now so heavily committed in combating infection—prevention is increasingly concerned with chronic disease and the limitation of disability and that means early detection and treatment through the clinical services, a shared exercise.

A Broader Idealism

Last July Sir George Pickering took as his text for a Presidential Address to the B.M.A. the Wykehamist motto, "Manners Makyth Man." He made the point that scholarship and science are less important ingredients in the make-up of the good doctor than humanity. This is a truth long known and often uttered, but more important now than ever before. All doctors must use more and more scientific aids as time goes by. Precision in diagnosis and treatment are the essential concomitants of greater therapeutic efficacy; but public knowledge of medicine has grown as fast and the patient needs and expects to be told more. There is no reason to believe that medical students compare less favourably in intellectual qualities with students in other faculties, but there is also the prime need that they should have and exercise the human qualities that have led doctors to their profession in the past. My observation has been that this generation of students is more concerned about the social aspects of disease than was my own; it has a broader idealism of which we may well be proud. Given the lead by their teachers I think they will certainly show us that the advancement of medical science need not be at the expense of humanity in medicine.

An earlier Regius Professor of Medicine at Oxford, Sir William Osler, said, "the hardest conviction to get into the mind of a beginner is that the education upon which he is engaged is not a college course, not a medical course, but a life course." In his day that life course could be followed by a man's own efforts. It will still need your efforts, but it also needs the continuing help of the schools.

Conclusion

I have tried to describe how I think we can progress within the framework of the N.H.S.; a framework within which nearly all of you are going to work. Doctors have played an essential part in the maintenance of that framework throughout the 15 years, and that must continue. Medical practice, as I have tried to show, is no longer a wholly individual thing which can be undertaken without partnership with others. The future of general practice lies, I believe, with group practice. The future of hospital practice lies not only in specialization but in collaboration between the specialties. Team-work has become more important than individual expertise. All doctors, and especially those engaged in hospital work, rely increasingly upon members of other professions—not only the nurses with whom we have always worked and the large group included in what Fox has called "the greater medical profession," but also other scientists such as biochemists, physicists, electronic engineers, statisticians, and social workers, but, above all, general and specialist practice are bound up together. Neither is viable without the other. We are one profession, and divisions between ourselves harm not only the profession but also the patients it serves. The day of exclusive individualism in medicine has ended; it is for you to see that in the future you have a better and closer partnership than we have yet devised.

TETANUS PROPHYLAXIS

BY

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Recent correspondence in the medical press reflects widespread anxiety concerning the extensive use of tetanus antitoxin (antitetanic serum; A.T.S.) as a prophylactic agent. Most casualty officers will agree that fear of litigation governs their decision to prescribe serum and that its dangers are a secondary consideration. Many advances have been made in the management of bacillary infections and in the proper management of surgical wounds since tetanus antitoxin was first introduced fifty years ago. Consideration must now be given to the possibility that tetanus antitoxin, especially in view of the risks involved in its administration, is no longer the ideal prophylactic agent against tetanus.

An investigation has therefore been made into the value of tetanus antitoxin. The particular aspects studied included a reassessment of its usefulness in the prevention of tetanus, a study of the incidence of reactions after serum, and an analysis of previous tetanus prophylaxis in a sample of the casualty population. The management of wounds in a casualty department in which the use of tetanus antitoxin has been progressively abolished over a period of four and a half years is described.

Survey of Cases of Tetanus

A study of previous cases of tetanus was made to determine the type of wound that had been associated with the disease and the use made of tetanus antitoxin in its management.

Clinical Material.—The records were traced of 33 cases of tetanus which had occurred in Sheffield and the Sheffield Region during 1955–62. The group comprised 23 males and 10 females, whose ages ranged from a few months to 75 years (Table I). The largest single age-group was that of boys from 5 to 14 years. There were 15 schoolchildren, 4 farm-workers, 3 housewives, and 2 old-age pensioners. Skilled manual workers from various trades completed the group.

TABLE I.—*Age Distribution of Cases of Tetanus*

Age in Years:	0–4	5–14	15–24	25–44	45+
Male	0	11	4	6	2
Female	1	4	2	1	2

Type of Wound.—None of the cases had been the result of a major injury (Table II). Because the wound was

trivial, two-thirds of the patients did not seek medical advice at the time of injury (Table III). In five of these the wound was not noticed until after the onset of tetanus, and in six no injury was found at all.

