trophins, and two days after the last injection a laparotomy was performed. The ovaries were unchanged in size; the cysts were punctured and the fluid was collected for examination, and bilateral wedge resections were then performed.

Case 4

A single woman aged 27 started to menstruate at the age of 14. She was regular for the first year and then had only one or two periods yearly until she was 21, when she was treated with stilboestrol. Since then she has had scanty irregular periods lasting two to four days at intervals of one to four months. She first noticed the growth of hair on her lips and chin at the age of 16. It became coarse and spread on to her breasts, abdominal wall, and legs. She complained of headache, pain in the limbs, and depression, for which she was treated by a psychiatrist. Her weight was constant. She was admitted and examined under anaesthesia, and her pelvis appeared to be normal. Culdoscopy was unsatisfactory. The left ovary was poorly visualized and its size could not be estimated. The left Fallopian tube was red and deformed. There was a tubovarian mass in the right side, but the size of the ovary could not be established. She was given gonadotrophin, and four days after the last injection a laparotomy was performed. The left ovary was enormous, measuring about 16 by 10 cm. It contained numerous haemorrhagic cysts and enlarged follicles. The Fallopian tube was stretched over its apex and was bound down by numerous adhesions into the pouch of Douglas. The right ovary was not recognized. The right Fallopian tube was enlarged with hydrosalpinx, and ended blind. It was thought that the right ovary might have become bound to the left with adhesions, but no line of demarcation could be established. The follicles were punctured and the fluid was collected and a wedge resection then performed.

Case 5

A married woman aged 25 had vaginal bleeding at the age of 13. It continued for a year, during which time she was given numerous injections. Then, after a few months' amenorrhoea, she had a further spell of bleeding which lasted for six months. This continued, usually with only short intervals, until after she married at the age of 22. Since then the intervals have got longer, usually two to four months, and the bleeding shorter, usually eight to eleven days, but there has been heavy loss of blood, the haemoglobin falling on occasions to 40% and she has had to have blood transfusions. During this time she has had dilatation and curettage on three occasions—at 14, 18, and 21—with very temporary improvement only. She wanted children but failed to conceive, and had gained about 20 lb. (9 kg.) in weight since she married. She developed a slight growth of hair on her lips and chin.

She was admitted to hospital and examined under anaesthesia. The uterus was bulky, the sound passing 8 cm. Culdoscopy revealed the right ovary to be about 3½ by 2 cm. and the left about 4 by 3 cm. They each contained a ruptured follicle and a few translucent cysts. She was given gonadotrophin, and four days after the last injection a laparotomy was performed. The peritoneal cavity contained blood from ruptured ovarian follicles. Both ovaries were greatly enlarged. The right was about 8 by 4.5 cm. and contained a large corpus luteum, and the left was about 6 by 4 cm. Both contained enlarged haemorrhagic follicles and numerous cysts. The follicles were punctured and the fluid was collected and bilateral wedge resections then performed.

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HUMAN ANTITETANUS SERUM IN THE TREATMENT OF TETANUS

BY

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Clinical tetanus manifests itself by a complete disorganization of the reflexes in the nervous system, producing the well-known manifestations of trismus and convulsions in the severe case. The neurotoxin reaches the central nervous system, where it acts on the susceptible cells, thereby producing these effects. In spite of this very severe disorganization of the nervous system which is present during the actual disease, when the patient recovers, by whatever means of treatment, the nervous system returns completely to normal. The neurotoxin must therefore have a transient effect on the nervous system, and when cure has taken place it has been eliminated or neutralized in some way. One of the possibilities, it seemed to me, was that the body had manufactured its own antitoxin during the course of the disease and thereby had neutralized the neurotoxin.

Stafford, Turner, and Goldman (1954) suggested the possibility of using human antitoxin for the treatment or prophylaxis of tetanus. The main reasons they gave for this were the elimination of the possibility of anaphylaxis due to the foreign proteins in the horse serum. Rubbo and Suri (1962) gave an account of their experiences in the use of human immune globulin for the prophylaxis of tetanus. When the tetanus unit was formed in this hospital in 1954 it seemed worth while trying human antitoxin in the treatment of clinical tetanus to see if the disease could be cut short and risks of long-continued positive-pressure respiration could be minimized.

