HUMAN HYPERLIPAEMIA AND HYPERCHOLESTEROLAEMIA RAPID CORRECTION WITH A SULPHATED POLYMANNURONIDE*

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The "clearing" action of heparin on alimentary lipaemia (Hahn, 1943) and the associated degradation of large lipoprotein molecules (Graham *et al.*, 1951) were established some time ago and are now attributed to the activation or release of a tissue lipolytic enzyme, the so-called "lipoprotein lipase" (Korn, 1958). The further demonstration that heparin can diminish exogenous or endogenous hypercholesterolaemia in animals (Constantinides *et al.*, 1953; Friedman and Byers, 1953) and that it will decrease the development of atherosclerosis in rabbits fed cholesterol (Constantinides *et al.*, 1953; Horlick and Duff, 1954) enhanced the rationale for the clinical use of this principle in various types of blood lipid anomalies.

Unfortunately, however, heparin has been found to be only a partially effective agent in the treatment of human lipaemias. While numerous investigators have confirmed that it can decrease lactescence and produce qualitative changes in the ultracentrifugal or electrophoretic lipoprotein pattern of the serum, its action in lowering the actual concentration of any elevated serum lipid, particularly cholesterol, is inadequately documented and has been found at best to be moderate and erratic, even when it is given by continuous intravenous infusion (Basu and Stewart, 1950; Block *et al.*, 1951; Lever *et al.*, 1955).

It therefore seemed desirable to search for a more potent antilipaemic agent than heparin, and, since this substance belongs to the chemical group of sulphated polysaccharides, a large series of such compounds were synthesized and screened for antilipaemic activity (Constantinides *et al.*, 1954). Of the numerous sulphated polysaccharides screened in that study, several proved to have antilipaemic properties, in agreement with other sporadic observations (Waldron and Friedman, 1948; Brown, 1952; Glazko *et al.*, 1954; Besterman and Evans, 1957); but one class, the sulphated derivatives of seaweed (alginic) polysaccharides with a mannuronic acid repeat unit, presented the greatest interest. They displayed the most pronounced antilipaemic activity, without toxicity, in short-term rat (Constantinides *et al.*, 1954) and rabbit (Forbes and Petterson, 1953) experiments; they also proved far superior to heparin both in preventing lipaemia in acute rat experiments (Schuler *et al.*, 1957) and in attacking a hypercholesterol-

aemia of long standing in chronic rabbit experiments (Gutmann and Constantinides, 1955; Constantinides *et al.*, 1956; Constantinides and Saunders, 1958a)—thus arresting the progress of pre-established atherosclerosis. So far as can be ascertained from animal work undertaken to date, sulphated polymannuronides attack a lipaemia both by activating the lipoprotein lipase and by stimulating the reticulo-endothelial system (Constantinides and Saunders, 1958b), whereas heparin acts only by the former mechanism.

The present study set out to discover whether sulphated polymannuronides can attack human lipaemias as effectively as animal ones. To this end, 15 selected cases of hyperlipaemia and hypercholesterolaemia were admitted to hospital, placed on a constant lipid and calorie intake, and, after a suitable control period, given intravenous or intramuscular "paritol" (a purified brand of sulphated polymannuronides) for various periods of time. Daily serum lipid values were determined during the treatment period as well as during a pre-treatment and post-treatment interval.

Materials and Methods

Lipid Studies with Paritol-C, an Intravenous Preparation

Paritol-C was given twice daily, intravenously, at 5 mg./kg. per injection, for five days to 10 male patients aged 34 to 70, with a serum total lipid range of 1,000–2,400 mg./100 ml. and a serum cholesterol range of 280–600 mg./100 ml. Of these cases, six were survivors of a proved myocardial infarction, two were hypothyroid, one had a familial lipaemia, and one had an idiopathic lipaemia. The two injections were administered at 8.50 a.m. (just before breakfast), and at 4.50 p.m. (just before supper), very slowly (1 ml. of a 10% solution per minute). Serum total lipids, turbidity, total cholesterol, and—in eight cases—phospholipids were determined every morning in blood samples obtained at 8.40 a.m.—that is, before breakfast and just prior to the morning injection. In addition, serum turbidity was determined every afternoon in postprandial blood obtained at 4.50 p.m. Case 5 constituted an exception, since prior to the usual treatment he received three injections of 1.5, 3, and 4.5 mg./kg., respectively, as well as 10 mg./kg./day (as a single injection) on three successive days.

