasions during a period of nine months from the second injection. The interval between successive bleedings from the same person was almost always one of months; many persons were first bled thirty-two to thirty-eight days after the second dose of toxoid, and again at the sixth to the ninth month. The titres obtained at various time-intervals are given in Table I.

It will be seen that a few blood samples were taken ten to twenty-one days after the second injection, and that the values attained were high. Again, only 13 of the whole series of 187 blood samples contained less than 0.01 unit of tetanus antitoxin per c.cm., and 11 of these 13 samples were obtained six to nine months after the second injection. This suggests that, while the great majority of persons respond well to the injections, there is some tendency to waning immunity after several months. Comparison of the data shown in heavy type in the table gives further evidence of this tendency. Thirty-two to thirty-eight days—i.e., approximately five weeks—after the injections only one of 61 samples contained less than 0.01 unit, and 11 less than 0.05 unit; 26 had 0.5 unit or more. Six to nine months after the injections, 11 of 89 samples contained less than 0.01 unit, and 31 less than 0.05 unit; only 15

had 0.5 unit or more. A scrutiny of the titres of individuals bled on two or more occasions showed that the circulating antitoxin fell to one-half or one-quarter in the majority of cases during a lapse of from six to nine months.

A striking feature of some of our preliminary results was that volunteers with comparatively low titres whom we thought should receive a third "boosting" dose were mainly men. We therefore decided to analyse the table of combined values for males and females into its component parts to ascertain whether there was any sex variation. In Table II are our figures for the largest groups of blood samples—namely, those set out in heavy type in Table I, and a further series from persons immunized with two doses of toxoid separated by two to three months.

It is evident that women responded much better than men, the difference between men and women being observed whether the tests were made five weeks after the second injection or many months later. We are indebted to Dr. J. W. Trevan for the following statistical note:

In the first group in Table II of 32 males and 29 females, 21 males had a titre below 0.2 unit and 11 a titre above 0.2 unit, whereas 6 females had a titre less than 0.2 unit and 23 greater. This is significant statistically for $\chi^2=14.5$ worked out with Yates's correction for discontinuity and P is less than 0.001.

In the second group in Table II, 34 out of 45 males had a titre of less than 0.1 unit, whereas only 8 out of 44 females showed less than 0.1 unit. $\chi^2=27.6$ and P is much less than 0.001.

We have also included in Table II seventeen blood samples withdrawn six to nine months after the second of two doses of tetanus toxoid spaced by two to three months instead of thirty-nine to forty-five days. The numbers are admittedly small, but the observed titres of the thirteen males tend to be higher than previously, indicating the advantage of the longer interval between injections. Again, the women have responded better than the men in the same group. Point is given to these observations by reference to the geometric means of the titres of the various groups given in the last column of Table II.

Many data other than those shown in the tables confirm the general findings. They have not been tabulated for publication because the intervals between doses were too irregular, varying from thirteen to fifteen days to nine months. Bleedings taken ten days or so after the second dose were almost always high, showing that the response to this injection was rapid. Although the values attained were variable, as a general rule the longer the interval between doses the better the response. It is noteworthy that the highest value in our series after two injections was 10 units, observed in a man bled for the first time five weeks after the second injection when the interval between doses was nine months. It was exceptional for a person to wait so long for the second injection.

Effect of Environment

The blood samples from twenty stablemen were submitted to special analysis, for it was felt that work in stables might reasonably be expected to entail frequent contacts with toxigenic tetanus bacilli and therefore enhanced immunizability and higher titres of circulating antitoxin. Most of the titres were in fact lower than those of our male laboratory assistants—a difference which may be attributable to the higher average age of our stablemen. Some of our other data suggest that younger men respond better to immunization against tetanus than older men, but our numbers are too few to

* All the results in this paper are expressed in terms of international units. In comparing our data with the other English series published by Boyd it should be remembered that he uses American units, one American unit being equivalent to two international units.

