Editorial.

THE CONTROL OF TETANUS.

In his paper on Tetanus in its statistical aspects, contributed to the Medical History of the War, Colonel S. Lyle Cummins states that the incidence of tetanus in pre-serum days varied within very wide limits in different campaigns. In the Peninsular campaigns, in spite of the excellence of the Medical Service under McGregor, tetanus carried off hundreds of our wounded. Rutherford Alcock in his statistics of the British Legion in Spain records an incidence of 12·5 per 1,000. Ballingall calculated the number of tetanus cases among wounded in armies was one in 79. Longmore quotes from Demme that tetanus occurred in 10 per cent of the wounded in Italian hospitals in 1859.

In the great wars coming later in the last century there was a decided diminution in the number of cases of tetanus. In the British forces in the Crimean War the records show only two cases per 1,000 wounded. In the American Civil War the incidence was two per 1,000, and in the Franco-German War, 1870–71, the records give 3·5 per 1,000.

In the South African Campaign, the Nile Expedition, and the Russo-Japanese War, tetanus seemed to have vanished completely. In the Franco-German War there were marked local variations. At Metz tetanus cases amounted to only 1·6 per 1,000, whilst in the northern theatre the incidence was 11 per 1,000. The factor of prime importance is the presence of the spores of the tetanus bacillus in the soil of the battle area and its introduction into the wound. When the environment is such as to favour the conservation of spores in the soil, tetanus will tend to be of common occurrence amongst the wounded in war.

In the war of 1914–18 the incidence of tetanus outside French and Belgian territory was insignificant.

Only seven cases occurred in Mesopotamia during the whole period of the operations. Six cases were reported in Gallipoli, all in patients with trench feet. Only four cases are known to have occurred in Salonika.

As in the Franco-German War of 1870–71, so in 1914–18 it was in the northern theatre of operations that tetanus became a serious problem, demanding a system of prophylaxis founded on modern conception of the disease. Cramer and Bullock alleged that calcium salts in the soil facilitated the establishment of tetanus germs introduced into wounds. This suggestion may help to explain the high incidence of tetanus in the northern part of France where a chalky soil is the rule.

Many records of the incidence of tetanus in 1914–18 have been published. Sir David Bruce was obliged to confine his figures to those available in

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England, and his incidence rates were based on the number of wounded reaching home hospitals. Sir William Leishman's first records were also not complete; they did not include slow-developing cases which occurred after cases had been admitted to home hospitals. Later, on the introduction of case sheets, reliable information was obtained for the war areas. The total number of cases estimated in hospitals in France was 1,071. Adding these numbers to those given by Bruce it would appear that there were 2,529 cases of tetanus as the result of the fighting in France and Flanders. Official figures give the number of wounded, less gassed, on the Western Front as 1,710,369, so that the incidence of tetanus in those wounded on that front for the whole war amounts to 1·47 per 1,000. This figure shows little improvement on that for the American Civil War or the Crimean War, but Cummins points out that in no previous war have the combatants been exposed to wounding by projectiles of so terrible a character and in conditions so calculated to ensure earth contamination of wounds. He considers that the true measure of the success of prophylactic methods is to be found in a comparison of earlier months of the war on the Western Front with the subsequent periods of operations in the same area. In Chart I of his article he gives the ratio per 1,000 of cases of tetanus to total wounded. The figures are 8·5 in August, 8·8 in September, 7·6 in October, 3·0 in November, and 1·5 in December, 1914. The issue of serum on an adequate scale in October and November, 1914, was followed by a rapid fall in the incidence of tetanus, which reached a low level by December. From 1914 onwards the constant use of antitetanic serum eliminated any satisfactory control group for comparison. One source of reliable information was obtained from the effect of serum on cases of trench foot. For some time the majority of these cases were not protected, but in December, 1917, the Director-General of Medical Services in France ordered that serum should be given to all cases of trench foot, and a dramatic fall occurred in the incidence of tetanus in cases of this kind. The drop occurred in mid-winter at the very time trench foot was most prevalent. Another point of interest is that while there was a marked fluctuation of the tetanus rates in 1915, 1916, and the early months of 1917, the incidence became much more regular and on a lower level following on repeated prophylactic inoculations which were ordered in June, 1917, and coincided with the fall of tetanus incidence to 1 per 1,000.

