of uninjured muscles left in the animal after death should prove toxic. This was found to be so; but the conditions necessary for production of the toxic material proved to be unexpectedly limited. Although demonstrable in muscle taken from a cat dead 4–10 hours, it was no longer present in muscle taken from a cat dead 24 hours. The results from 16 injections in 13 different experiments (charted in fig. 3, together with the average effect of control extracts) demonstrate not only the unstable nature of the toxic material formed in ischæmic muscle but also the relative size of its molecule. Simple dialysis (in 'Cellophane' sacs suspended in a large volume of saline in the refrigerator for 24 hours, with a change of saline at half-time), under conditions in which creatinine was reduced to 3% of its original concentration, failed to remove the toxic substance.

Several factors contribute to the variable error of the results, of which one is the use on some occasions of a partially eviscerate animal as the test preparation. Removal of large and small intestine (to the upper third of the duodenum) reduces the portal circulation considerably; the preparation is a stable one and more sensitive than the whole animal to the effect of ischæmic muscle extracts.

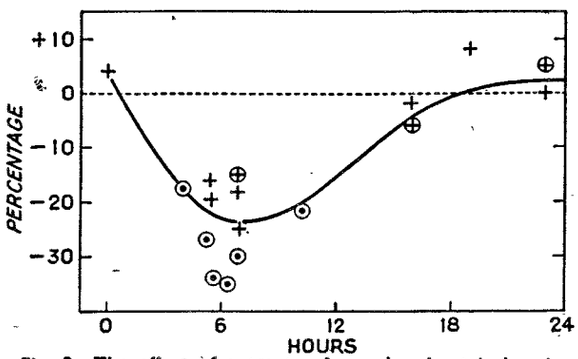


Fig. 3—The effect of extracts of muscles, kept ischæmic (in dead body) for varying periods, on the creatinine clearance. *Abscissa:* Duration of ischæmia in muscle from which extracts were made. *Ordinate:* Percentage change in creatinine clearance induced by the injection of ischæmic muscle extracts.

+ = denotes extract injected into the intact animal.
⊕ = denotes dialysed extract injected into the intact animal.
⊙ = denotes dialysed extract injected into the partially eviscerate animal.

The temperature of the ischæmic muscles fell from body temperature to room temperature, reaching 20° C. in about 5 hours.

During these experiments, it became apparent that the toxic effect of ischæmic muscle extracts on the kidney was gradual in onset, the maximum being observed 15–30 min. after the end of the injection. Had sampling been carried out at this point in all experiments, the results shown in fig. 3 would probably have been more regular; in fact, the sampling times varied from 0–80 min. after the end of the injection.

In several experiments in which sampling was continued for 2–3 hours after the end of the injection, some recovery of renal function took place. In one animal (not eviscerate) it was complete in 2¼ hours, while in another (partially eviscerate) none was observable after 3 hours. These, and other intermediate stages of recovery, could be roughly correlated with the individual's requirements for nembutal, suggesting that recovery largely depended on the functional capacity of the liver.

No similar information concerning the toxic action of the release of bound limbs on the kidney is as yet available. For technical reasons, sampling cannot be made sooner than 20–30 min. after the release, by which time the maximum degree of renal impairment would be apparent, whether gradual or sudden in onset; and any gradual recovery might well be masked by a continued leak of toxic products from the muscles after release.

CONCLUSION

A substance toxic to the kidney can be extracted from the muscles of limbs which have been tightly bound for some hours, but not from normal muscle. Such a substance develops in undamaged muscle, however, if the muscle is kept ischæmic (by death of the animal) for 4–10 hours. Thereafter it disappears again. It is non-dialysable. These facts suggest that the toxic material is some early intermediate breakdown product of a large molecule, formed only under strictly anaerobic conditions. Its unstable nature may help to account for the lack of correlation between the severity of renal symptoms and duration of crush in human air-raid casualties (Bywaters). It may also explain the erratic results obtained by Green (1943) with extracts made from completely disrupted (frozen) cells or from denatured (acetone precipitation) cells. Any further conclusion as to the chemical nature of this toxic material must be conjectural at present, but the possibilities are limited. Recent work on proteinase activity (Bergmann and Fruton 1941) suggests that the toxic material might well be an early breakdown product of protein, formed only during strict long-continued anaerobiosis and never during normal aerobic protein katabolism in the cell.

