comparison is possible in the effects of a fall in prothrombin concentration below 10%, which was regarded in the tromexan group with relative equanimity.

None of the cardiac patients receiving tromexan suffered a recurrence of ischaemic pain while in the therapeutic range of 10 to 30% prothrombin. Two patients in the 40 to 50% range sustained further thrombotic episodes, and the return of ischaemic cardiac pain, not amounting to infarction, was always coincident with inadequate dosage. Two of the cardiac cases receiving dicoumarol developed fresh infarctions while ostensibly admirably controlled.

There were marked variations in susceptibility to tromexan. Indeed, a given patient's tolerance may alter widely from day to day, and there is a tendency to sudden escapes from control. It is therefore not desirable to give the drug without laboratory control. No correlation of dosage with weight or age is possible, but an initial prothrombin reading may assist in gauging the size of the loading dose.

Caution is necessary in treating peptic ulcer patients. Benzidine tests on the faeces may be helpful in the control of their treatment.

Summary

Clinical results are recorded in 130 patients suffering from vascular thrombosis and its sequelae.

Ninety-six of these had sustained a cardiac infarct. Sixty received tromexan and 36 dicoumarol.

A scheme for the use of tromexan is proposed and the literature briefly reviewed.

I wish to express my thanks to Dr. H. N. Robson, who suggested this investigation; to the physicians and surgeons of the Northern Hospitals Group, Edinburgh, who permitted access to their patients; and to the staff of the haematological laboratory for technical assistance. The tromexan was supplied by Pharmaceutical Laboratories, Geigy Ltd., Manchester.

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In New York during the 32 years 1918-50 there were 104 fatal injuries from competitive sports, and 73 post-mortem examinations were made. Writing in the *Journal of the American Medical Association*, August 18, page 1506, Dr. T. A. Gonzales discusses the kinds of lethal injury sustained in different sports and their frequency, without, unfortunately, stating the numbers at risk in each activity. There surely cannot be many people in New York who play cricket, for instance, yet one death is recorded in this game—that of a player struck in the abdomen by a ball which ruptured the small intestine and led to acute peritonitis. This must be as rare a cause of death in England as that of the relay runner who ran into a railing alongside the track and ruptured his large bowel. Baseball has the highest total, with 43 deaths, and football (with 22 fatalities) was about level with boxing (21); but surely there are fewer boxers than football players in New York City?

DOSAGE OF PENICILLIN IN WEIL'S DISEASE

BY

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Penicillin has been used for some years in the treatment of Weil's disease (leptospirosis icterohaemorrhagica), and its efficacy, especially in the pre-icteric stage of the disease, is generally accepted. There is, however, wide variation in the dosage recommended. Chang (1946) recommended a total daily dosage of 250,000-300,000 units of sodium penicillin. Patterson (1947) used three-hourly injections of 15,000 units. Suchett-Kaye (1951) used 100,000 units four-hourly and raised the dose to 500,000 units four-hourly if the patient's condition warranted it. The following cases illustrate some of the important clinical aspects of the disease and lend support to the use of a dosage of the order recommended by Suchett-Kaye.

Case 1

A butcher aged 32, who had bathed several times in a canal during the three weeks preceding his illness, was admitted on the sixth day of the disease, having had severe pains in the limbs for five days and frequent vomiting for three days.

He was a big, well-nourished man, obviously ill, with a temperature of 102.6° F. (39.2° C.). He had an erythematous rash on the face and trunk. There was marked suffusion of the conjunctivae, which were bright red. Jaundice was not present. The tongue was coated and dry. Slight neck rigidity was present, but Kernig's sign was negative. The muscles of the thighs and forearms were tender. The liver was not palpable, but he was tender in the right hypochondrium. The spleen was not palpable. His blood pressure was 110/80. The rest of the physical examination was negative. A provisional diagnosis of Weil's disease was made and various confirmatory tests were carried out. The urine contained a moderate amount of albumin, but was otherwise normal. The haemoglobin was 84%; white cells, 2,900 (polymorphs 74%, lymphocytes 22%, monocytes 4%); serum bilirubin, less than 0.5 mg. per 100 ml.; blood urea, 165 mg. per 100 ml. N.P.N., 97 mg. per 100 ml. A radiograph of the chest was normal. Blood taken at the time of admission for agglutination for *Leptospira icterohaemorrhagiae* was later reported as negative.