In former wars the case mortality from tetanus was about 85 per cent. This figure is given by Gilbert Blane, Rutherford Alcock, and Longmore. In the American Civil War the mortality was 89·3 per cent, and in the Franco-German War, 1870–71, the mortality was 90 per cent. In 1914–18 there were 1,254 deaths in the total of 2,529 cases, amounting to nearly 50 per cent. This would be an over-statement as regards tetanus as many of the deaths were due to wounds. The figure also includes the whole period of the war and the case mortality was much greater during the earlier months than in any subsequent period.

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The gradual reduction in case mortality was noted by the Adviser in Pathology on the Western Front and by Sir David Bruce. To get an idea of the real fall in mortality in all cases Colonel Cummins sorted the records of the Western Front into two-yearly periods. In 1914–15 the case mortality was 63·5 per cent; in 1916–17, 45·2 per cent; in 1918–19, 37·9 per cent. For the period 1916 to 1918 the case mortality was 43·2 per cent, showing that when the period of insufficient prophylaxis was excluded the death-rate from tetanus was only half that in previous wars.

The War Office Tetanus Committee classified cases of tetanus into four clinical types—I (*a*), (*b*), (*c*), II, III, IV. Bruce classified the cases in home hospitals and Cummins those in French hospitals in 1918. In order to deal with tetanus on the Western Front as a whole, Cummins combined these two analyses. Type I (*c*) trismus, the earliest symptom with incomplete closure of the jaws, was the commonest variety and the least fatal. Type I (*a*) with trismus coming on within twenty-four hours with complete closure of the jaws was the most fatal and the death-rate was comparable to that in earlier wars. No case of local tetanus (IV) proved fatal in home hospitals.

The interval between the date of injury and the onset of tetanus is important, and a long interval is all in favour of the patient. The surgeons in the American Civil War concluded that the later the appearance of tetanus after injury the better was the chance of recovery. Cummins gives a chart of the frequency curve of the incubation period up to the forty-fifth day after wounding. There is a rapid ascent in the curve to the seventh day, the highest peak is reached on the eleventh day, after which, with one peak on the fourteenth day, it gradually falls to a level at which the numbers cease to be significant. He concludes that the prophylactic inoculation was the factor leading to an increase in the incubation period.

With the exception of a few hundred doses purchased in Paris early in the War, all the serum used in the British Expeditionary Force came from England or America, and was standardized in terms of the United States units. On this system one unit of antitoxin neutralizes one thousand minimal lethal doses of toxin. It was usual to administer to each patient 500 units, and this was the dose recommended throughout the War by the War Office Tetanus Committee. In 1916 the Director-General, Medical Services, in France, issued a circular recommending 1,000 units for all injuries to vessels and to bone, and in all lacerated wounds. Every endeavour was made to give the first dose as soon as possible. As a rule it was given at the field ambulance and the amount given was recorded on the field medical card. In June, 1917, instructions were given that four prophylactic inoculations should be given at intervals of seven days. Cummins states that while giving full weight to efficient surgery in ameliorating and diminishing the mortality of tetanus, more especially when excision of wounds is practised as in the latter part of the War, the administration of antitoxic serum rather than surgery was the cause of the diminution of incidence, severity, and mortality and the prolongation of the incubation period.

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In his article on the pathology and bacteriology of tetanus Sir F. Andrewes pointed out that Tulloch's work proved the existence of at least four distinct serological races, each agglutinated only with its own serum. The distribution of the types in the wounds of 100 cases of tetanus in English military hospitals was: 41 strains belonged to Type 1; 22 to Type 2; 33 to Type 3; and 4 to Type 4. Type 2 was most prevalent in Flanders, and Types 1 and 3 on the Somme, but all four types were found in cases receiving their injury in England. The seven strains employed in various serum institutes for the preparation of antitoxin were all found to belong to Type 1.

It is known that after a dose of antitoxin has been injected there is a considerable drop in the antitoxin content of the blood after a week has elapsed, and that after a fortnight it is difficult to demonstrate its presence. In an experiment MacConkey found that after the injection of 1,700 units the blood in three days contained $\frac{1}{2}$ unit per c.c., after ten days the amount was less, $\frac{1}{10}$ unit, but after fifteen days it was still more than $\frac{1}{20}$ unit. The experience of the War, however, showed that long after such tests are of any avail enough antitoxin remained in the body to modify the action of the toxin though it could not prevent it, and some degree of protection remained after a hundred and forty-five days. Local tetanus occurred only in inoculated persons. The proportion of local tetanus rose from 1·1 per cent in 1914 to 23·4 per cent.