This paper gives an account of (a) the method of the collection of human antitoxin; (b) a review of the titres of antitoxin in the serum collected, with the implications on prophylaxis; and (c) the results of the use of this serum in some 26 out of the 57 cases treated in this unit over the past years.

Collection of Serum

The story of the collection of the serum is very gratifying to relate. About 160 subjects volunteered to give blood. The organization for the immunization of

these volunteers, the taking of the blood at the right time, the assay of the titres of the serum from the blood, and its storage required the co-operation of a large number of people. Once the organization of the routine had been established, successive secretaries in my department took control of the procedure, and credit is due to them for its smooth running.

Donors were of two types: (a) those who had not been previously immunized against tetanus and (b) those who had been immunized against tetanus in the Forces during the war. The majority of the former were medical students and physiotherapy students from this hospital who had not been previously immunized. The vast majority of the latter were from the factories in Leeds. Immunization was carried out by three injections of 1 ml. of tetanus toxoid, six weeks between the first and second and six months between the second and third injections. Ten days after the third injection a small amount of blood was withdrawn from the volunteer. Professor Oakley, the bacteriologist to the tetanus unit and the professor of bacteriology in Leeds University, carried out an assay of the titre of the antitoxin. Those volunteers with a titre of above five units thereupon gave 1 pint (570 ml.) of blood, from which the serum was extracted. It was very early found, however, that the seven to ten days required for the assay of the toxin and the calling up of the volunteer allowed a very considerable fall in the titre of the antitoxin in the serum extracted from the pint of blood. It was therefore thought desirable that the pint of blood should be taken on the tenth day rather than wait for the assay of the original small specimen. This arbitrary time of the tenth day was recommended by Professor Oakley from his great experience in the commercial production of antitoxin.

The Regional Blood Transfusion Centre took charge of the actual withdrawal of the blood. The weekly bleeding of donors at the blood transfusion centre in Leeds takes place every Thursday. The transfusion centre promised that they could fit in six donors for antitoxin without any special arrangements being necessary. The secretary therefore made sure that the third injection of tetanus toxoid was always given on a Monday and that the volunteers attended the blood transfusion centre on the Thursday of the following week. The secretary in the meantime informed the blood transfusion centre of the names of the volunteers. After the blood had been withdrawn and allowed to clot the transfusion centre withdrew the serum into an ordinary transfusion bottle, putting a small amount into a pilot tube for assay. This tube was then given to Professor Oakley and the main bottle was kept in the deep-freeze and was available when required for treatment.

As shown below, the titre of antitoxin in the serum of volunteers who had had the one course of immunization was often disappointingly low. It was suggested that a booster dose of toxoid given to volunteers who had been fully immunized some years before might produce much higher titres. One or two ex-Service volunteers in the hospital gave blood, and the titres of their serum seemed to confirm this suggestion. An approach was therefore made to the Services for volunteers to have booster doses and to give blood for this purpose. Although high-ranking officers in the Army and the Air Force received our request for co-operation sympathetically and gave permission for us to approach units of the Army and Air Force

stationed near by, so far we have not obtained a single volunteer. An approach was therefore made to big factories in the town.

I would like to acknowledge the kindness and courtesy with which I was received by the directors of Montague Burton, Ltd., and the managing director of a local factory of I.C.I. I was given facilities by these firms to address meetings of their employees, notably their gardening clubs, and tell them what we were doing and what we hoped to do with human antitoxin. A number of subjects volunteered. The works medical departments in these firms undertook to give the booster dose of tetanus toxoid (supplied by us) on a Monday and to send the volunteers to the blood transfusion centre on the Thursday of the following week. In the meantime the names of the volunteers were communicated to my secretary, who transferred them to the blood transfusion centre. Later these same works medical departments obtained a full record so far as was possible of the inoculations received by these volunteers in the Services. It is very gratifying to be able to record such splendid co-operation from these two firms and their medical departments.