TABLE II.—*Type of Injury Causing Tetanus*

Type of Injury	No. of Cases	Type of Injury	No. of Cases
Abrasions	10	Penetrating wound of foot	2
Lacerations	7	Thorn in finger	1
Trapped finger	2	Cracks on hands	1
Compound fracture of finger	2	No injury	6
Varicose ulcer of leg	2		33

TABLE III.—*Use of Prophylactic Tetanus Antitoxin*

	No. of Cases	
Wound not seen at time of injury		22
Patient thought wound too trivial	11	
Wound not found until onset of tetanus	5	
No wound found	6	
Wound seen at time of injury		11
Wound too small to give A.T.S.	6	
A.T.S. given	5	
		33

Use of Tetanus Antitoxin

In Prophylaxis.—Antitoxin had not been thought necessary for the wounds of 6 of the 11 patients who sought medical advice at the time of injury. Five others received tetanus antitoxin—four at the time of injury and one five days later (but five days before tetanus was clinically apparent). One patient was given the first dose of tetanus toxoid at the time of injury.

In Treatment.—Therapeutic tetanus antitoxin was prescribed in all the cases. In the 28 patients who had not received it prophylactically a full therapeutic dose was given, usually 100,000 I.U. Although none of the patients had any immediate reaction, serum sickness developed in six a few days after the injection. None of these reactions was serious and all subsided eventually. There were five deaths in this group, a mortality of 18%.

A test dose of serum was given in the five patients who had received prophylactic serum. One had no reaction to the test dose or full therapeutic dose of antitoxin but later died from tetanus. The other four patients collapsed either after the test dose or at the start of the therapeutic dose of the serum. Three recovered from this anaphylactic reaction, but the fourth died despite intensive efforts to resuscitate him. This case, of which there must doubtless be other examples in the country from time to time, warrants some additional description.

A motor-cyclist skidded on a country road and sustained minor injuries, including an abrasion of the left elbow. He was treated at the local hospital, and, after a 0.1-ml. test dose produced no severe local or general reaction, was given a prophylactic dose of 1,500 I.U. of tetanus antitoxin. He had never been exposed to tetanus antitoxin or horse serum before. Four hours later he developed a generalized urticarial reaction severe enough to warrant his admission to the hospital overnight for treatment. One week later a recurrence of urticaria was treated by his own doctor. The elbow wound became septic. On the 15th day symptoms of mild tetanus developed, and four days later he was transferred to Sheffield Royal Infirmary. His symptoms were not severe, but in the state of our knowledge at that time it was felt that an intravenous dose of tetanus antitoxin was indicated if appropriate precautions allowed. He was given 50 mg. of antihistamine (promethazine hydrochloride) and 100 mg. of hydrocortisone intravenously. Forty minutes later a test dose of 150 I.U. of tetanus antitoxin was given intramuscularly. Fifty minutes after this, there having been no reaction of any kind, 100,000 I.U. of tetanus antitoxin in 20 ml. was prepared and intravenous injection begun. After 2 ml. had been given in three minutes the patient complained of itching. The injection was stopped and 1 ml. of 1 in 1,000 adrenaline was given intravenously. He became pulseless, but after administration of a further 1 ml. of adrenaline intramuscularly the pulse returned. In spite of vigorous resuscitation, his heart stopped again. He was revived by cardiac massage but died one hour later.

Reactions to Tetanus Antitoxin

A controlled clinical trial was conducted to compare the incidence of reactions in two groups of patients, one group receiving antitoxin and the other toxoid.

Design of the Trial

Clinical Material.—Patients attending the casualty department with a simple wound requiring prophylaxis were included in the trial if either tetanus antitoxin or tetanus toxoid could be given to them without restriction. Many patients were ineligible for a variety of reasons—those with the type of wound at that time thought to be tetanus-prone received serum; those with a history of allergy, previous injections of serum, or active immunization against tetanus received tetanus toxoid; some patients were receiving antibiotics and were excluded to avoid confusion between reactions due to antibiotics and those due to the tetanus prophylactic agent; for practical reasons the study was confined to English-speaking people living in Sheffield. All eligible patients were given a preliminary test dose of 0.1 ml. of tetanus antitoxin subcutaneously in the forearm and were observed for 30 minutes. If symptoms suggestive of anaphylaxis occurred during this time the full dose of serum could not be given with safety. The patient was therefore excluded from the trial at this stage, since the choice of prophylactic was restricted.

Choice of Prophylactic.—All patients who had no general reaction to the test dose of serum received a full dose of prophylactic in the thigh, serum or toxoid being given in alternate weeks during the study. Two groups were thus formed. Group A contained those who received 1,500 I.U. of tetanus antitoxin. Group B contained those who received 1 ml. of single-strength tetanus toxoid.

Follow-up of Patients.—Patients were requested to report back in two weeks in addition to their routine attendance for dressings to the wound. At this interview they were asked about any symptoms that they had noticed since the injections, and were again questioned about their history of allergy or previous injections of serum, which in a small number of patients had been forgotten at the time of injury. These patients remained in the trial as their history had not restricted the choice of prophylactic. The opportunity was also taken to question patients about any family history of allergy. A reminder letter was sent to those who did not attend, asking them either to return to the hospital or to make arrangements to be visited at home. If this produced no response a second reminder letter was sent.