Soon after admission, before penicillin was started, his temperature rose to 104.8° F. (40.5° C.) and he became delirious and hallucinated, seeing people moving on the wall. Penicillin was therefore begun in doses of 30,000 units four-hourly by intramuscular injection. Thirty-six hours later his condition had not improved much, though his temperature was a little lower and he was no longer hallucinated. He was very drowsy. The dosage of penicillin was therefore increased to 100,000 units six-hourly. After this his temperature fell to normal over the next 48 hours and his clinical condition rapidly improved. This dosage was continued for eight days until a total of 3,500,000 units had been given. Convalescence was uneventful apart from a mild attack of gout in the left great toe on the eleventh day of the disease. He had never had gout before, but his mother suffered from it.

Blood taken on the eleventh day of the disease gave positive agglutinations for *L. icterohaemorrhagiae* at a dilution of 1/3,000.

Case 2

A hosiery packer aged 17, who had often bathed in a river during the month preceding his illness and whose workplace was infested with rats, was admitted on the third day

of the disease complaining of headache, feverishness, and severe pains in the back and limbs. His mother said that he had become increasingly drowsy and mentally confused since the onset of the illness three days before.

He was a well-nourished boy. His temperature was 101° F. (38.3° C.). He was drowsy and uncooperative, resenting examination. There was no rash, but the conjunctivae were markedly inflamed. Jaundice and neck rigidity were not present, and Kernig's sign was negative. The liver and spleen were not palpable. There was no hepatic tenderness. The remainder of the physical examination was negative. His blood pressure was 120/80. Lumbar puncture gave a clear colourless fluid with a normal pressure. The C.S.F. examination showed: total protein, 40 mg. per 100 ml.; globulin, slightly increased; chlorides, 728 mg. per 100 ml.; cells, 24 per c.mm. (mainly lymphocytes). The blood showed a slight leucocytosis of 11,200 per c.mm. (polymorphs 86%, lymphocytes 12%, monocytes 2%). The urine contained a trace of albumin, but was otherwise normal. The blood urea was 55 mg. per 100 ml. X-ray examination of the chest was normal.

Penicillin, 250,000 units three-hourly by intramuscular injection, was begun. The temperature, after an initial rise to 104° F. (40° C.) became normal after 12 hours, and remained so. A total of 14,000,000 units of penicillin was given over the next seven days. Convalescence was uneventful and he made an uninterrupted recovery. Blood taken on the fourth day of the disease gave negative agglutinations for *L. icterohaemorrhagiae*, but blood taken on the eleventh day was positive at 1/3,000 for *L. icterohaemorrhagiae* and at 1/300 for *L. canicola*.

Case 3

A schoolboy aged 13, who had no known contact with rats but who had recently paddled in a stream several times, was admitted with a seven-day history of malaise, pyrexia, anorexia, and vague pains in the limbs. His eyes had become red on the day of admission. He was slightly lethargic and had a temperature of 101° F. (38.3° C.). The tongue was coated. Enlarged glands were present in the neck, axillae, and groins. The conjunctivae were moderately inflamed. The liver and spleen were not palpable. There was no meningism. His blood pressure was 110/75; E.S.R., 10; white cells, 6,000 (polymorphs 54%, eosinophils 4%, lymphocytes 42%); Paul-Bunnell reaction, titre 1 in 32. The urine was quite normal and contained no albumin.

He did not appear at all ill, and after 24 hours in hospital all his symptoms disappeared and the temperature became normal without any treatment. The true nature of his illness was not clear until the blood agglutinations, from a specimen taken on admission, were reported as positive at 1/10,000 for *L. icterohaemorrhagiae*. He was then given a four-day course of 250,000 units of penicillin three-hourly.

Case 4

This patient, a sheet-metal worker aged 18, had an unusual history. He had been feeding his hens 10 days before admission, when a rat ran up his trouser leg and bit him on the right buttock. Seven days later he had aching limbs and an occipital headache, was feeling cold, and was shivering. He later developed dull upper abdominal pain, and on the tenth day after the bite he became jaundiced and was admitted to hospital. His urine had been dark and his stools rather pale.