Titres of Serum Obtained

In all 115 new immunization donors of blood and 45 previously immunized volunteered. The difference in titre between these two groups was very striking. The average amount of serum obtained from each pint (570 ml.) of blood was 160 ml. A titre of less than 5 units per ml. was of little use in treatment because of the large amount of serum that would have to be given to supply a reasonable dose of antitoxin. Therefore, in assaying the titre, apart from proving that an assayable titre was present in these small concentrations, the exact titre was not ascertained. When the titre was above 5 ml. an assay accurate to 5 units per ml. was carried out. Thus when this serum was used for treatment the dose given could be accurately recorded. The accompanying Table gives a classified record of the titres obtained.

	Newly Immunized	Previously Immunized
Less than 5 units ..	71 (61.5%)	4 (9%)
5-20 units ..	28 (24.5%)	17 (38%)
21-50 ..	11 (9.5%)	12 (26.5%)
51-100 ..	5 (4.5%)	10 (22%)
Above 100 units ..	0	2 (4.5%)
Total ..	115	45

The highest titre recorded for a newly immunized person was 90 units per ml. and for a previously immunized person was 135 units per ml. The comparison of these two sets of figures shows very clearly the much higher titres of antitoxin that we expected from the giving of a booster dose to a previously immunized person compared with the titres obtained from a newly immunized person.

As pointed out above, the works medical departments furnished information on the recorded time of immunization in the Forces of these volunteers. All except three of these 45 volunteers had been immunized before 1948. This is at least 10 years before the booster dose had been administered, and in half of them it had been at least 15 years. It has been recommended that patients needing prophylaxis for a contaminated wound occurring 10 years after a previous immunization require antitetanus serum rather than a booster dose of toxoid. Gosling (1962) even suggests that a complete new course of three injections is required.

From the figures provided, however, it would appear that if the initial course of immunization has been properly carried out a latent immunity is present for a very much longer period and that this immunity is well stimulated by a booster dose of toxoid. It must be made clear, however, that the booster dose of toxoid was twice the normal dose—that is, 2 ml. instead of 1 ml. (It is to be remembered that since 1958 Burroughs Wellcome have introduced a stronger form of toxoid, of which the standard dose is 0.5 ml.) Whether this double dose of toxoid did in fact cause the high titres we obtained is debatable, but unless a latent immunity was there to be stimulated this double dose could not be expected to produce any response. The use of this double dose, however, does make comparison with the figures obtained by Stafford, Turner, and Goldman (1954) and Barr and Sachs (1955) difficult. The figures in the present paper do suggest a modification of the recommendation by Parish, Laurent, and Moynihan (1957) that five years after a full course of immunization the subject should be regarded as non-immune.

Results of Treatment

The tetanus unit at the General Infirmary at Leeds has so far treated 57 cases of tetanus. Adequate supplies of human antitetanus serum became available for the first time at the ninth case in the series. Thereafter, whenever possible, only human serum was used to provide the antitoxin in treatment. In a number of patients, however, large doses of horse antitetanus serum had been given by the hospital in which the diagnosis had been made before the patient was sent on to us. (Only three cases in the series came from the City of Leeds.) The more scientific procedure of using horse serum and human serum alternately was therefore not possible. In one patient the disease was so severe that it was not thought proper to withhold the possible additional advantage of human serum, although a large dose of horse serum had already been given.

Dosage.—In adults the number of units of antitoxin from the human serum varied from 20,000 to 80,000. In children the dose was proportionately less, varying from 8,000 to 16,000. In all patients an assay of the titres of antitoxin in the blood was made two days after the serum had been given. These assays showed that a titre of 2 units of antitoxin per ml. was the lowest concentration produced. The human serum was given intravenously. In one patient an additional dose of 5,000 units was given intramuscularly, and in another 1,500 units was given intrathecally.

Death Rate

In this series of 57 cases there were seven deaths. In 31 patients given horse serum only there were five deaths and in 25 patients given human serum only there were two deaths. One patient given both human and horse serum recovered. Therefore the death rate in patients given antitoxin by human serum was half that in patients given horse serum.