Results

During the study period of 18 weeks (nine of serum and nine of toxoid) 1,938 patients required prophylaxis. Many of these were not eligible for inclusion in the trial for the reasons already given. Of the 548 eligible patients, 294 presented in serum weeks and 254 in toxoid weeks. Nineteen of the former group and 16 of the latter were then excluded because of symptoms suggestive of anaphylaxis following the test dose of tetanus antitoxin (Table IV). A follow-up of 89% of the 275 patients in group A and 88% of the 238 patients in group B was eventually obtained.

TABLE IV.—*Composition of Groups*

No. of Patients	Group A	Group B
Considered eligible initially	294	254
General reaction to test dose ..	19	16
Eligible	275	238
Lost to follow-up	31	29
Final number of patients	244	209

Incidence of Reactions

1. *Local Reactions in Forearm.*—These were all due to the test dose of antitoxin and were divided into immediate and delayed reactions. (*a*) *Immediate local forearm reactions* consisted of erythema and occasionally a weal occurring within 30 minutes of the test dose. They were noted in approximately one-quarter of patients in both groups and were equally common in males and females. (*b*) *Delayed local forearm reactions* consisted of erythema and irritation at the test-dose site, reported by the patient at the second interview. The overall incidence of these reactions was the same in both groups, irrespective of the full prophylactic dose that the patient received. These reactions occurred in 26% of the women but in only 11% of the men, a sex difference which was not observed in any of the other reactions considered.

2. *Delayed Reactions in Thigh.*—These consisted of erythema and irritation at the injection site in the thigh and were due to the full dose of either antitoxin or toxoid, depending on which prophylactic the patient had received. The local reactions following antitoxin (5%) were more common than those following toxoid (1%), but there was no marked sex difference in either group (Table V).

TABLE V.—*Incidence of Delayed Reaction to Full Dose of Prophylactic in Groups A and B*

Sex	No. of Patients	Reactions to Full Dose: Local Thigh No.	Local Thigh %	General No.	General %	Total No.	Total %
Group A (Serum)							
Males ..	178	8	*4*	14	*8*	22	*12*
Females ..	66	3	*5*	5	*8*	8	*12*
Both sexes	244	11	*5*	19	*8*	30	*12*
Group B (Toxoid)							
Males ..	135	1	*1*	0	*0*	1	*1*
Females ..	74	2	*3*	2	*3*	4	*5*
Both sexes	209	3	*1*	2	*1*	5	*2*

3. *Delayed General Reactions.*—These were characterized by generalized urticaria accompanied by systemic symptoms such as malaise, oedema of the face, respiratory symptoms, and joint pains. The incidence of general reactions was significantly higher in group A than in group B (Table V), and the two in group B appeared on clinical grounds to be due to the test dose of tetanus antitoxin.

In order to study a group in which no antitoxin had been used, even as a test dose, a further group of 464 casualty patients given toxoid were investigated. This group, unlike the previous one studied, included those with a history of allergy or previous active immunization. The follow-up of patients was carried out as in the controlled trial. The total incidence of reactions was found to be 2% (1% local and 1% general), similar to that in group B above.

4. *Prognostic Value of Forearm Reactions.—Immediate* local reactions to the test dose of serum were at one time thought to indicate sensitivity to serum and were used to predict delayed general reactions to the full dose. In this trial the incidence of general reactions was no higher in patients with immediate forearm reactions than in those without (Table VI). This finding is in agreement with the views expressed by Moynihan (1956) and Laurent and Parish (1962).

TABLE VI.—*Influence of Immediate Local Reaction on Delayed Reactions to Tetanus Antitoxin (Group A)*

Immediate Reaction to Test Dose of A.T.S.	No. of Patients	Delayed Reactions to A.T.S.: Local Forearm No.	Local Forearm %	Local Thigh No.	Local Thigh %	General No.	General %	No Reaction No.	No Reaction %
Present ..	59	11	*19*	4	*7*	5	*8*	43	*73*
Absent ..	185	28	*15*	7	*4*	14	*8*	141	*76*

The numbers are not additive, as some patients had local reactions in both forearm and thigh.

Delayed local forearm reactions were a better indication of subsequent general reactions: 19% of patients with delayed forearm reactions developed a general reaction compared with 5% of those with no delayed forearm reactions.

5. *Factors Influencing Incidence of Reactions.*—Because of the design of the trial, in group A only four patients had previously received serum and four had a history of allergy. In 32 patients there was a family history of allergy, and in one a personal and family history of allergy. As the numbers were small, the influence of these factors was not considered separately. Although the presence of one or more of these factors had no influence on local reactions, there appeared to be some influence on general reactions: 15% of patients with such a factor in the history developed a general reaction compared with 6% of those with no such factors (Table VII). In group B a similar number of patients had factors in the history, but the incidence of reactions was too small for their influence to be studied.