On examination he was seen to be a well-nourished youth with a moderate degree of jaundice. A small healing wound was present on the right buttock close to the sacrum. His temperature was 102° F. (38.9° C.), pulse 130 a minute, and respirations 27 a minute. The conjunctivae were moderately inflamed. The tongue was clean. No rashes were present. There was no abdominal tenderness. The liver, spleen, and lymph glands were not enlarged. The remainder of the physical examination was negative. The urine contained a large amount of albumin and bile; granular and

cellular casts were present. Blood urea was 134 mg. per 100 ml.; serum bilirubin, 16.2 mg. per 100 ml.; thymol turbidity, 3 units. An initial dose of 100,000 units of penicillin was given, followed by 50,000 units three-hourly by intramuscular injection, but his condition deteriorated. He became increasingly drowsy and jaundiced over the next seven days and had epistaxis, haemoptysis, and melaena. Intravenous glucose, saline, and vitamin K were given, but he died on the seventh day from what was clinically liver failure.

At necropsy the liver, spleen, and kidneys were pale, soft, and swollen. The lungs showed considerable oedema, with a macroscopic appearance suggestive of a haemorrhagic bronchopneumonia. There was flattening of the convolutions of the brain with engorgement of the superficial vessels. A smear taken from the liver showed many active leptospire on dark-ground illumination. Microscopically the brain showed generalized vascular engorgement. The liver and kidneys showed a fairly marked degree of cloudy swelling but were not grossly abnormal. The lungs showed a haemorrhagic bronchopneumonia. Blood taken on admission gave positive agglutinations for *L. icterohaemorrhagiae* at 1/10,000.

Discussion

As many writers, notably Broom and Alston (1948), have now pointed out, infection with *L. icterohaemorrhagiae* may be commoner than is generally recognized. It is by no means confined to those who are exposed to infection as an industrial hazard. Agglutination tests for this organism might well form part of the routine investigation of a case of P.U.O., especially in those parts of the country where the disease is known to be endemic. It is important that the diagnosis should be made and treatment begun as soon as possible (Smith, 1949).

The diagnosis in the first instance must be a clinical one, because jaundice, if it occurs, is a late phenomenon; because there may be a leucopenia rather than a leucocytosis in the early stages; because albuminuria may at first be slight or even absent; and because the agglutinations do not become positive until about the ninth day (Smith, 1949). The blood urea and non-protein nitrogen may begin to rise early, especially in the more severe cases. Smith states that the organism can always be recovered in the first four days by intraperitoneal injection of a guinea-pig with fragmented blood-clot, but the method takes time. Examination of the cerebrospinal fluid may help, as this is frequently altered (Cargill and Beeson, 1947), the main change being in the cell count, which may rise to 50–300 cells per c.mm., with varying proportions of granulocytes and lymphocytes (Buzzard and Wylie, 1947).

Clinically, Weil's disease should be considered in influenza-like illnesses in which there is marked reddening of the conjunctivae and severe pains in the limbs. The muscles may be distinctly tender, and slight neck rigidity may be present but not Kernig's sign (Buzzard and Wylie, 1947). The disease should also be thought of in cases presenting as aseptic meningitis, as in Buzzard and Wylie's series. Patterson (1947) noted that eye complications in the form of iritis, iridocyclitis, and uveitis sometimes occur one month to one year after the acute infection, so that if the original illness is not diagnosed the true nature of these complications may be difficult to explain.

Bulmer (1945) stated that the value of penicillin in Weil's disease can be assessed only by observing its effect during the pre-icteric phase. Cases 1 and 2 fall into this category. Case 1 showed little response to 30,000 units of penicillin four-hourly. The response on raising the

dose to 100,000 units six-hourly was quite dramatic and a rapid improvement set in. Case 2 received 250,000 units three-hourly. After the first dose there was a sharp rise of temperature from 100 to 104° F. (37.8 to 40° C.), the patient became violent and abusive, and he had to be given a sedative. Thereafter he improved rapidly and the temperature was normal by next morning. Suchett-Kaye drew attention to a reaction resembling the Jarisch-Herxheimer reaction which may occur at the beginning of treatment of Weil's disease with penicillin.