Serum total lipids were estimated gravimetrically with a modified Bloor (1939) technique (employing acetone-ethanol as the primary extracting solvent), turbidity as previously (Constantinides *et al.*, 1956), and cholesterol by the method of Sperry and Webb (1950). Phospholipids were calculated from the lipid phosphorus values obtained after Youngburg and Youngburg (1930).

Total calorie intake and total lipid intake were kept constant from day to day and from meal to meal, throughout the entire investigation (treatment as well as pre- and post-treatment control periods). Daily total calorie intake was fixed at slightly above basal from height-age tables, while daily total lipid intake was fixed at 0.76 g./kg./day. The composition of the ingested fat was that of the average North American diet, care being taken to maintain approximately the same proportion of saturated to unsaturated triglycerides throughout the investigation. The duration of the pre-treatment control period was five days, while that of the post-treatment control interval was usually longer.

Lipid Studies with Paritol-M, an Intramuscular Preparation

Paritol-M was given to five male patients (Cases 11–15) aged 44 to 68 at daily dosages varying from

*This study was presented, in part, at the annual meeting of the Canadian Society for Clinical Investigation at Vancouver, B.C., on January 22, 1959.

FIG. 1

1.25 to 10 mg./kg. and for periods varying from 6 to 22 days, with the purpose of determining its minimum effective dosage and its efficacy on more prolonged administration. The range of serum total lipids in this series was 1,100–1,600 mg./100 ml., that of serum cholesterol 270–430 mg./100 ml. Of these cases, two were survivors of a myocardial infarction with recurrent angina, two had manifestations of peripheral atherosclerosis (carotid artery syndrome and beginning gangrene of the toes, respectively), and one had an idiopathic lipaemia. Their general management was as in the preceding (intravenous) series, with the following exceptions: (a) only serum total lipids and cholesterol were determined, in fasting morning blood

FIG. 2

FIG. 3

FIG. 4

samples, (b) total lipid intake was fixed at 1.2 g./kg./day. For comparison, two of these cases were also given intramuscular injections of heparin (Connaught's), at 1.25–2.5 mg./kg./day, for 6 to 10 days (before and after the paritol period, respectively).

Non-lipid Studies

To assess the general systemic effects of paritol apart from its antilipaemic action, the following studies were made in most cases, before, during, and after treatment: (a) *Blood*: Haemoglobin, differential count, erythrocyte sedimentation rate, serum proteins (total, albumin,

globulin), clotting and prothrombin time before and 1, 6, and 24 hours after drug injection. (b) *Liver-function tests*: Serum bilirubin (direct and indirect), alkaline phosphatase, thymol turbidity, cephalin-cholesterol flocculation, bromsulphalein excretion at 30 minutes. (c) *Kidney*: serum non-protein nitrogen, complete urinalysis. (d) *E.C.G.* Daily body weight, blood-pressure, pulse, and temperature were recorded throughout every patient's stay in hospital.

Results

The 10 Cases Given Intravenous Paritol-C

Figs. 1–3 give details of this group of cases. To save space, data from only the first eight are presented graphically: Cases 1–4 are grouped together in Fig. 1 and Cases 6–8 in Fig. 3. Furthermore, since the serum turbidity response to treatment was identical in almost all cases, only two turbidity figures are presented—those of Cases 3 (Fig. 1) and 5 (Fig. 2)—to serve as examples of all the others.