TABLE VII.—*Factors Influencing the Incidence of Reactions to Tetanus Antitoxin*

Previous Treatment with Serum; History of Allergy	No. of Patients	Delayed Reactions to A.T.S.: Local Forearm No.	Local Forearm %	Local Thigh No.	Local Thigh %	General No.	General %	No Reaction No.	No Reaction %
Present ..	40	8	*20*	2	*5*	6	*15*	25	*63*
Absent ..	204	31	*15*	9	*4*	13	*6*	159	*78*

The numbers are not additive, as some patients had local reactions at more than one site.

6. *Total Incidence of Delayed Reactions.*—The total incidence of delayed reactions after tetanus antitoxin, including those following the test dose, was 25%. (17%

TABLE VIII.—*Influence of Follow-up on Incidence of Reactions*

Stage of Follow-up	No. of Patients	Delayed Forearm Reaction to A.T.S. Test Dose No.	Delayed Forearm Reaction to A.T.S. Test Dose %	Delayed Reactions to Full Dose: Local Thigh No.	Local Thigh %	General No.	General %	Total No.	Total %
Group A									
Kept appointment	116	30	*26*	10	*9*	11	*9*	21	*18*
Seen after 1st letter	111	8	*7*	1	*1*	8	*7*	9	*8*
,, ,, 2nd ,,	17	1	*6*	0	*0*	0	*0*	0	*0*
Total No. seen ..	244	39	*16*	11	*5*	19	*8*	30	*12*
Group B									
Kept appointment	101	16	*16*	3	*3*	2	*2*	5	*5*
Seen after 1st letter	96	15	*16*	0	*0*	0	*0*	0	*0*
,, ,, 2nd ,,	12	3	*25*	0	*0*	0	*0*	0	*0*
Total No. seen ..	209	34	*16*	3	*1*	2	*1*	5	*2*

local and 8% general). This incidence of reactions is higher than has been generally reported, a circumstance that is largely explained by the active follow-up of patients. Had reliance been placed alone on patients returning to report reactions nearly half the general reactions to serum would not have been traced (Table VIII).

The case cards of a further 500 casualty patients given serum were studied. In this group, where there was no active follow-up, 37 reactions were reported. The total incidence was 7.4% (5% local and 2.4% general reactions). Comparison of the two results emphasizes the need for adequate follow-up of patients.

Tetanus Prophylaxis in a Sample of the Casualty Population

In this study 443 unselected casualty patients were questioned about previous immunization against tetanus; both passive and active (Table IX).

TABLE IX.—*Previous Tetanus Prophylaxis in a Sample of a Casualty Population*

Age in Years	Males					Females				
	No. of Patients	Previous T.T.		Previous A.T.S.		No. of Patients	Previous T.T.		Previous A.T.S.	
		No.	%	No.	%		No.	%	No.	%
0–4	16	10	63	0	0	9	7	78	0	0
5–9	22	4	18	10	45	16	7	44	2	13
10–14	37	1	3	20	54	11	1	9	3	27
15–19	52	2	4	20	38	13	2	15	5	38
20–24	28	9	32	13	46	13	0	0	2	16
25–34	43	25	58	13	30	12	0	0	6	50
35–44	46	30	65	17	37	8	0	0	2	25
45–54	47	19	40	17	36	14	1	7	2	14
55+	37	2	5	11	30	19	1	5	2	11
All ages	328	102	31	121	37	115	19	17	24	21

Passive Immunization.—Between 30 and 50% of all males over the age of 5 years had received prophylactic antitoxin previously. The highest proportion was in those between 5 and 24 years, which corresponds to the age-group with the lowest proportion of those actively immunized and includes the group in which the risk of tetanus is highest (Conybeare and Logan, 1951). At least 12 men had received tetanus antitoxin although they were already actively immunized against tetanus. Approximately 20% of females over the age of 5 years had previously been given serum; the numbers were insufficient to demonstrate a definite trend with age.

Active Immunization.—A high proportion of infants under 5 years had received a course of triple vaccine (against diphtheria, whooping-cough, and tetanus) either from local health authority clinics or from their own doctor. Eighty per cent. of males had been actively immunized while serving in H.M. Forces and the remainder either at hospitals after injury, at school, or by their own doctor. Over 5 years of age the number of females who had been actively immunized was very small, and in those over school age the incidence was only 5%. As National Service is no longer compulsory the main source of active immunization has been lost. Many hospitals, including our own, already have schemes for active immunization after injury, but these meet with varying success in the face of public apathy.

Tetanus Investigation—Significance of the Findings

1. Type of Wound

The absence of tetanus after major injuries in this group of cases is a striking though not an original finding in cases in recent years (Stafford, 1955). It was not true of wounds in the first world war, nor is it true to-day in primitive communities. Although it might be argued that tetanus now rarely follows major injuries because in these prophylactic tetanus antitoxin is invariably given, it can equally be argued that the reduced incidence of tetanus after such injuries is due to better primary wound treatment and the use of antibiotics. None of the wounds in this series in which tetanus developed received adequate primary wound toilet or sufficient antibiotic treatment.