The expenses of this research, of which a more detailed account will be published elsewhere, were met by a grant from the Research Fund of the University of London.

REFERENCES

Bywaters, E. G. L. Personal communication.
Bergmann M. and Fruton, J. S. (1941) Advances in Enzymology vol. I, p. 63.
Eggleton, M. G., Richardson, K. C., Schild, H. O. and Winton, F. R. (1943) *Quart. J. exp. Physiol.* **32**, 89.
Green, H. N. (1943) *Lancet*, ii, 147.

TREATMENT OF TYPHUS WITH ANTI-TYPHUS HORSE SERUM*

M. WOLMAN, M D ROME
CAPTAIN RAMC
Menelik Hospital, Addis Ababa, Ethiopia

SERUM from convalescents and from immunised animals has been used against louse-borne typhus without convincing results. The present study was suggested by the apparent benefit obtained with convalescent serum in a series of more than 30 cases. The supply of convalescent serum being rather irregular, production of anti-typhus horse serum was started in July, 1942. At that time I was unaware of the successful use of similar serum by Durand and Balozet (1941).

Preparation of the serum.—The Ethiopian Army Animal Transport and Veterinary Corps kindly lent two horses for the experiment. They were both healthy, and had been under the observation of a veterinary officer (Dr. Ingueda Yohannes) for more than a year.

Living rickettsiæ contained in the intestines of lice, prepared for Weigl vaccine, were obtained from the Medical Services Laboratory, and were injected into the horses, usually every 5–6 days, in doses increasing over a period of 2½ months. The horses were then bled twice (5 and 10 days after the last injection). In each subsequent month a further series of injections was given (ordinarily 250, 375 and 500 louse intestines) followed by two further bleedings.

The blood was collected in large sterile bottles one-tenth full of 5% sodium citrate, and after two or three days the supernatant serum was siphoned off and enclosed in rubber-capped bottles, with merthiolate or phenol as a preservative.

At first faulty preparation resulted in a number of abscesses, but with improved technique there were no more.

CLINICAL TEST

Type of disease.—Typhus in Addis Ababa is louse-borne. Epidemiological, immunological and clinical studies have shown that it is epidemic typhus, identical with the European disease. The mortality varies from year to year and from month to month. About 80 cases (approximately 40 treated with serum, with an equal number of controls) belonged to a temporary epidemic of very mild typhus lasting only 7–12 days with a very low mortality. On the other hand in certain months sudden exacerbations occurred with many severe cases. This experiment lasted 18 months and covered two major epidemics of the rainy season. The patients were mostly Ethiopians, though a few were Arabs; no Europeans were included. Many complicating diseases had to be dealt with. One out of five patients had malaria.

Arrangement of the experiment.—All patients admitted with symptoms of typhus were given a special chart with a serial number. Venous blood, taken on the day the provisional diagnosis was made, was sent to the Medical Services Laboratory for Weil-Felix and Weigl tests. Patients with even numbers were given symp-

* This article has been abridged. To prevent delay it is published without awaiting the return of a proof from the author.—ED. L.

tomatic treatment only. They will be termed the "untreated group." Patients with uneven numbers were given the same symptomatic treatment, plus serum.

The normal dosage of serum was 20 c.cm. subcutaneously twice on the first day and once on three succeeding days. Altogether 100 c.cm. was given. Those patients whose temperature dropped to normal before the 100 c.cm. was completed received only 60–80 c.cm.

In both groups the symptomatic treatment was the same. Aspirin, caffeine, camphor, codeine and salt were given as required, together with specific remedies such as sulphapyridine and quinine for complications.

To obtain an objective idea of the effect of serum certain rules were followed:

(*a*) Patients were not told when they could leave their beds for the first time. Each day the senior dresser was asked whether the patient had or had not left his bed. Thus patients began to walk strictly according to their own sense of well-being.

(*b*) After patients had started walking they were asked daily if they wanted to go home. Again their decision, not the experimenter's, was final.

Information as to the date of onset was usually obtained from the patients, but sometimes required the help of his family and neighbours. Cases in which the date of onset could not be determined were included in the series, but the relevant columns in their charts were not filled in. The number in which any of the data important for statistical evaluation were missing was small.