In 1936 the question of the provision of adequate supplies of tetanus antitoxin for the Army in the event of a European war was brought before the Army Pathological Advisory Committee by the Director of Pathology. Attention was directed to the fact that insufficient supplies of antitoxin existed at the outset of the last war and that it was several months before provision on a satisfactory scale was possible. He emphasized that it was necessary to make forward arrangements to prevent a repetition of this unsatisfactory position.

As a result of the deliberations of the Committee, contracts were placed with the Serum Institute for sufficient supplies of antitoxin for all medical units in the field in the event of the occurrence of a major war.

As a direct result of these preliminary arrangements the question of supplies of antitoxin for civilian needs in the event of air raids was taken up by a committee which had been brought into existence owing to the necessity of considering other questions of a bacteriological nature. Treasury sanction was obtained for the provision of a large quantity of antitoxin and the organization for the provision of a National Pool of antitoxin was undertaken by the Medical Research Council.

It was agreed that the Army would provide the antitoxin required on mobilization and the first week of war through its own arrangements. Subsequent supplies would be obtained from the National Pool. The antitoxin was dispensed in containers of ten doses provided with puncturable rubber caps and the prophylactic dosage decided upon was 3,000 inter-

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national units, which is contained in approximately 3 c.c. of the serum. In addition supplies of antitoxin for therapeutic use were provided.

At the same meeting of the Army Pathological Advisory Committee in 1936, the Director of Pathology pointed out that the normal time taken to immunize a horse to the degree adequate to produce a satisfactory antitoxin was from four to six months. In the case of horses that had at some time or another received injections of alum tetanus toxoid and were subsequently employed to produce antitoxin the period was shortened to two or three months. He suggested the advisability of arranging that certain Army horses should receive two injections of toxoid at intervals of a month. They could carry on with their normal work during peace time, but in the event of mobilization could be handed over to the Serum Institute. This arrangement was made through the Army Veterinary Service, and for the last three years 30 Army horses pre-immunized in this manner have been available. During this period certain horses were lost for one or another reason, but further animals were inoculated to ensure that 30 remained available. At the outbreak of war fourteen horses were handed over to the Wellcome Serum Institute, Beckenham, and sixteen to the Lister Institute, Elstree. These thirty horses will provide a valuable addition for the accelerated production of antitoxin.

While prophylactic antitetanus serum accomplished much, it did not as used in the field, give absolute protection against tetanus, and there were the additional disadvantages of serum-sickness and serum-shock from repeated injections of foreign protein.

Recent years have seen the introduction of active immunization chiefly by the use of formol-toxoid. In 1924 Ramon discovered that toxin, if treated with a low concentration of formalin and kept at a temperature of 37° C. for about a month, lost its toxic action but retained its antigenic properties. This altered toxin was named "anatoxin" by Ramon, but on account of possible confusion with the word "antitoxin" it is more commonly known as "toxoid." Immunization with tetanus toxoid was first carried out on laboratory animals and horses. The inoculations gave rise to no ill-effects and produced satisfactory immunization which could be tested by estimating the concentration of antitoxin in the serum. The results of the first experiments on man were published by Ramon and Zoeller in 1927.

Ramon and his colleagues give three injections, the first of 1 c.c., the second, a month later, of 1·5 c.c., and the third, ten or fifteen days later, of 1·5 c.c., the last being designed to act as an *injection de rappel*. With this method they claim to obtain a titre of from 0·1 to 1 unit of antitoxin per c.c. of serum. The three-dose system of giving formol-toxoid has been followed by most workers on the Continent and in America and Canada.

It has been generally assumed that when the concentration of antitoxin in the serum of an animal reaches a certain level, it affords protection against infection with tetanus spores. Ramon and Zoeller state that in the horse 0·001 unit per c.c. of serum—that is sufficient to neutralize one minimum

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lethal dose of toxin—will protect the animal from infection when a splinter of wood charged with spores is inserted into a muscle. They regard the horse and man as equally susceptible to tetanus.