2. Tetanus Antitoxin in Prevention of Tetanus

There is a belief, widely held in lay circles, that tetanus antitoxin is certain to prevent tetanus. That this is not so is shown by the fact that 5 of the 33 cases in the present series developed tetanus after prophylactic serum. The value of prophylactic tetanus antitoxin has never been conclusively proved by a controlled clinical trial, although circumstantial evidence is often quoted in its support. Deaths from tetanus after firework injuries on Independence Day in the United States fell from 102 per 1,000 injuries in 1903 to 3 per 1,000 injuries in 1913 (*J. Amer. med. Ass.*, 1913), and this was ascribed to the extensive use of prophylactic tetanus antitoxin. However, the figures are open to other interpretations. It is possible that the importance of other factors, such as greater awareness of the risk of tetanus and adequate primary wound toilet, may not have been fully appreciated. Prophylactic serum may have been of great value in reducing the mortality, but the data available would not be accepted as conclusive evidence at the present time.

Figures for the incidence of tetanus in the 1914–18 war are also quoted in support of prophylactic serum. During the first three months of that war the incidence of tetanus was 8 per 1,000 wounded. The incidence fell to 1 per 1,000 wounded when adequate supplies of antitoxin became available (Bruce, 1920). Other important factors also altered at this time, however, including the stabilization of the front and the establishment of proper surgical stations, with a general improvement in facilities for early treatment of injuries (Stafford, 1955).

Doubts concerning the value of tetanus antitoxin are further strengthened by the observation of Lancaster (1953) that there was no marked fall in mortality from tetanus in Australia corresponding to the introduction of passive immunization as there was corresponding to the introduction of active immunization.

Even if tetanus antitoxin or any other measure were completely effective in preventing tetanus, it is unlikely that tetanus could be abolished completely. In the review of cases of tetanus, two-thirds of the patients had not sought medical advice at the time of the injury and prophylaxis was considered unnecessary in half of those who did. Similar findings have been reported elsewhere (Press, 1948; Moynihan, 1956).

3. Sensitivity Reactions to Tetanus Antitoxin

An incidence of 8% of general reactions discovered in a population already selected as being unlikely to be sensitive to horse serum by inclusion of those who had previously been given tetanus antitoxin or were liable to allergic reactions, represents a serious amount of morbidity in a working population. In this series, 15 of the 19 patients with a general reaction to tetanus antitoxin were confined to bed for at least part of their illness, and, although there was no threat to life, a total of 66 days' incapacity was caused. The delayed local reactions were of nuisance value only, but, in common with the more severe serum sickness, they caused discomfort to the patient. The

implication is that during the period before 1959, when all patients at risk in Sheffield were given tetanus antitoxin, approximately 40 individuals per week were suffering general reactions with sufficient illness to make them unable to work for several days. The total amount of disability throughout the country resulting from prophylactic tetanus antitoxin must be considerable, and a source of annoyance to patients who dislike losing time from work because of an injection for what is often a minor injury.

There is little agreement in the literature about the incidence of sensitivity reactions after injections of horse serum. Goodall (1918) estimated that serum sickness occurred in 40% of patients after therapeutic serum and that the incidence rose to 65% after reinjection. Lyall and Murdick (1938) found an incidence of 15.2% general and 12.5% local reactions in 1,000 patients seen after prophylactic tetanus antitoxin, but Newell and McVea (1940) reported a total incidence of only 11.8%, of which 4.4% were general reactions, in 500 patients given prophylactic serum.

Improved methods of purifying serum and a greater awareness of the possible dangers led to an apparent reduction in the incidence of reactions, and Moynihan (1955), who noted reactions reported by the patients, recorded a total incidence of 5.3% reactions (2.7% local and 2.5% general). The results of the present trial suggest that the reduced incidence of reactions is to some extent illusory, since only active follow-up of patients will reveal the true situation. Furthermore, had more patients with a history of allergy or previous injections of serum been included in the trial the incidence of reactions would have been higher than the figure of 25% actually found.

A further and equally important drawback of routine prophylactic antitoxin relates to the effect of one injection of serum on subsequent injections. Several workers have studied this subject since the classical experiments of Glenny and Hopkins (1922, 1923). Reviewing the literature, Littlewood, Mant, and Wright (1954) agreed with other authorities that after the first injection of serum the effectiveness of subsequent injections was minimized because of their accelerated elimination. This would apply to one-third of the patients in the sample of a casualty population recently studied, since that number had previously received prophylactic tetanus antitoxin. In the group most prone to tetanus the proportion reached one-half.