This apparently favourable result from the use of human serum fails to take into account many other factors. In the last four years, almost exactly, 36 patients have been treated and there have been no deaths; 22 received human serum and 14 horse serum. Two of the latter cases were so mild that treatment by paralysis was not necessary. All the other 34 cases were treated by paralysis with curare and positive-pressure

artificial respiration. Increased skill in the management of patients under this regime must also be given credit for this long series of cases without a death.

The cause of death in the seven patients who died was found to be respiratory complications in three, pulmonary embolus from prolonged intravenous drip in one, secondary haemorrhage in one, and agranulocytosis in one. In the seventh case no definite cause of death was found. This patient was given human serum. In all the other six cases the complications causing death can reasonably be regarded as avoidable with increased skill and experience in the management of the patient under paralysis and positive-pressure artificial respiration.

Comment

The use of antitoxin from human serum might be thought to cut short the period of treatment under positive-pressure respiration and thereby lessen the chances of complications occurring. In Case 9 it certainly did appear that this had occurred, as follows:

A Polish textile worker aged 50 was admitted to the tetanus unit in October, 1956. He gave a history of having crushed his right index finger in a textile machine 12 days previously. The wound was cleaned and dressed at the local hospital. No A.T.S. was given. Two days later a partial amputation of the crushed tissues was carried out. Again no A.T.S. was given. Eight days later he had neck stiffness and a little difficulty in swallowing. Two days later he was admitted to the tetanus unit as a moderately severe case of tetanus.

Next morning a gastrostomy was performed for feeding. A tracheostomy was then carried out and a cuffed endotracheal tube was inserted. Finally the index finger was amputated. *Clostridium tetani* was subsequently isolated from the septic wound in the amputated finger.

Antitoxin, 22,500 units, in about 2 litres of human serum, was given by an intravenous drip. Full sedation was instituted as the symptoms grew worse. However, on the evening of the fourth day the symptoms began to disappear rapidly, and all sedation was stopped. On the following afternoon, five days from the start of the treatment, the tracheostomy tube was removed. Next day the gastrostomy tube was removed, the patient got out of bed, and normal activity was resumed. Two days later the gastrostomy and tracheostomy wounds were almost healed and he was discharged to a rehabilitation unit.

This dramatic change in the pattern of the disease has not occurred again in any succeeding case. As already stated, 34 out of the 36 cases treated consecutively without a death were treated by paralysis with curare and positive-pressure respiration. The length of time these patients were on the positive-pressure machine varied from 16 to 29 days. The length of time artificial respiration was required in this manner was not related to the use of human serum or horse serum. The patient on the machine for 29 days was given human serum. In most cases, whether given human or horse serum, some muscular twitching and stiffness persisted for a few, variable number of days after total paralysis had been discontinued. The rapid disappearance of symptoms as seen in Case 9 was never seen. In these 34 cases, therefore, there was no evidence that the use of antitoxin from human serum cut short the course of the disease.

Summary

The use of antitoxin from human serum in the treatment of clinical tetanus in the tetanus unit of the General Infirmary at Leeds is described.

The serum was collected from student volunteers fully immunized for the first time and from volunteers from factories in Leeds who had been previously fully immunized in the Forces.

The titres of antitoxin in the serum of those volunteers given a booster dose of toxoid after previous immunization were on average much higher than the titres in those newly immunized. It is suggested that the high titres obtained in these donors 10 to 15 years after the previous immunization show that latent immunity persists for much longer than previously estimated.

The results of treatment with antitoxin from horse serum and human serum in 57 cases showed that the crude death rate in 25 cases treated by human serum was found to be half that in 31 cases treated by horse serum. In one very severe case given both human and

horse serum recovery occurred. In the last four years 36 patients were treated without a death, 22 of them having been given human serum. Increased skill in the management of the patient under total paralysis is thought to be the chief cause of this successful run. Human serum was not found to cut short the course of the disease except in one case.