TABLE I.—187 Blood Samples from 116 Persons (Male and Female) injected with *Two Doses of 1 c.cm. of Tetanus Toxoid at Intervals of 39-45 Days*

Interval between 2nd Dose of Toxoid and Blood Sample	No. of Samples tested	Antitoxic Titre in International Units per c.cm.									
		Less than 0.005	0.005-0.01	0.01-0.02	0.02-0.05	0.05-0.1	0.1-0.2	0.2-0.5	0.5-1	1-2	2-5
10-21 days	6	0	0	0	0	0	2	1	0	1	2
25-31 days	5	0	0	0	0	2	0	1	1	1	0
32-38 days	61	0	1	4	6	10	6	8	15	9	2
39-45 days	6	0	0	0	1	0	1	1	0	2	1
2-6 months	20	0	1	4	6	1	4	1	3	0	0
6-9 months	89	5	6	10	10	11	18	14	15	0	0

Note.—A titre of 2 but not 5 is shown as 2-5 and not as 1-2. Similarly 1 is shown as 1-2 and not as 0.5-1 unit per c.cm.

TABLE II.—Analysis of Data shown in Heavy Type in Table I, and Comparison with Similar Data when Interval between the Two Doses of Tetanus Toxoid is increased from 39-45 Days to 2-3 Months

Interval between 2 Doses of Tetanus Toxoid	Interval between 2nd Dose of Toxoid and Blood Sample	No. and Origin of Samples tested	Antitoxic Titre in International Units per c.cm.										Geometric Mean of Titres
			Less than 0.005	0.005-0.01	0.01-0.02	0.02-0.05	0.05-0.1	0.1-0.2	0.2-0.5	0.5-1	1-2	2-5	
39-45 days	32-38 days	61 { 32 males 29 females	0	1	3	5	7	5	5	4	2	0	0.0744
			0	0	1	1	3	1	3	11	7	2	0.3445
	6-9 months	89 { 45 males 44 females	5	5	9	6	9	6	2	3	0	0	0.0236
			0	1	1	4	2	12	12	12	0	0	0.1391
2-3 months	6-9 months	17 { 13 males 4 females	0	0	3	0	4	4	1	1	0	0	0.0808
			0	0	0	0	0	1	3	0	0	0	0.1682

TABLE III.—Blood Samples from 27 Persons (23 Males and 4 Females) Shortly Before and at Intervals After Third Injection of 1 c.cm. of Tetanus Toxoid

Case and Sex	Interval Between 2nd and 3rd Injections	Antitoxic Titre in International Units per c.cm.								
		Before 3rd Injection	After							
			5 Days	10 Days	12 Days	17 Days	1 Month	6 Weeks	2 Months	5 Months
1 M	2-3 months	0.01		2-5			10			
2 "		"								
3 "		0.01-0.02							0.1-0.2	0.2
4 "		0.02								0.05-0.1
5 "		"								0.5-1
6 F		0.05								0.2-0.5
7 M	7-9 months	<0.005		0.5-1						0.05-0.1
8 "		"		0.05-0.1			0.1			
9 "		"		0.2-0.5				0.1-0.2		
10 "		"		1-2				2		
11 "		"				0.2-0.5				
12 "		0.005		1			1-2	1-2		
13 "		"			2-5		2-5			
14 "		0.01		1-2			2			
15 "		"	0.05		2-5		2-5			
16 "		"		0.5-1			1-2			
17 "		"	0.05		2-5					
18 "		0.01-0.02		20-50					10-20	
19 "		0.02				1-2				
20 "		0.02-0.05	0.05-0.1		2-5	2-5				
21 "		"				5-10				
22 F		0.1		10-20						
23 F		0.5	0.2-0.5		10-20		10-20	5-10		
24 "		"		5-10			5-10			
25 "		"		20-50			10-20			
26 M		"		20-50			20-50			
27 "		0.5-1		10			5-10			

enable us to express an opinion on the influence of age on immunizability. It is clear, however, from our results with stablemen that environment does not play an important part in the response to active immunization.

Technicians in the tetanus laboratory did not respond better to immunization than other male assistants.