Of more immediate concern to the patient is the increased risk of reactions after subsequent injections of serum. Goodall (1918) estimated that the incidence of serum sickness rose from 40% after the first therapeutic dose of serum to 65% after reinjection. In addition Newell and McVea (1940), who noted an overall incidence of 11.8% reactions, found there were 18.2% in those who had previously received serum, and the incidence rose to 44% where there was a history of previous reactions to serum. Moynihan (1955) also reported 5.7% of serum sickness in patients with a history of previous serum, compared with 2.5% in his whole series.

Since prophylactic tetanus antitoxin does not afford complete protection against tetanus, patients who develop the disease after a prophylactic dose may have been sensitized by the initial injection, so that an alarming reaction may follow the therapeutic dose. In the present study of tetanus cases four such reactions occurred, and in one of these cases the reaction was fatal. Littlewood *et al.* (1954) reported a similar case of anaphylaxis following therapeutic serum. When the patient recovered from the initial reaction the remainder of the dose was given and the patient experienced no further ill effects. Such reactions are so alarming, however, that many physicians prefer to withhold the remainder of the dose.

Danger can also arise among medical or nursing staff who may have to administer the drug. In 1959 a house officer working in the casualty department at Sheffield Royal Infirmary almost succumbed to the effects of tetanus antitoxin. Without ever having received an injection, she became sensitized through her conjunctivae to the extent that 0.2 ml. of 1 in 10 dilution of antitoxin produced a severe reaction with coma (Sneddon, 1960). In addition to the more immediate effects of reaction to antitoxin some patients may show lasting effects. Severe eczema, controlled only by permanent steroid therapy, exacerbations of asthma leading to many months of illness, and other allergic complications presenting in spite of attempts to avoid them by adequate questioning of the patient about any history of sensitivity, all served to reinforce the view that tetanus antitoxin is a potentially dangerous drug.

4. Present State of Active Immunization in the Population

No one would seriously doubt the superiority of active immunization in the prevention of tetanus. Long and Sartwell (1947) reported one case of tetanus among 160,254 fully immunized American soldiers wounded in the second world war. Creech, Glover, and Ochsner (1957) thought that the tragedy of tetanus was that it had not been eradicated 25 years before by a vigorous programme of active immunization. Despite these and similar observations, the number of people actively immunized in this country remains small, as shown in the present study of tetanus prophylaxis in a casualty population.

None of the patients in the survey of cases of tetanus had previously been actively immunized. One man had been in the Army in 1947 but had not received tetanus toxoid. It is not widely appreciated that the practice of active immunization against tetanus was stopped at the end of the war in 1945 in both the Army and the Royal Navy. It was not started again until September, 1949, in the Army and 1958 in the Navy. Only in the Royal Air Force has it been continued without interruption since 1939.

It is thus our duty in casualty work to ensure that as many patients as possible receive active immunization following an injury. Since it has been our experience that one-third of the patients treated in any one year will return at least once with a further injury at a later date, this policy can do nothing but good in selecting particularly those who are liable to injury either because of their work or because of their personality.

Practical Application in the Casualty Department

Concurrently with the investigations into tetanus prophylaxis, policy with regard to the administration of tetanus antitoxin in the casualty department was progressively modified between 1959 and the present time.

Policy before 1959

The casualty department receives approximately 35,000 new patients a year, of whom 29,500 have suffered injuries and 26,400 have wounds for which tetanus prophylaxis is indicated. In common with the practice in most casualty departments, all unimmunized patients were given a prophylactic dose of 1,500 I.U. of tetanus antitoxin unless a test dose produced a severe local or a generalized reaction. An average of 72 doses were given per day. Those who

had previously received active immunization were given a booster dose of tetanus toxoid.

Policy during 1959–62

To limit the administration of tetanus antitoxin to the minimum that could then be medico-legally justified, policy was modified as follows:

No antitoxin was given for clean wounds with minimal tissue damage, or to any patient to whom antitoxin had been given at any earlier date or who gave a history of asthma, eczema, including eczema in childhood, or any other allergic condition, or who showed other than a slight local reaction to a test dose. Antitoxin was not given when there was a history of active immunization, a booster dose of tetanus toxoid being given instead. Tetanus toxoid was also given to those who would previously have received antitoxin but did not now do so, the dose acting as the first in a series of active immunization, but with no thought that it could serve to prevent tetanus should it present on that occasion. The patient felt assured that he had received an injection against lockjaw, though it was made clear to him that the protection on that occasion was inadequate and was intended to protect for future wounds. Antitoxin was continued in the same prophylactic dose for dirty wounds, wounds sustained in the road or garden, and penetrating wounds unable to be excised, for patients in whom there were none of the contraindications listed above. The management of wounds in every other way—that is, wound toilet and excision and the prescription of antibiotics—was continued as it was in the years preceding 1959. The only exceptions to this regime were made during the course of the investigations described above. The result was a drop in the number of doses of antitoxin given from 72 to 8 per day.

Policy since July, 1962

The results of the tetanus prophylaxis survey and the experience of the previous three years warranted the total abandonment of the use of tetanus antitoxin as a prophylactic agent.