In the Current Literature, November number of this Journal, 1937, we published an extract of some experiments by Sneath, Kerslake and Scruby bearing on this point. These workers established a standard technique for introducing measured doses of spores using calcium chloride as an irritant to secure their development. They immunized guinea-pigs in varying degrees, estimated the antitoxin of their serums, and then injected infective doses of spores. Forty-five animals had a titre exceeding 0·01 unit of antitoxin per c.c. of serum ; these all survived. Seven had a titre ranging from 0·001 to 0·01 : of these four died. The dose of spores injected was invariably fatal to unprotected animals. From these observations the authors conclude that an antitoxin content of 0·01 unit or over per c.c. of serum will confer protection against tetanus.

In his article written in May, 1938, Major Boyd points out that Sneath and his colleagues did not estimate the level of antitoxin after experiment in those animals which survived infection and especially in those which had a low antitoxin titre. This point has a close bearing on the problem of immunization. It is known that a further injection of toxoid in an immunized subject will lead to an immediate and vigorous production of antitoxin resulting from the stimulation of the sensitized reticulo-endothelial cells, or whatever the reacting mechanism may be.

If toxin has the same properties as toxoid, as seems probable, then the first few molecules of toxin produced from the germinated spores in an infected wound will set this mechanism in action and lead to an outpouring of antitoxin. If antitoxin is produced with the same rapidity as in toxoid stimulation it is probable that the antitoxin production will exceed and dominate the curve of toxin production, so that effective neutralization of the toxin will ensue. If the titre of antitoxin is high it is possible that the toxin produced by the spores will be immediately neutralized and fail to reach the reacting mechanism in a form capable of provoking antitoxin production. Observations with toxin-antitoxin mixtures revealed that over-neutralized toxin lost its antigenic properties.

Boyd writes that if these ideas are correct then the level of antitoxin in the serum is not the sole criterion of immunity : the property of producing antitoxin in response to stimulation with toxin plays an even more fundamental part. When the antitoxin titre is sufficiently high there is no doubt that direct neutralization of the toxin will occur without the intervention of the antitoxin-producing mechanism. But where the antitoxin titre is low and is backed up by a sensitive reacting mechanism, there is reason to believe that protection will be maintained by a rapid production of antitoxin in response to the first threat of tissue invasion by toxin.

The persistence of active immunity against tetanus has been tested by titrating the serum of immunized subjects at increasing intervals after

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inoculation. Ramon and Zoeller found that men immunized by them had a titre of 0·1 to 1 unit per c.c. of serum shortly after inoculation. Thirteen of the men were examined four and five years later; one showed a titre of 0·004, eleven ranged between 0·01 and 0·1, and one reached 0·3 unit.

Sneath and Kerslake tested thirteen subjects one year and two years after immunization; there was some decline after one year, and little change in the figures obtained after two years.

Experiments on the use of tetanus alum precipitated toxoid were made in 1930 by Glenny. Birgey, Gold, Hall, and others have also tested the method. The results seemed to show that when the doses are given at long intervals a rather higher titre is obtained than that given by Ramon's three-dose method. After the injection of alum precipitated toxoid local reactions may occur, and there may be some local induration at the site of injection.

In the further treatment of immunized subjects who have been exposed to infection, Ramon and Zoeller recommend simultaneous injection with antitoxin and anatoxin. The antitoxin will give immediate protection and the anatoxin will rapidly increase the antitoxin production and active immunization will come into play before the passive immunity has faded.

Some observers criticize this proposal: they say the serum will over-neutralize the toxoid and destroy its antigenic properties.

Wolters and Dehmal have found in experiments with guinea-pigs that alum precipitated toxoid is absorbed very slowly, and when given at the same time as antitoxin will produce a satisfactory response.

Since 1928 more than 50,000 horses of the French Army have been immunized against tetanus. All have received at an interval of one month two initial doses of 10 c.c. of anatoxin, and 35,000 have received a third dose at varying intervals up to two years after the primary inoculation. No case of tetanus has occurred in the 35,000 horses which received three doses. Cases were very rare in horses which received only two doses, while they occurred with usual frequency in unprotected animals.