Three Doses

Men who had responded badly to two injections of toxoid were given a third dose of 1 c.cm. in an attempt to "boost" their titres, and we were also successful in securing the co-operation of other members of the staff who had already considerable amounts of antitoxin in their serum. From all these persons blood samples were taken shortly before and at intervals after the third dose (Table III).

The table shows that the response to the third dose is often dramatic: in one person there was an increase from 0.01-0.02 to 20-50 units of circulating antitoxin within ten days, and increases to 1 unit and upwards from low initial values were common within this period. There was usually some increase in titre in five days, followed by a

marked increase to the tenth to twelfth day, and sometimes for a considerably longer period. Some of the titres had dropped again slightly at the time of the last blood sample.

There was a marked difference in the degree of response of the two groups shown in the table. Relatively low values were obtained when the interval between the second and third injections of toxoid was two to three months, and higher values when seven to nine months.

Discussion

In analysing our data we were surprised to find that females gave a better response to the injections than males, and we therefore inquired whether this greater immunizability could be correlated with lower annual death rates of females from tetanus. According to the Registrar-General's Statistical Review of England and Wales for 1938, there were 1,021 deaths from tetanus in males and 296 in females in the eleven years 1928 to 1938 inclusive. It is generally accepted that the explanation of the difference in mortality rates is the greater risk of infection to which males are exposed. That some other factor may be involved is borne out by tables published in

a paper by Young (1927) showing the mean annual death rates from tetanus per million at certain ages in the two periods 1901-9 and 1919-25. In the age group 0-1 year the mean annual death rates from tetanus for England and Wales were 105 for boys and 57 for girls for the years 1901-9. The figures for the age group 0-4 years were 25.3 for boys and 13.2 for girls for 1901-9, and 8.3 for boys and 4.2 for girls for 1919-25. It is unlikely that there is an appreciable difference in the risks of tetanus incurred by males and females aged 0-4 years, and therefore the figures we have quoted must be taken as suggesting that females have greater inborn resistance to this infection. This may perhaps be correlated with the greater response of females to immunization which has been observed in our investigation.

The other results given in this paper are in accordance with immunological principles and experiences. We have cited *inter alia* (1) our failure, as expected, to obtain reasonable titres with a single dose of antigen; (2) marked improvement in titres when two widely spaced doses are given (two to three months was a better interval than six weeks); and (3) very large increases in titre following three doses when seven to nine months separated the second and third doses.

We were not surprised to find that a single injection was inadequate: Glenny and Südmersen (1921) first showed that there is a marked difference between the response to an initial dose given to a normal animal ("primary stimulus response") and that which follows an injection of antigen into animals that have acquired basal or potential immunity ("secondary stimulus response"). This difference was first noted in guinea-pigs, rabbits, goats, and horses in connexion with diphtheria immunization, and similar differences have been established for many other antigens, including tetanus, Welch, *septique*, and *oedematiens* toxins (Glenny, 1925). In man results with different antigens have been entirely confirmatory of the principles of primary and secondary stimulus response. In diphtheria immunization two examples involving these fundamentals come to mind. First, as small an amount of toxin as a Schick dose frequently acts as a "secondary stimulus" and produces a rapid rise in the circulating antitoxin in persons who have "relapsed" to the Schick-positive state but are still potentially immune (Copeman, O'Brien, Eagleton, and Glenny, 1922; Parish and Okell, 1928). Secondly, in contradistinction to the spectacular responses which may from time to time follow a minute stimulus given to the potentially immune we have the unsuccessful attempts to find a diphtheria prophylactic effective in one dose in all circumstances; results with "one-shot" methods with alum-precipitated toxoid, A.P.T., depend on whether or not the immunizing mechanism has been trained by previous experience of the specific toxin. Evidence of this training is often afforded by the occurrence of natural diphtheria antitoxin in the serum.