The prophylaxis now used is an antibiotic—penicillin or tetracycline—and adequate and careful wound treatment. Small dirty wounds, or wounds that might possibly be contaminated with the tetanus bacillus, are excised as a larger wound or compound fracture would be, but on a correspondingly smaller scale and usually under a local anaesthetic. A wound that is so small or inaccessible that excision is not justifiable or practicable is kept under careful observation and an antibiotic is given for four to seven days. Active immunization with tetanus toxoid is begun for those who have not been immunized before, and reminders are sent for these patients to attend for their later doses at six weeks and six months.

Results

There has been no catastrophic rise in the incidence of tetanus. In 1961 a simple fracture of the distal phalanx of the great toe was unexpectedly complicated by gangrene of the tip of the toe on the third or fourth day, but this was not discovered until the patient's attendance at the end of a week after the injury. He subsequently developed tetanus and died of bronchopneumonia. Had the injury been sustained before 1959 there would have been no indication to give antitoxin on the first day, and had the patient been seen on the third or fourth day and the toe amputated it is possible that tetanus would have been avoided.

The incidence of tetanus is too low to allow any statistical comparison to be made with tetanus before 1959, but it can be noted that in the four years preceding the change of policy in 1959 there were two cases of tetanus—one in a patient who had a history very like that recorded above but involving a finger and who did not receive antitoxin, and one who did receive antitoxin prophylactically. Thus, while it is not yet possible to produce absolute evidence that the incidence is remaining unchanged or is less, there has been no question of a return to the incidence of tetanus described by Bruce (1920). The numbers given above do not include patients who were suffering from tetanus at their first attendance at the hospital.

Discussion

Some important basic facts, old and new, about tetanus antitoxin need to be restated.

1. Tetanus antitoxin does not attack or destroy the tetanus bacillus whenever it is given.

2. Tetanus antitoxin does not give absolute protection against the effects of tetanus even in those who are not sensitive to it.

3. A single dose of prophylactic tetanus antitoxin is likely to sensitize an individual not only to any future dose of antitoxin, which may be eliminated rapidly, but to a therapeutic dose should it be needed.

4. The investigations that have formed the basis for the use of prophylactic tetanus antitoxin for the past 50 years were made on a population not yet sensitized to horse serum, not yet able to receive the benefits of antibiotics, and unlikely to receive wound treatment of the standard that is now practised.

5. A dangerous drug should be used only so long as its morbidity and mortality do not approach that of the disease for which it is indicated. The mortality of tetanus antitoxin has been estimated by Laurent and Parish (1952) to be between 1 in 50.000 and 1 in 200.000. The mortality from tetanus in wounds treated by adequate wound surgery and, where indicated, by antibiotics, is certainly no greater.

The accepted modern treatment for a bacillary infection that is likely to respond to antibiotics is to give an antibiotic. It is no more logical to give tetanus antitoxin to a patient who may have a tetanus-infected wound than it is to give gas-gangrene serum in the prophylaxis of gas gangrene. In both instances a prophylactic antibiotic is indicated to-day.

Many casualty officers are well aware of these facts, yet the usual answer given in any casualty department to the question " Why do you give A.T.S. ? " is that it is a medico-legal obligation to do so. It is our duty to advise those who administer the law that other agents have superseded tetanus antitoxin, and that the proper question that should be asked in a fatal case of tetanus is, " Did you treat the wound properly and give an adequate course of an appropriate antibiotic ? "

The decision to abandon the use of tetanus antitoxin has solved several problems. Fear of causing anaphylactic reactions, occasionally fatal, often severe, has been abolished. No longer does the difficulty arise, in a patient who does not know whether he has been actively immunized or who is unconscious, as to whether antitoxin or toxoid should be given. All are given 1 ml. of toxoid unless a test dose produces a severe local or a general reaction, which is rare. Moreover, since one-third of all patients attending a casualty department have been injured on a previous occasion, the steady flow of actively immunized patients will result in due time in protection for an increasing number of those who, by their work or their nature, are likely to be involved in future injury. There is

no advantage in giving tetanus antitoxin and toxoid together. All the disadvantages that apply to antitoxin given by itself apply equally when it is given with any other drug.

Summary and Conclusions

The limitations of prophylactic tetanus antitoxin in the prevention of tetanus are demonstrated. In a survey of 33 cases of tetanus, 80% of patients did not receive prophylactic serum because of the trivial nature of their wounds. Anaphylaxis followed therapeutic use of serum in four of the five patients who developed tetanus in spite of prophylactic antitoxin given at the time of injury. One of these reactions was fatal.

In a controlled clinical trial the incidence of reactions after tetanus antitoxin and that after tetanus toxoid are compared. Reactions after tetanus antitoxin are more common than those after tetanus toxoid. Active follow-up of patients reveals that the total incidence of reactions after serum, excluding subjects known or likely to be sensitive to it, is about 25% and is higher than is generally appreciated.