Case 1 showed a slight rise of temperature, which might or might not have been of significance. In Case 2 the reaction was marked. Prognostically it may be regarded as a favourable sign, as it may mean that the strain of organism is sensitive to penicillin and is being destroyed. Case 4 showed no such reaction, and he went steadily downhill. He was jaundiced on admission, but his general condition was good. He received 100,000 units of penicillin initially and 50,000 units three-hourly thereafter. Necropsy revealed two striking features. The first was that neither macroscopically nor microscopically did the brain, lungs, liver, or kidneys appear to be irreparably damaged. The second was that a smear from the liver showed so many leptospire. One was left with the impression that had it been possible to destroy the organisms a few days earlier the outcome might not have been fatal.

Case 3 had recovered spontaneously, but a course of 250,000 units of penicillin three-hourly was given for four days with the object of avoiding the carrier state or the possibility of smouldering renal damage. Patterson found that in his cases a large number of leptospire continued to be excreted in the urine for many weeks after clinical recovery.

Summary and Conclusions

Four cases of Weil's disease treated with penicillin are described, including one which was presumably contracted by actual rat-bite.

The diagnosis in the first instance is a clinical one, and treatment should be started without delay.

The dosage of penicillin recommended is 250,000 three-hourly by intramuscular injection. If there is no favourable response after 24 hours it may be advisable to try doubling the dose. Penicillin should be continued until the patient is clearly out of danger—usually at least a week.

A rise of temperature after the initial doses of penicillin would appear to be a favourable sign.

A four-day course of penicillin in this dosage might reasonably be given to spontaneously recovering cases in order to avoid the carrier state.

I wish to thank Dr. J. P. W. Jamie, Dr. W. D. Jeans, and Dr. S. E. Tanner for permission to use their cases.

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A British Standard for hospital bedside lockers has been prepared by a technical committee representative of medical and nursing interests and manufacturers of wood and metal lockers. It indicates the kind of articles—for example, food, toilet requisites, personal effects, etc.—for which the locker should provide separate accommodation and the minimum space to be allotted to each kind of article.

ERGOT POISONING AT PONT ST. ESPRIT

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The outbreak of poisoning at Pont St. Esprit has drawn attention again to ergot of rye. Old accounts are concerned chiefly with repeated poisoning; here absorption of the poison was a single though major event. The frequent occurrence of mental symptoms has again called to mind the old name of the disease, "Mal des Ardents."

Alimentary poison was immediately suspected because of the large number of people attacked. It was easy to incriminate the bread, the more so because animals which ate some of the poisoned bread died making convulsive movements. From the first, ergotism seemed very probable. Setting aside the problems posed by the presence in bread of this poison, alone or associated with others, we shall briefly describe the symptoms observed during the first 15 days. The disturbances can be divided into four phases.

The First Symptoms

Absorption took place during a single day (for most, August 15). The bread certainly contained a high proportion of poison, for the amounts eaten were often very small. The first symptoms appeared after a latent period of 6 to 48 hours. In this first phase, the symptoms were generalized, and consisted in a depressive state with anguish and slight agitation. After some hours the symptoms became more clearly defined, and most of the patients presented with digestive disturbances. Particularly notable was the state of nausea, with diffuse abdominal pain; less often noted were vomiting and diarrhoea (in about 30% of cases). There was often a sensation of distressing pharyngeal constriction.

Disturbances of the autonomic nervous system accompanied the digestive disorders—gusts of warmth, followed by the impression of "cold waves," with intense sweating crises. We also noted frequent excessive salivation. The patients were pale and often showed a regular bradycardia (40 to 50 beats a minute), with weakness of the pulse. The heart sounds were rather muffled; the extremities were cold. The temperature of most of the patients was low, both in the morning and in the evening (36.5–36.8° C. (97.8–98.2° F.)). Arterial tension was in general rather low. In some patients we noted a disquieting fall in pressure during fainting attacks. Mydriasis was very frequent, with diminution of the light reflex. Some patients complained of pain at the nape of the neck, more rarely of true headaches.

Thereafter a constant symptom appeared—insomnia lasting several days. The digestive disorders quickly became worse, and there was diffuse or subhepatic abdominal pain, with burning sensations throughout the whole of the digestive tract. They were accompanied by frequent colicky pains, and some experienced sensations of burning at the anus. A state of giddiness