With regard to immunity to tetanus there is no record in these laboratories of the successful demonstration of natural antibody in human serum, and we have already referred to the failure of Lahiri (1939) to find any. This fact in itself discourages rapid methods of immunization with current formal toxoids—for example, the use of only one dose, or of two doses at intervals of one to three weeks. According to Boyd (1938), six weeks' interval is much more effective than an interval of three weeks, and is usually quite convenient in practice. Two doses of 1 c.cm. spaced by six weeks are the official recommendation for the Services in this country, and compare favourably with the three doses of 1, 2, and 2 c.cm. given at shorter intervals to French troops. It is to be noted that

the total volume of material used in this country is less than half that used by the French, thus effecting economy of toxoid; this may be of considerable importance under wartime conditions.

The question may be asked whether the provision of a better type of antigen would lead to some simplification of methods of immunization. We have already noted the poor response which follows a single injection of 1 c.cm. of toxoid in most people, but our colleague, Mr. Glenny, has pointed out that, if the toxoid could be so purified that the amount injected was many times greater in antigenic value than the dose given at present, it might be possible to obtain titres high enough to afford protection with one injection only. The response would be that due to a primary stimulus, and increase in titre would not be expected until after a latent period of several weeks. The rise would then be gradual up to a maximum after several more weeks, with a subsequent fall to an appreciable level which should be maintained with only a slow decrease for a considerable period. In support of the possible "one-shot" method of active immunization with high-potency material, guinea-pigs injected with 5 c.cm. of tetanus toxoid produce on the whole titres of 1/10 to 1 unit and in many cases 1 to 10 units in a period of six weeks.

An interesting but not unexpected observation in this paper is the response to a third dose of toxoid given seven to nine months after a course of two doses. The extent of this response more than counteracted the effect of any waning immunity. The wide interval before the "boosting" dose is the important factor in achieving a rapid rise in circulating antitoxin—an observation which recalls that in the immunization of horses for serum production Mr. Glenny has found it an advantage to allow at least several months to elapse between the first specific stimuli and the course of injections proper. The French have applied the principle of a wide interval to military practice, for an "injection de rappel" has been given after one year to members of the fighting Forces. It has also been their custom to give a further injection of toxoid to the wounded soldier on the basis that his response should be extensive and sufficiently rapid to ensure safety from any infection due to toxigenic tetanus bacilli. The publication of the official records after this war will be awaited with interest.

Ramon and Zøller (1933) and Sneath and Kerslake (1935) have published figures showing that useful amounts of antitoxin were still present in the serum of patients after four to five years and one to two years respectively. Decline in values was very slow, an observation which has been confirmed by other workers. But to ensure that all have a sufficiently high level of antitoxin, the advantage is obvious of a "boosting" dose of toxoid after an interval of, say, nine months to one year, or possibly on receipt of a wound. As in immunity to typhoid or diphtheria, a re-injection of prophylactic maintains a higher level of antibody and a more durable immunity than a single course of injections.

The minimum level of antitoxin necessary to protect against infection is still a matter for speculation. In the last war it was believed that a titre of 0.01 unit, induced passively, was an adequate level. In the present conflict safety should be ensured by such a titre, induced actively, and probably in many subjects by much smaller titres, for these may be rapidly augmented in response to the stimulus of minute amounts of toxin from tetanus bacilli multiplying in a wound. But although a secondary stimulus response is expected in animals and man injected with a "boosting" dose of tetanus toxoid, it must not be assumed that such a marked increase in titre within a few days will occur when inoculated men with relatively low titres are wounded and infected with tetanus.

Our colleague, A. T. Glenny, points out, first, that work in conjunction with one of us (D. M. M.) has shown a difference in

response between two groups of guinea-pigs in good and bad condition injected with 5 c.cm. toxoid. The mean response six weeks after injection of the former group was 0.284 unit, and of the latter group 0.041 unit. This observation has also been fully established in relation to diphtheria immunization in animals. Secondly, during the last war Mr. Glenny had a horse which had been injected with tetanus toxin-antitoxin mixture. Some time later it received a larger dose of toxin than was usual for a horse undergoing immunization, but although it responded by a considerable increase in antitoxin it suddenly developed tetanus and died.