One-third of casualty patients give a history of having had serum previously. This is associated with accelerated elimination of a subsequent dose of serum and increased risk of sensitivity reactions.

In view of the doubt concerning the value of tetanus antitoxin in prophylaxis, the high incidence of reactions, and the adverse effect on the therapeutic use of serum if tetanus should develop subsequently, a trial has been made in a large casualty department of progressive abandonment of the use of tetanus antitoxin. There is no evidence that the incidence of tetanus has increased since policy with regard to tetanus antitoxin was first modified four years ago. It is recommended that adequate wound treatment and antibiotics be substituted for tetanus antitoxin as the modern prophylaxis against tetanus, together with active immunization by toxoid against future injury.

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References

Bruce, D. (1920). *J. Hyg. (Camb.)*, **19**, 1.
Conybeare, E. T., and Logan, W. P. D. (1951). *Brit. med. J.*, **1**, 504.
Creech, O., Glover, A., and Ochsner, A. (1957). *Ann. Surg.*, **146**, 369.
Glenny, A. T., and Hopkins, B. E. (1922). *J. Hyg. (Camb.)*, **21**, 142.
—— —— (1923). Ibid., **22**, 12.
Goodall, E. W. (1918). *Lancet*, **1**, 323.
J. Amer. med. Ass., 1913, **61**, 679.
Lancaster, H. O. (1953). *Med. J. Aust.*, **2**, 417.
Laurent, L. J. M., and Parish, H. J. (1952). *Brit. med. J.*, **1**, 1294.
—— —— (1962). *Brit. J. prev. soc. Med.*, **16**, 111.
Littlewood, A. H. M., Mant, A. K., and Payling Wright, G. (1954). *Brit. med. J.*, **2**, 444.
Long, A. P., and Sartwell, P. E. (1947). *Bull. U.S. Army med. Dep.*, **7**, 371.
Lyall, H. W., and Murdick, P. P. (1938). *N.Y. St. J. Med.*, **38**, 882.
Moynihan, N. H. (1955). *Lancet*, **2**, 264.
—— (1956). *Brit. med. J.*, **1**, 260.
Newell, C. E., and McVea, C. (1940). *Sth. med. J. (Bgham, Ala.)*, **33**, 962.
Press, E. (1948). *New Engl. J. Med.*, **239**, 50.
Sneddon, I. B. (1960). *Brit. med. J.*, **1**, 1468.
Stafford, E. S. (1955). *Surg. Gynec. Obstet.*, **100**, 552.

LONG-TERM ADMINISTRATION OF CORN OIL IN MANAGEMENT OF PATIENTS AFTER MYOCARDIAL INFARCTION: A FOUR-YEAR STUDY

BY

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There is still no proof that hypercholesterolaemia is a direct cause of atherosclerosis or myocardial infarction. It is generally agreed, however, that the reduction of high serum cholesterol levels is desirable in the overall management of atherosclerosis and its complications. Pharmacological approaches to the problem have generally proved disappointing, but the demonstration by Beveridge *et al.* (1955) that the addition of corn oil to a diet low in animal fat would significantly reduce the serum cholesterol encouraged the idea that a physiological approach was feasible, and the corroboration of his findings (Ahrens *et al.*, 1957; Keys *et al.*, 1957) supported the hope that this might be a practical procedure.

This hospital was already involved in the M.R.C. anticoagulant trial, and the large number of patients which would have been necessary for significant comparisons of mortality and morbidity between treated and control groups were not available. The outcome, therefore, was a less ambitious trial which it was hoped would answer the following questions. Firstly, was some kind of dietary programme feasible, and if so what? Secondly, did it have a sustained or merely transient effect on the serum lipids? Thirdly, were its clinical results encouraging?

At the time of writing all patients have been on this regime for at least two and a half years, and some for more than four years.

Methods and Subjects

Corn oil—maize oil (B.P.), linoleic acid content 56%—was chosen as the supplementary dietary oil. Messrs. Boots Ltd. undertook to supply and distribute it to all patients included in the trial and to guarantee its fatty-acid composition. Two diets were prepared—one of 1,630 calories (155 g. carbohydrate, 65 g. protein, and 80 g. fat), and the other of 2,080 calories (245 g. carbohydrate, 75 g. protein, and 85 g. fat). When 57 g. of corn oil is added to these diets the daily intakes become 2,045 and 2,595 calories respectively, and the oil comprises 41.5% of the total fat in the former and 40.0% of the total fat in the latter. This small percentage difference is of no practical significance. A diet was allocated according to the height, build, and occupation of the patient, and in this way some degree of metabolic parity was achieved. The 1,630-calorie diet is reproduced in Table I.

Each patient was given a 2-oz. (57-ml.) medicine glass and told to take the oil as it suited him. Each patient under-