

was multiple, frequently because of small mining camps with numerous pre-school children in daily communication with each other (most of whom developed an acute febrile illness after exposure to poliomyelitis). The virus of poliomyelitis was recovered from flies trapped near a privy used by families of four acute cases in such a camp.³ In 37 instances of multiple contact the children lived within 300 yards of each other.

In 36 instances the contact with prior poliomyelitis was single, and took place in 30 (83 per cent.) before the contacted child or the victim became ill. In 18 of the 30 it occurred on the day of onset and in the remainder during the 3 days before the onset of the prodromal period in the contacted child. Among the 30 single contacts on or before the day of onset 16 of the visits were made by the child about to become ill (average distance covered was 7 miles) and 14 by the victim (average distance covered was 10 miles). The group represented for the most part the first cases in their respective neighborhoods and the most severe instances of poliomyelitis in the epidemic. Four of the 5 deaths among the 121 reported cases (and the only death among the unreported prior contacts) were in this 30; in 27 instances both contacted child and victim developed paralytic or myelitic poliomyelitis. For the 30 victims there were 20 different places of contact (and 20 different contacted children) separated by an average distance of 4.5 miles from the nearest prior poliomyelitis, reported or unreported. The prodromal period in the 30 victims began 3 to 21 days after the exposure to the contacted child (the average incubation period was 12.3 days) (Fig. 1).

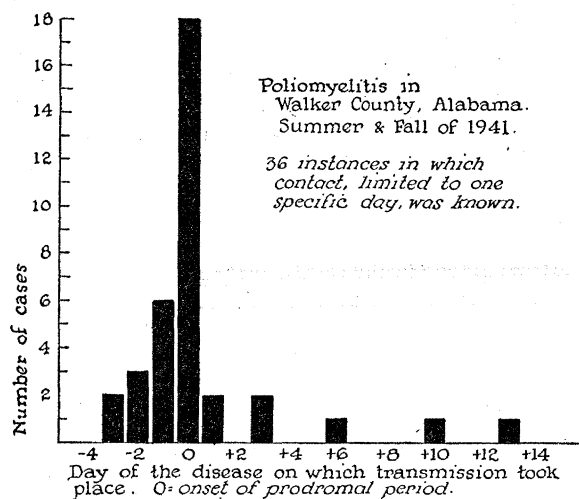


FIG. 1.

It was improbable that infected insects or other agents^{3, 4, 5} traveled the average distance of seven

³ J. R. Paul, J. D. Trask, M. B. Bishop, J. L. Melnick and A. E. Casey, *SCIENCE*, 94: 395, 1941.

⁴ A. B. Sabin and R. Ward, *SCIENCE*, 94: 590, 1941.

miles and selected the same 16 victims out of a pre-school child population of over 3,000 as were visited by the 16 incipient poliomyelitis patients. If a mobile human reservoir was responsible in the 16 instances where the about-to-be-ill child did the visiting, it was equally true in the reverse, since only 14 instances were recorded of the victim visiting the incipient patient under the same circumstances. The mobile human reservoir was also a transient one, since half of the children who developed the disease visited with the patient on the day of onset (in the 36 instances where there was a single visit). It was unlikely that 50 of each clinically non-infected visitors who came from distant neighborhoods would do so on the day of onset in the incipient patient. How the virus was spread from one child to the other was not attacked in the study. The premise of insect transmission to be compatible with the present findings would require the insect to have acquired the virus from the blood, secretions or excreta of an incipient poliomyelitis patient and to have transferred it within 24 to 72 hours to a second child generally on or near the premises where the visit took place. For the premise of direct transmission of the virus from the secretions or excreta of one child to the nose, eye or mouth of the other the histories are also compatible.

Summary and Conclusions: An epidemic of poliomyelitis was observed in which human travel was a major factor in the spread of the disease from neighborhood to neighborhood and from person to person. Eighty per cent. of the poliomyelitis patients had probably visited or been visited by a prior poliomyelitis patient who was in the late incubation or early prodromal period. The effective reservoir of the virus was seemingly a patient within three days before or three days after the onset of the first prodromal symptom. Whether the effective virus was present in the blood, the secretions or the excreta of the patient at this critical period and how the transfer was accomplished was not determined.

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THE INTRAVENOUS DRIP AND OTHER INTENSIVE METHODS FOR THE TREATMENT OF EARLY SYPHILIS¹

The finding² that early syphilis may be effectively treated, and in most cases definitively cured, within 5

⁵ J. A. Toomey, W. S. Takacs and L. A. Tischer, *Proc. Soc. Exp. Biol.*, 48: 637, 1941.