It can be seen at a glance that in all of these cases there was marked response to treatment by one or more criteria, the elevated serum lipids dropping rapidly towards normal values during the injection period and returning partially or completely to their previous high levels upon withdrawal of the drug. An exception to this general pattern was seen in Cases 6 and 7 (the two hypothyroid patients), whose serum cholesterol response to treatment was somewhat delayed when compared with the others.

If it is considered that serum with turbidity values greater than approximately 15 was visibly milky, a study of Case 3 (Fig. 1) shows that in the pre-treatment period the turbidity was swinging daily, the serum being least turbid every morning, after the night's fast, and becoming most turbid every afternoon, postprandially.

FIG. 5

FIG. 6

LEGENDS

FIGS. 1 (Cases 1–4), 2 (Case 5), and 3 (Cases 6–8).—The black boxes indicate the intravenous paritol-C treatment periods. With the exception of Case 5, all others received I.V. 5 mg./kg. of this drug twice daily for five days. Case 5 received in succession three single daily injections of 1.5, 3, and 4.5 mg./kg., respectively, then 10 mg./kg. once daily for three consecutive days, and finally 5 mg./kg. twice daily for six days. Serum turbidity is expressed in Klett units (K.U.)—that is, direct readings of the Klett-Summerson colorimeter, while serum total lipids and serum cholesterol are expressed as mg. per 100 ml. of serum. All values are plotted synchronously.

FIGS. 4–6 (Cases 11, 12, and 15 respectively).—The black boxes indicate the intramuscular paritol-M treatment periods, while the shaded boxes in Fig. 6 indicate the intramuscular heparin treatment interval. Dosages of drugs varied as recorded in the graphs. Serum total lipids and cholesterol are expressed and plotted as in the preceding intravenous series.

Paritol treatment promptly suppressed both the fasting and the postprandial lactescence, keeping the serum clear all day throughout its administration, this effect being reversed immediately upon withdrawal of the drug. The marked depression of serum turbidity values during treatment, exactly as illustrated in Cases 3 and 5 (Figs. 1 and 2), was obtained in all except Case 10—in which the serum was continuously clear even before treatment was started.

If it is further considered that the upper "normal" limit of serum total lipids is 800–900 mg./100 ml. and that of serum cholesterol 240 mg./100 ml., it can be seen that this treatment caused a return of the total lipids to normal values within 24 hours in seven cases (Nos. 1–6 and 8); it caused a return of the cholesterol to normal within 48 hours in four cases (Nos. 1, 2, 4, and 5) and depressed it significantly within six days in another four cases (Nos. 3 and 6–8).

Cases 9 and 10 were those with only partial or minimal response to treatment. Case 9 showed a marked turbidity response but no significant depression of total lipid or cholesterol values, which were close to normal, however, before treatment began. Case 10 displayed only a slight and transitory total lipid depression and deserves special attention, since, in addition to his hyperlipaemia, this patient also had tuberous xanthomatosis and was suffering from rheumatoid arthritis, requiring continuous glucocorticoid treatment (5 mg. of prednisone t.i.d.). Thus in this case paritol was given in the presence of steroid treatment.

In the eight cases in which they were studied (Nos. 1–6, 8, and 10) the serum phospholipids were found to parallel closely the changes of serum cholesterol levels. Thus, in all except Case 10, paritol caused a significant reduction of the serum phospholipid value, with a slow return towards the previous level after withdrawal of the drug. Since, however, the cholesterol was reduced more than the phospholipid, the cholesterol:phospholipid ratio decreased significantly in most instances during treatment.

The 5 Cases Given Intramuscular Paritol-M

The intramuscular preparation of paritol had a prompt and pronounced antilipaemic effect in all five cases, with a sustained action over the more prolonged periods during which it was tested (up to three weeks). In view of this uniform response, data from only three of the five cases are presented graphically (Figs. 4–6).