Whenever the provisional diagnosis of typhus was found to be wrong, the case was discarded and the next case of typhus admitted was given the same serial number and treatment. Cases already in defervescence on arrival were omitted from the series.

The two groups proved to be similar in respect of complicating diseases (table I).

TABLE I—COMPLICATING DISEASES

	Treated (220 *cases*)	*Untreated* (220 *cases*)
Malaria	44	45
Relapsing fever	7	7
Lobar pneumonia	7	11
Bronchopneumonia	1	2
Bronchitis	11	14
Measles	1	0

Influence of the serum.—The main results are shown in table II. It is probable that one or two deaths in the treated group are attributable to injection of serum intravenously, which was adopted at first in severe cases but afterwards abandoned.

TABLE II—INFLUENCE OF SERUM

(Days calculated from onset of illness)

	Treated (220 *cases*)	*Untreated* (220 *cases*)
Duration of illness*	11·99 days	13·25 days
Patients left bed for first time after	12·2 ,,	14·0 ,,
Patients left hospital after	17·3 ,,	20·2 ,,
Deaths	8	24

* Period from onset to return of temperature to normal.

In addition, the influence of the serum has been examined according to the day on which treatment started, and table III shows that not one patient died among the 71 receiving treatment before the 7th day of the illness. The later the treatment is started, the less effective the serum seems to be, and after the 10th day its influence is almost negligible.

There were no cases of gangrene in the treated group (2 in the untreated), and no serious ulcerations attributable to local failure of circulation (3 in the untreated). Only 5 patients became seriously psychotic, and in 2 of these the condition was already fully developed when the patient was first given serum. Of the untreated group 17 became psychotic; and in general the influence of serum on the mental condition was conspicuous.

There were 7 cases of abscesses from injections, due to faulty preparation or handling of the serum. These did not occur after the technique of preparation had been improved and the native dressers had learned to handle it properly.

In 4 patients there were serum reactions, one of which was quite serious. The small number of reactions in about 900 injections of crude serum may be explained by the fact that hardly any of the patients had ever had any previous serum injections.

TABLE III—EFFECT OF SERUM RELATED TO DAY ON WHICH IT STARTED

Day serum started	No. of cases	Deaths	Day serum started	No. of cases	Deaths
3rd	6	0	8th	23	1
4th	19	0	9th	26	2
5th	27	0	10th	15	1
6th	25	0	After 10th day	19	2
7th	31	2			

Cases in which the date of onset of the disease could not be ascertained are not included in this table.

SPECIAL OBSERVATIONS

Of many observations made before and during this experiment, the following may be mentioned:

(1) *Wassermann reactions.*—Over 50 WR were performed on typhus patients, and a considerable number of false-positive reactions were found. Very often a second WR in defervescence was negative. How many such false-positive reactions persisted could not be determined, because both acquired and congenital syphilis are very common in this country, and no reliable history could be obtained.

(2) *Parotitis.*—In one case the donor of convalescent serum was a patient who had had parotitis as a complication of his typhus. The parotitis had seemed clinically a typhus parotitis and not mumps. At the time of withdrawal of the serum, this donor showed no clinical signs of either typhus or the complication. The recipient of the serum, a patient with severe typhus, developed parotitis two days after the injection. This happening may be purely accidental, but it raises questions of interest. (*a*) Do the rickettsiæ stay longer than usual in the blood of typhus patients who have had parotitis? (*b*) Is typhus parotitis due to another superimposed virus?

(3) The *rash* was usually petechial, but on four occasions it was definitely raised and papular. The date of appearance of the rash could be determined only in about a third of the 220 patients treated with horse serum. In more than half of these it appeared on the 5th or 6th day of the illness, while the extreme limits were the 2nd and 10th days.

(4) The *Weil-Felix reaction.*—An attempt was made to determine whether a rise of titre during the illness was the rule. Of 176 untreated patients on whom two Weil-Felix tests were made at seven days' interval, 106 (60·2%) showed an increase: in 53 cases (30·1%) the titre increased to double, in 29 (16·5%) to four times, in 15 (8·5%) to eight times, and in 9 (5·1%) to more than eight times the original. On the other hand, in 32 cases (18·2%) the Weil-Felix titre decreased during the seven days' interval—in 22 (12·8%) to a half, in 5 (2·8%) to a quarter, and in 2 (1·1%) to an eighth. In 38 cases (21·6%) no change occurred.