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ACUTE OLIGURIC RENAL FAILURE ASSOCIATED WITH MULTIPLE MYELOMA

REPORT OF THREE CASES

BY

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Renal insufficiency is responsible for 43% of deaths in multiple myeloma (Allen, 1951). This commonly takes the form of chronic renal failure, often without significant hypertension (Osserman, 1959). Acute oliguric renal failure developing in a few days has been described in only eight cases (Holman, 1939; Addis, 1948; Bartels *et al.*, 1954; Myhre *et al.* 1956 (2 cases); Killmann *et al.*, 1957; Perillie and Conn, 1958; Macalister and Addison, 1961). This paper presents three new cases of acute oliguric renal failure occurring in multiple myeloma and briefly examines their clinical and pathological data along with those of the eight other cases. The new cases are referred to as Cases 9, 10, and 11.

Case 9

A woman aged 64 was admitted to the renal unit of Sydney Hospital on August 26, 1961. She had suffered pain over the left lower ribs and back for two years. X-ray films of her spine had shown moderate decalcification. Osteoporosis had been diagnosed and female hormones given. Over 12 months prior to admission she had become increasingly tired, and had lost 1 stone (6.4 kg.) in weight. In July, 1961, she developed cough, sputum, and a sore throat. Her ankles became swollen and she vomited occasionally. Weakness became marked. On August 19 she was admitted to another hospital with thrombophlebitis of the left leg. There she was found to be oliguric and basal crepitations were noted. Heparin was given in view of the thrombosis and several epistaxes developed on August 21. Her blood urea at that time was 200 mg./100 ml. and haemoglobin 9.4 g./100 ml. Anuria developed over the following week, and she was transferred to the renal unit on August 26. She was not noted to be hypotensive at any stage.

Physical examination revealed a pale and slightly confused patient. The liver edge was felt 3 cm. below the costal margin. Her blood-pressure was 160/85 mm. Hg. There were no other abnormal findings.

Investigations at Sydney Hospital revealed: blood-urea nitrogen, 250 mg./100 ml.; haematocrit, 25%; erythrocyte sedimentation rate, 86 mm. per hour (Westergren); white-cell count, 8,900/c.mm.; the blood film showed a normo-

cytic normochromic anaemia with a few myelocytes and a number of rouleaux. Platelets were plentiful. Serum electrolytes: potassium, 7.4 mEq/l.; chloride, 86 mEq/l.; otherwise normal. Microscopy of urine—5–10 red cells per high-power field with leucocytes covering 50% of the field. Culture grew *Proteus vulgaris*. Serum albumin, 4.0 g./100 ml.; serum globulin, 3.3 g. Electrophoretogram of plasma showed elevated alpha-2 and beta-1 bands and also an abnormal gamma-globulin. X-ray examination showed several pathological fractures of ribs, several rounded areas of bone erosion in the skull, and generalized decalcification of the thoracic and lumbar spine with collapse of several vertebrae. Marrow aspiration showed 27% plasma cells and 10% lymphocytes. Serum calcium, 8.6 mg./100 ml., serum phosphorus, 17.1 mg./100 ml., serum magnesium, 3.0 mg./100 ml., serum alkaline phosphatase, 21 King-Armstrong units.

The patient was given a high-carbohydrate low-protein diet and a basal water requirement of 400 ml. per day plus replacement of obvious fluid losses. Vitamin supplements and anabolic hormones were given. Chloramphenicol was given for the urinary-tract infection. Dialysis with the artificial kidney was not performed. She remained anuric and died 14 days after admission.

Necropsy showed congestion of lower lobes of both lungs. The kidneys weighed 170 and 190 g. Their capsules stripped easily to reveal a pale finely granular surface. The cortex was pale and 0.4 cm. in average width. The medulla was congested. Melaena stool was present in the small and large bowels. The histology of the kidneys is dealt with later.

Case 10

A diabetic woman aged 64 was admitted to the renal unit of Sydney Hospital on August 6, 1961. Diabetes had been diagnosed in 1955 and had recently been controlled by diet alone.

In February, 1961, she complained of intermittent back pains and progressive weakness and tiredness. Pallor, ankle oedema, and effort dyspnoea developed and the weakness became such that she spent much of her time in bed. She was admitted to another hospital on July 13 because of pallor and oedema. The electrocardiogram showed left bundle-branch block. Her haemoglobin value was 8.4 g./100