Dosage studies in Cases 12 and 13 indicated that the minimum effective dosage with regard to serum cholesterol depression was approximately 2.5 mg./kg. once daily. Even smaller amounts, however, seem to affect serum total lipids and turbidity, as shown by untabulated data. The full cholesterol-depressing effect took up to 72–96 hours for its manifestation, at the dosages tested.

In the last two cases the minimum effective dosage of paritol was compared with equivalent amounts of heparin, administered in identical fashion and given either before (Case 15) or after (Case 14) the polymannuronide. As can be seen in Fig. 6, given at 2.5 mg./kg./day for six days, paritol-M significantly depressed both serum total lipid and cholesterol levels, whereas heparin failed to influence either of these two serum constituents. Similar results were obtained in Case 14.

Non-lipid Studies in All Cases

Blood.—At all dosages and routes given, paritol did not alter the blood haemoglobin, cell numbers, or morphology, and it did not affect the erythrocyte sedimentation rate or the serum proteins. A single intravenous dose of 5 mg./kg. was moderately anticoagulant, prolonging the Lee-White clotting-time to 20–40 minutes one hour after injection, with a return to normal five hours later. This dosage level usually also depressed the prothrombin time to 70–80% of normal one hour after injection, with a return to normal within six hours, except in the two hypothyroid patients in whom the depression was greater and lasted longer. Given at 3.5 mg./kg. intramuscularly or less, however, the drug had no effect on the Lee-White clotting-time or prothrombin time. There was no effect on the bleeding-time under any circumstances.

Liver.—Paritol did not alter hepatic function as judged by any of the six criteria employed. In two cases, however, that were admitted with a moderately depressed hepatic function before treatment was started (Cases 6 and 11) a further slight rise of the 30-minute bromsulphalein retention (from 14% to 31% and from 12% to 27%, respectively), without a change in any other hepatic parameter, occurred during the injection period.

Kidney.—As judged by the consistently normal N.P.N. and urinalysis, the treatment did not alter renal function in any case.

General Clinical Findings.—Blood-pressure, pulse, and temperature remained unaffected by the drug. There was no significant change of body weight during treatment, except in Cases 5 and 12, in which there was a slight loss of weight (2 and 1 kg., respectively) during the period of high-dosage injection.

Despite occasional side-effects in half the cases of the intravenous series at the high-dosage level (5 mg./kg. twice daily), the drug was on the whole well tolerated, and almost all patients expressed the desire to continue this treatment after discharge. Side-effects at the high intravenous dosage consisted of transitory paraesthesiae (Cases 1–5) ranging from "tingling" or "pressure" sensations in tongue, scalp, or extremities to "muscle pains"; these appeared from one-half to one hour after injection (usually only in the initial treatment period), and lasted for a few minutes. Patient 5, who for three days received the highest amount of paritol ever given in a single intravenous injection in this study (10 mg./kg.), claimed that he experienced a fainting spell after three such injections. A slight loss of scalp hair occurred in the same patient at about a month after treatment, lasting for a few weeks, but it was rapidly and completely restored.

There were no side-effects of any sort at the lower-dosage levels 2.5 mg./kg./day or less). The intramuscular injections occasionally produced slight local discomfort when given in high concentration or large volume, but small doses caused no complaints.

All patients who were admitted with symptoms of vascular origin claimed marked relief or complete disappearance of these symptoms during treatment and for several weeks thereafter. This was claimed of angina pectoris (Cases 2, 3, 5, 6, 8, 9, 10, 14, and 15), intermittent claudication (Cases 5 and 9), pain from incipient gangrene of the right great toe (Case 12), and right-sided recurrent paresis and numbness in a carotid artery syndrome (Case 13). During treatment the

nitroglycerin requirements of most angina cases greatly decreased or disappeared, local circulation visibly improved in the afflicted toes of patient 12 (as judged by colour, temperature, and dorsalis pedis pulsation), and there was marked acceleration in the slow cerebration of the patient with the carotid syndrome. It should be pointed out, however, that as the paritol injections were not controlled by placebo injections the above improvements in symptoms of vascular origin may have been entirely subjective.