(5) The *Weigl reaction* (microscopic agglutination of rickettsiæ) was kindly performed by Dr. Codeleoncini of the Medical Services Laboratory. It was determined twice with 7 days' interval on 118 untreated patients. The titre of this reaction increased in 54 cases (45·8%), decreased in 30 (25·4%), and remained the same in 38 (32·2%). This reaction therefore seems to be of less diagnostic value than the Weil-Felix reaction.

6. *Widal reaction.*—In quite a large proportion of cases, probably more than 20%, the Widal reaction with any or all three of the typhoid and paratyphoid bacilli gave a positive result at a certain stage of the illness.

DISCUSSION

It seems to be clear that specific horse-serum therapy is effective in typhus. The reason why the whole group of the treated patients does not show a striking difference (except in mortality) from the untreated group presumably is that most of them did not report at the hospital until they had been ill at home for a few days. Those admitted early in the course of the disease benefited greatly, as seen in table III.

In view of the necessity for early treatment I believe that serum should be given immediately, at the first suspicion of the disease. There seems to be no need to

take the blood for agglutination before starting serum therapy, for serum treatment does not influence the titres of agglutination.

The influence of serum on the course of typhus appears to correspond with the natural history of the infection. It is usually only during the first week or so that rickettsiæ can be found in the blood, while later they are fixed in the tissues. Probably the serum takes effect only, or mostly, on the newly arrived rickettsiæ floating in the blood-stream. Later, when the rickettsiæ become fixed to the tissues, the damage is done, and the serum antibodies cannot reach them.

SUMMARY

(1) Antityphus serum has been prepared by injecting horses with living rickettsiæ contained in the intestines of infected lice.

(2) The serum was given to every second patient in a series of 440 consecutive typhus patients during 18 months in Addis Ababa.

(3) The mortality of the treated group was 3·6% compared with 10·9% in the controls.

(4) The serum seemed to shorten the illness and reduce the incidence of psychotic symptoms. Its influence was far greater when given early in the illness.

I wish to thank Colonel Maclean, DGMS Ethiopia, and Lieut.-Colonel Drew, MBE, ADMS BMME, for permission to carry out this research, and for their active help and encouragement. I am also indebted to the staff of the Medical Services Laboratory for their assistance in preparing the virus and carrying out all the agglutination tests, and to the staff of the Ethiopian Army AT and VC for putting the horses at my disposal, and for their invaluable help in preparation of the serum. Finally I must pay tribute to my colleagues of this hospital, RAMC officers, and medical officers of the Friends Ambulance Unit and the USAMC temporarily attached to this hospital, who have all coöperated in the investigation.

Reference.—Durand, P. and Balozet, L. (1941) *Arch. Inst. Pasteur, Tunis*, **30**, 1. (Quoted in *Trop. Dis. Bull.* 1942, **39**, 369.)

Reviews of Books

Handbook of Tropical Medicine

ALFRED C. REED, MD, associate clinical professor of medicine, Stanford University; J. C. GEIGER, MD, director of public health, San Francisco (Stanford University Press. Pp. 188. 9*s.* 6*d.*)

THIS little book was designed as an emergency help to those medical men who during the war or after may be faced for the first time with sufferers from tropical disease. The more important and commoner diseases associated with warm climates are described, particular emphasis being laid on their clinical aspects and on their treatment. There are a few statements which might be reconsidered in later editions. It is a little surprising to read that " emetine is a toxic drug of little value in curing amœbiasis " and that " carbarsone is the drug of choice." The section on the treatment of bacillary dysentery is also a little confused, the dose of sulphaguanidine being given in one place as 0·5–1 g. 2- or 4-hourly, and in another as 0·05 g. per kg. of body-weight 4-hourly. There is no mention of the new stilbamidine series in the treatment of leishmaniasis or trypanosomiasis; in the latter disease gland-puncture, now a common diagnostic procedure, goes unnoticed, as does the use of X rays in the diagnosis of cysticercosis. The book is however not intended to be more than a handbook and provided its limitations are realised it may be of value.