The inference is that an animal even in good condition may have quite a high titre of circulating antitoxin in its serum but still develop tetanus from toxin fixed before the rise in antitoxin occurred. Although in the case of the horse the toxin was given in one large dose, and in wounded men it would be produced much more slowly, we cannot say that a lethal dose might not be present in these patients before sufficient antitoxin had been produced to overcome it. The risk of inadequate response is perhaps greater in men suffering from severe shock than in healthy individuals. To ensure safety it was decided by the medical authorities of the British Army that all wounded men should receive a prophylactic dose of antitoxic serum, irrespective of whether or not they might have had active immunization with toxoid. Provision was thus made for persons who respond badly to immunization—either to injections of toxoid or to the stimuli of small doses of tetanus toxin absorbed from a wound.

The writers of recent leading articles have stated that toxoid which is given before receipt of a wound has a distinct advantage at the present time not only for the armed Forces but also for certain classes of civilians—e.g., fire brigades, A.R.P. workers, police officers, ambulance men, and perhaps medical and nursing staffs. The alternative is the administration of tetanus antitoxin as soon as possible after an injury has been received. The main disadvantage of relying solely on antitoxin prophylaxis is that the method becomes impracticable when wounded men cannot be rescued immediately; moreover, the injection of a foreign serum protects only for a few weeks, permits the occurrence of late tetanus, and involves the risk of serum sickness not only after the protecting dose of serum but to an even greater degree after any further dose which may be necessary during the next few months. Admittedly the introduction of new methods of concentration of horse serum has greatly reduced the risks of serum sickness, but the higher and more durable immunity which can be induced by toxoid is a potent argument in favour of its use for active immunization. At least 0.01 unit is attained by most persons after two well-spaced injections of toxoid, and much higher titres may follow suitable reinoculation. The special value of antitoxic serum is not to replace toxoid but to reinforce it by affording additional and immediate protection to those few persons whose response to specific stimuli may have been inadequate.

Ramon (1940) has recently advocated for the non-vaccinated wounded patient one injection of antitoxic serum and repeated injections of toxoid (combined active-passive prophylaxis). The method is also claimed to give a better chance of success in the treatment of tetanus.

Conclusions

1. Two doses of tetanus toxoid at an interval of six weeks induce useful amounts of circulating antitoxin. Wider spacing of the doses than six weeks gives better immunity, but is usually inconvenient administratively.

2. Women on our staff gave significantly higher titres than men immunized with two doses.

3. A third injection of 1 c.cm. given after a long interval—e.g., seven to nine months in our series—often produces a dramatic increase in circulating antitoxin, and more than counteracts any tendency of titres to drop below levels which might be considered safe. One year may be a more convenient interval for this “boosting” dose of toxoid.

We are indebted to Mr. A. T. Glenny for his valuable help and criticism.

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HOSPITAL INFECTION OF WAR WOUNDS *

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The Effect of Hospital Infection

From the experience gained in the last five months there emerges a strong impression of widespread hospital infection of wounds. In the greater number of cases the infection is not obvious, because sepsis is often added to existing sepsis. The significance of hospital infection is often missed; the striking cases, which are rare, are attributed to unavoidable accident, and the many exacerbations of illness, which are in fact accompanied by the appearance of a new infecting bacterium in the wound, are put down to “pocketing,” etc. Haemolytic streptococci produce the most severe infections. They are rarely present in the early hours of a wound (Colebrook, 1940). In a series of seventeen air-raid wounds sampled within forty-eight hours of injury a colony of haemolytic streptococci was obtained in one wound. Yet it is not unusual to find, as we have, that 70% of the wounds in a ward are infected with *Strep. pyogenes*. Only rarely does the acquired streptococcus kill (one such case is reported above). More frequently it produces cellulitis, erysipelas, extension of the wound, delayed healing, extensive scarring, and inhibition of successful skin grafting in apparently healthy granulating wounds. It is responsible, in our experience, for many sore throats in patients and personnel, occasional bouts of pyrexia and ill-health, and infection of nurses' fingers and hands.

Even among patients treated with closed plasters, which are thought to reduce the spread of infection in the tissues, those infected with streptococci are apparently worse off than others. The following table, based on the clinical

* Concluding an Interim Report to the War Wounds Committee of the Medical Research Council. The first part appeared last week at page 855.