Discussion

The above results show that paritol caused a very rapid return to normal or a marked reduction of the elevated serum total lipid and cholesterol values in the majority of the hyperlipaemic patients to whom it was given. The antilipaemic effect was obtained with the intramuscular as well as with the intravenous route of administration, it was sustained for the duration of the treatment, and it was reversed only gradually after withdrawal of the drug. In the most responsive cases the dramatic action of this principle on hyperlipaemia was comparable to the effect of insulin on hyperglycaemia. Indeed, in one instance high amounts of the drug depressed the serum cholesterol value below the generally accepted lower limit of normal (cf. Case 12).

Compared with heparin, milligram for milligram, paritol proved by far the superior agent for reducing cholesterol and total lipid values, thus confirming in the human the results of animal experiments under both acute (Schuler *et al.*, 1957) and chronic conditions (Constantinides *et al.*, 1956). The effectiveness of paritol will be further appreciated if it is considered that it successfully cleared the serum turbidity of the persons with coronary disease, a group whose serum lactescence has been reported to be refractory to the clearing action of heparin (Block *et al.*, 1951).

At higher dosages (5 mg./kg. or more), paritol exhibited its known moderate anticoagulant action and occasional side-effects (Sollmann, 1957), but at lower dosages (3.5 mg./kg. or less) it showed neither anticoagulant action nor side-effects, while maintaining its full antilipaemic activity—in agreement with findings in animals (Constantinides and Saunders, 1958b). Since alopecia and other side-effects are encountered only with high anticoagulant dosages of sulphated polysaccharides (including heparin) (Fischer *et al.*, 1953; Sollmann, 1957), it can be anticipated that low subanticoagulant dosages of paritol would permit effective long-term control of hypercholesterolaemia without any undesirable manifestation. Repository preparations requiring only one or two intramuscular injections a week would seem the ideal method of administration for chronic treatment.

The precise mechanism through which sulphated polymannuronides depress cholesterol level in the blood is not yet known. Though they have been shown to activate the lipoprotein lipase (Constantinides *et al.*, 1954) and to stimulate removal of lipids by the reticulo-endothelial system (Constantinides and Saunders, 1958b), a detailed fat balance study is needed in order to determine the fate of the lipids they drive out of the blood-stream. From the data obtained so far it appears that—at least with the intravenous route of administration—the serum concentration of triglycerides decreases first, followed after a slight time-lag by the drop in cholesterol concentration.

The great majority of positive results were obtained in the absence of any detectable change of hepatic function or body weight. In the two cases where the pre-existing hepatic dysfunction was somewhat aggravated by the high-dosage treatment, as well as in the two cases that showed a slight loss of body weight under the same circumstances, there was no correlation whatsoever between these phenomena and the lipid movements. Thus, serum lipid depression in these cases occurred only *after* hepatic function improved or well *before* loss of body weight was manifested, respectively.

It is of interest that the only refractory case of this study was maintained on glucocorticoids before and during the paritol treatment. Since it has been found in animals that glucocorticoid-supported lipaemias are resistant to the clearing action of heparin (Constantinides *et al.*, 1955), the concurrent steroid treatment may have been responsible for the refractory nature of that case. On the other hand, as this case also presented tuberous xanthomata, it may well be that some or all hypercholesterolaemias associated with xanthomatosis are resistant to the action of sulphated polymannuronides, possibly because of an unresponsive reticulo-endothelial system. More work is needed to clarify this problem.

Though the marked subjective improvements claimed by most patients should not be overlooked, they cannot be assessed critically in the present study, which was not designed for that purpose. A placebo-controlled investigation, using the "double blind" technique and objective end-points, will be necessary before any conclusions on vascular effects can be drawn.