Ramon and Lemétayer have tested the serum of twenty-six horses inoculated several years previously, and twenty-two showed 0·03 unit per c.c. of serum. All with one exception had more than 0·001 unit, which the authors consider sufficient to protect horses against experimental infection.

At a meeting of the Army Pathological Advisory Committee the Director of Pathology raised the question of active immunization against tetanus as a routine measure in the British Army. As a result investigations were undertaken at the Royal Army Medical College in collaboration with Dr. R. A. O'Brien and his staff at the Wellcome Research Laboratories, where the various toxoids were prepared and the titrations of serums for antitoxin performed. The results of these investigations were so successful that active immunization against tetanus was introduced into the Army in 1938.

Boyd, O'Brien, *et al.*, found that tetanus toxoid antitoxin floccules

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gave a negligible production of antitoxin; on account of this poor response and the difficulty of preparing the floccules it was decided not to pursue this investigation further.

Tests with tetanus toxoid were then undertaken; no reaction was produced in the volunteers, and the results as regards the production of antitoxin were satisfactory.

Glenny and his co-workers have pointed out that in immunizing animals it is an advantage to allow a long interval to elapse between the first and second doses. This principle has been accepted, and in immunizing man with formol-toxoid an interval of four weeks has been generally adopted. It was decided to experiment at the College with a longer gap between doses in the hope that it might be possible to effect satisfactory immunization with two instead of three doses.

A number of volunteers were given a preliminary dose of 1 c.c. of toxoid and from twenty-one to twenty-six days later were given a second dose of 1 c.c. A month later the antitoxin titre varied from 0·005 to 0·02 unit of antitoxin per c.c. of serum. This was not regarded as adequate. Another group of men received the second dose from six to seven weeks after the first dose, and on testing them four weeks later the antitoxin titre varied from 0·01 to 0·1 unit per c.c. of serum. These results were above the average level believed to confer protection against tetanus infection and were equal to those given by the three-dose method as advocated by Ramon and his colleagues and widely practised in France.

Ramon and Zoeller found the first dose of toxoid produced little or no antitoxin in the serum but resulted in the development of a remarkable aptitude for antitoxin production when further doses of toxin were given. Their figures showed a gradual development of sensitization up to a month from the original dose. The two doses given by Boyd and O'Brien were practically at the same interval as Ramon's first and third dose, and the final results were so similar that it would appear that an intermediate dose given during the period when sensitization is developing, has little or no action in enhancing the final titre of antitoxin.

Following on the decision to employ active immunization against tetanus, the Director of Pathology arranged that an Army Council Instruction on inoculation against tetanus with tetanus toxoid should be issued in 1938. The Instruction stated that "the inoculation consists of two injections given at intervals of six weeks. It is not necessary to repeat the injections as the protection lasts for many years. While inoculations will be on a voluntary basis, officers commanding units will encourage officers and men to take advantage of this simple method of securing protection." A record of inoculations was to be kept in accordance with Regulations for the Medical Services of the Army, 1932. An Army form was also designed for reporting cases of tetanus.

A notice on the prevention of lockjaw was posted up in barrack rooms, canteens, etc., and officers were asked to bring the information to the notice

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of all ranks. Some 70 per cent of the men of the Regular Army have availed themselves of this means of protection.

On the declaration of war and the expansion of the Army, the use of formol-toxoid was greatly extended and the Canadian and Australian contingents adopted it as a routine measure; active immunization, however, still remains on a voluntary basis.

The policy of the British Army regarding the subsequent administration of tetanus antitoxin in the event of men, previously actively immunized, being wounded, differs from the French practice. The French advocate an immediate injection of toxoid for the freshly wounded and already immunized soldier. If the man has not been previously immunized he should receive first 1 c.c. of tetanus toxoid followed by 3,000 units of anti-tetanus serum, and then at fifteen days' interval two further injections of toxoid.

In the British Army the immediate administration of 3,000 units of anti-tetanus serum is required as an additional safeguard against infection; this serum should be given at the earliest possible moment, but under the conditions of active service, when a casualty may remain many hours without receiving medical attention, the injection is often delayed. In these circumstances previous active immunization will be of great importance and may save many lives. Unfortunately it is not always possible to ascertain whether a recently wounded man has been immunized, though this information will be given in his documents when available, and the importance of immediate injection of antitetanus serum is obvious.

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