Nelson Loose-Leaf Medicine

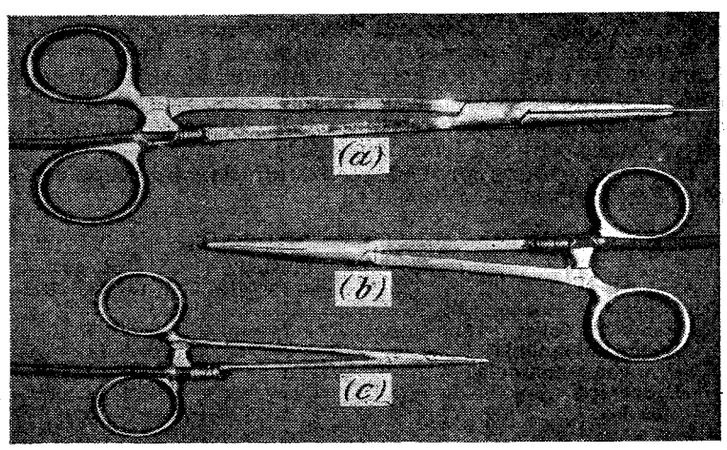
THIS latest batch of renewal pages includes some topical items, such as A. L. Barach's aviation medicine and L. K. Diamond's blood-transfusion reactions. Probably the contribution of most general interest to practitioners is H. A. Riley's monograph on headache and migraine. This runs to eighty pages, exclusive of references, and covers the subject thoroughly. The acute infections are strongly represented. Thus, A. B. Wadsworth contributes a short but inclusive section on virus diseases; knowledge of tetanus and its treatment is brought up to date by W. J. Stone; H. S. Jeck records recent progress in the management of gonorrhœal infections, and J. M. Nielsen writes of epidemic encephalitis. Two rare conditions of great interest are discussed by F. M. Hanger—erythema arthriticum epidemicum (Haverhill fever), which is a type of rat-bite fever caused by *Streptobacillus moniliformis*; and Von Gierke's disease, a form of glycogen disorder in which there is a complete or partial inability of the liver to transform glycogen into dextrose, or possibly dextrose into glycogen.

New Inventions

A DIATHERMY HÆMOSTAT

THE instrument described here should, I think, be more widely known and used at operation. I claim no originality for its design, although I have been unable to find any published reference to it.

Its construction is simple. To the shaft of a pair of Wells forceps near the handle about 10 feet of rubber-covered electric wire is soldered (see figure) and the junction is bound over with plaited silk. I find ordinary electric flex as good as any other cable we have tested. The complete instrument is sterilised by boiling, and when ready for use the lead is connected to the diathermy in the usual way and the hæmostat is clipped to



Three sizes of diathermy hæmostat. The upper one shows a needle being used as a cutting electrode.

the sterile towel beside the operator or assistant, where it is close at hand without the continual fear of it falling to the floor. We have three different sizes of the instrument, the size used depending on the operation and preference of the surgeon. For instance, when controlling bleeding from the prostatic bed the large pair, and in plastic work the fine pair, is used. If the operator requires a cutting electrode all he need do is to place a fine intestinal needle in a shallow groove cut in the jaws of the Wells forceps, which are then clamped and the electrode used with the cutting current (*a* in figure).

The hæmostat can be used for either coagulation or cutting purposes. Its most frequent use will doubtless be coagulation, and some practice and care is required before one recognises its limitations and becomes an adept with it—this is just a word of warning to the beginner. For radical amputations of the breast, block dissections of the neck, prostatectomies, &c., it saves no end of time and bleeding. In many of these cases a competent assistant may use the hæmostat as the operation proceeds, thus dispensing with a mass of Wells forceps and reducing loss of blood. All our operation patients are now connected up to the diathermy as a routine, and so far we have not had any reason to alter this practice, which we adopted some years ago. When bleeding occurs from friable tissues and in situations where ligatures are difficult to place because of the nature of the tissue or the depth at which one is working, this hæmostat cannot be bettered for coagulation purposes. Its greatest usefulness is undoubtedly in extensive operations, but it should prove serviceable in the everyday work of the general surgeon.

Christie Hospital and Holt Radium Institute, Manchester. DAVID AIKEN, MB DUBL.