In overall appraisal, paritol offers great promise as a treatment for lipaemias which are resistant to heparin or other agents and for cases where an immediate reduction of blood lipids is required. Further research is indicated on its precise mechanism of action and on the most responsive types of lipaemias.

Summary

Paritol, a synthetic sulphated polysaccharide with a mannuronic acid building block, was given under conditions of controlled calorie and lipid intake to 15 hospital cases of hyperlipaemia and hypercholesterolaemia for periods ranging from five days to three weeks. Serum total lipids, cholesterol, turbidity, and in most cases phospholipids were determined daily throughout the treatment period as well as during pre-treatment and post-treatment control intervals.

This principle proved capable of exceedingly rapid and intense action on the elevated serum lipids, both intravenously and intramuscularly. It caused a return to normal of the total lipid values within 24 hours and of the cholesterol values within 72 hours in 10 cases, while reducing them greatly within a slightly longer interval in another four cases. The antilipaemic effect was sustained for the duration of the treatment, and it was gradually reversed after withdrawal of the drug.

The minimum effective cholesterol-depressing dose by the intramuscular route was found to be 2.5 mg./kg./day. At this dosage paritol showed no anticoagulant action or side-effects, and it displayed a far greater antilipaemic activity than equivalent amounts of the natural sulphated polysaccharide heparin.

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REFERENCES

- Basu, D. P., and Stewart, C. P. (1950). *Edinb. med. J.*, **57**, 596.
 Besterman, E. M. M., and Evans, J. (1957). *Brit. med. J.*, **1**, 310.
 Block, W. J., Barker, N. W., and Mann, F. D. (1951). *Circulation*, **4**, 674.
 Bloor, W. R. (1939). *Physiol. Rev.*, **19**, 557.
 Brown, W. D. (1952). *Quart. J. exp. Physiol.*, **37**, 215.
 Constantinides, P., Cairns, A., and Werner, A. (1954). *Arch. int. Pharmacodyn.*, **99**, 334.
 — and Saunders, P. (1958a). *A.M.A. Arch. Path.*, **65**, 360.
 — (1958b). *Ibid.*, **65**, 499.
 — and Wood, A. (1956). *Ibid.*, **62**, 369.
 — Szasz, G., and Darrach, M. (1955). *Canad. J. Biochem.*, **33**, 226.
 — and Harder, F. (1953). *A.M.A. Arch. Path.*, **56**, 36.
 Fischer, R., Bircher, J., and Reich, T. (1953). *Schweiz. med. Wschr.*, **83**, 509.
 Forbes, J. C., and Petterson, O. M. (1953). *Proc. Soc. exp. Biol. (N.Y.)*, **83**, 665.
 Friedman, M., and Byers, S. O. (1953). *J. exp. Med.*, **97**, 117.
 Glazko, A. J., Strong, J., and Kazenko, A. (1954). *Fed. Proc.*, **13**, 55.
 Graham, D. M., Lyon, T. P., Gofman, J. W., Jones, H. B., Yankley, A., Simonton, J., and White, S. (1951). *Circulation*, **4**, 666.
 Gutmann, N., and Constantinides, P. (1955). *A.M.A. Arch. Path.*, **59**, 717.
 Hahn, P. F. (1943). *Science*, **98**, 19.
 Horlick, L., and Duff, G. L. (1954). *A.M.A. Arch. Path.*, **57**, 417.
 Korn, E. D. (1958). In *Chemistry of Lipides as Related to Atherosclerosis*, A Symposium, edited by I. H. Page, p. 169. Thomas, Springfield, Ill.
 Lever, W. F., Herbst, F. S. M., and Hurley, N. A. (1955). *A.M.A. Arch. Derm. Syph.*, **71**, 150.
 Schuler, W., Müller, G., and Maier, F. (1957). *Schweiz. med. Wschr.*, **87**, 787.
 Sollmann, T. (1957). *A Manual of Pharmacology*, 8th ed., p. 573. Saunders, Philadelphia.
 Sperry, W. M., and Webb, M. (1950). *J. biol. Chem.*, **187**, 97.
 Waldron, J. M., and Friedman, M. H. F. (1948). *Fed. Proc.*, **7**, 130.
 Youngburg, G. E., and Youngburg, M. V. (1930). *J. Lab. clin. Med.*, **16**, 158.

"The triennial reports of the [joint Bethlem Royal Hospital and Maudsley] hospital have two objects. The first is the provision of statistics relating to the medical administration of the hospital departments. The second is the provision of demographic, social, and diagnostic data on the patient population attending the hospital. While these two objects have much in common, there is a basic difference between them. The administrator is concerned with the amount of work done by the various departments of the hospital in providing treatment for its patients. This work is most conveniently assessed by taking into account the total number of admissions of patients to (or their discharges from) a department during a given time. On the other hand, statistics relating to demography, social factors, and diagnoses need for the most part to be based on the number of individual patients that attend the hospital, irrespective of the number of occasions on which they are admitted. As compared with previous reports, the present report puts rather more emphasis on the clinical and rather less on the administrative aspects of the data. One of the principal objects of this change is to allow the presentation of data concerning the whole population attending the hospital. Most of the published data on the statistics of mental illness in Great Britain deal only with in-patients. But psychiatric hospitals are becoming increasingly concerned with out-patient care and treatment. Moreover, because of changes in administration and in treatment, many cases that a few years ago would have been treated as in-patients are now treated as out-patients. There is consequently an increasing need for clinical statistics on all patients under care at psychiatric hospitals and not merely on the in-patients. It is in the belief that hospital statistics of this kind will have a growing value that the present editor has emphasized the clinical aspects of the data." (*Triennial Statistical Report: Years 1955-7*. Bethlem Royal Hospital and the Maudsley Hospital.)

TOTAL PARALYSIS REGIME IN SEVERE TETANUS

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In an era of remarkable therapeutic advances the search for an effective treatment of severe tetanus has been disappointing. In New Orleans, Creech *et al.* (1957) demonstrated a small and steady decline in mortality over the past fifty years, but were unable to relate this fall to the many changes in treatment. In Malaya tetanus is common: from 1952 to 1956 an average of 20 patients with tetanus (excluding neonatal tetanus) have been admitted each year to the Penang General Hospital. About one-third of these victims were children. The mortality was 40%, varying yearly from 20% to 50%. We soon recognized that patients with mild tetanus recover with conservative treatment.

Our concern in this paper is confined to non-neonatal severe cases—patients who develop generalized spasms that stop respiration despite conservative treatment. In 1957 we started treating such patients with the total paralysis regime (T.P.R.), consisting of tracheostomy, total paralysis of skeletal muscles, and intermittent positive- or positive/negative-pressure artificial respiration. In reviewing our experience with this treatment, the two main questions we wish to consider are: (1) How may severe tetanus be recognized at the outset? (2) Is the T.P.R. effective in treating severe tetanus?

Material and Methods

All patients aged over 6 with tetanus were admitted under the charge of one of us (S. M. A. A.), those aged 6 or less under the charge of D. P. B. During the 16 months June, 1957, to September, 1958, a total of 40 consecutive cases were seen (excluding neonatal tetanus) and 11 were selected for treatment with T.P.R. One subject died during tracheostomy on the day of admission and has not been included in the series. Details of age, site of infection, incubation period, onset period (the time between the first symptom and the first spasm whether local or generalized), duration of T.P.R., and result in the 10 patients are given in the Table.

All patients received antiserum (50,000 to 100,000 units), intramuscular chlorpromazine (50-100 mg. four- or six-hourly), intravenous thiopentone, and crystalline penicillin. Four patients in addition had promethazine, 25 mg. 12-hourly, and sodium amylobarbitone, 200 mg. six-hourly. If feasible, the wound causing the infection was excised at a suitable interval after starting the antiserum. When it seemed that this conservative treatment was failing, all consultants met to assess the

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