¹ From the U. S. Public Health Service, Washington, D. C., and the Syphilis Division of the Department of Medicine, the Johns Hopkins Medical School, Baltimore, Md.

² George Baehr, William Leifer, Louis Chargin, H. T. Hyman, *et al.*, *Arch. Derm. and Syph.*, 42: 239, 1940.

days by administering nearsphenamine or Mapharsen in an intravenous drip, is of obvious importance both to the individual patient and to the current control program. This intensive procedure is, however, many times more dangerous than standard clinic practice.³ Whether this increased risk is justified by the somewhat more rapid control of infectiousness, and by the perhaps more favorable early results achieved by the intravenous drip as compared with average clinic practice, is debatable. Nevertheless, it seems clear that the traditional schedule of weekly injections for 18 months, however effective and however safe, is wholly arbitrary. Given as three variables, (a) the total duration of treatment, (b) the number of injections and (c) the size of the individual dose, there are obviously an infinite number of possible combinations. Given further the fact that a 5-day and an 18-month schedule may be of comparable therapeutic efficacy, it should be possible, with the same drugs, to find effective methods of treatment which combine the speed of one and the safety of the other to an optimum degree.

Because of the very number of possible combinations of time and dose and because of the difficulties inherent in any clinical evaluation, the initial problem of orientation seemed clearly one for the laboratory rather than the clinic.

Accordingly, in the fall of 1939, we undertook to determine in syphilitic rabbits the toxicity and the therapeutic activity of twelve different treatment schedules, embracing wide variations in the frequency and duration of treatment. Mapharsen (3-amino-4-hydroxy phenylarsine oxide) was used throughout. The twelve experimental treatment schedules were as follows:

Intravenous drip (5 and 6 hours daily) for 1, 2 and 4 days.

Multiple injections each day for 1, 2 and 4 days.

Single daily injections for 1, 4 and 12 days.

Injections every other day (3 times weekly) for 4 and 8 weeks.

Weekly injections for 6 weeks.

A total of 2,000 animals has been used to date. Although the study is not yet completed, the results are sufficiently clear-cut to justify certain generalizations, presented at this time because of their implications with respect to the present-day treatment of early syphilis.

A. THERAPEUTIC EFFICACY

Within broad limits, the curative dose of Mapharsen with any one type of treatment was largely independent of the time period over which that treatment was

given. Indeed, in seven schedules involving rapid intravenous injections, in which the total duration of treatment varied from 10 seconds to 6 weeks, the interval between injections from 2 hours to 1 week, and the total number of injections from 1 to 16, the minimal curative dose⁴ varied only between 4 and 8 mg per kg. Although there was some suggestion that repeated doses at short intervals were more effective than either one large dose, or repeated doses at weekly intervals, the data are as yet inconclusive.

The minimal curative dose of the intravenous drip procedure, whether for one day or for four days, varied only between 7 to 12 mg per kg. It is of interest to note that Mapharsen administered by intravenous drip has been consistently less effective than Mapharsen administered by repeated injections over the same time period.

B. TOXICITY

Of primary importance is the fact that, on every treatment schedule yet tried, the total amount of arsenical which could be administered without killing the animal increased directly with the total duration of treatment. Of secondary importance is the fact that, within a fixed time period, somewhat larger amounts of arsenical could be administered by increasing the frequency of injections. Thus, on daily injections for 4 days, the maximal tolerated dose was 30 mg per kg. This was increased to 40 mg per kg by giving 4 injections daily over the same time period, and to 48 mg per kg by giving a continuous intravenous drip for six hours daily on each of four consecutive days.

This apparent advantage of the short-term intravenous drip with respect to toxicity is, however, illusory on two scores. In the first place, Mapharsen given by intravenous drip is apparently less effective than the same amount of arsenical given by simple intravenous injection. More important, since the total tolerated dose of arsenical given by simple injection can apparently be increased almost without limit merely by prolonging the duration of treatment, it is possible to administer far larger amounts of arsenical with greater safety by injections repeated daily, every other day or weekly, over a sufficient period of time.

C. MARGIN OF SAFETY ("CHEMOTHERAPEUTIC INDEX")

Since the total curative dose of Mapharsen in rabbits is, within broad limits, approximately constant, and since the total tolerated dose on any schedule of injections increases directly with the duration of treatment, it necessarily follows that *the margin of safety*

³ David C. Elliott, George Baehr, Loren W. Shaffer, Glenn S. Usher and S. Allan Lough, *Jour. Am. Med. Assn.*, 117: 1160, 1941.

⁴ The dose which cures more than 95 per cent. of the animals, as shown by negative lymph node transfers 6 weeks and again at 6 months after treatment.

between the toxic and therapeutic dose ("chemotherapeutic index") may be increased continuously by prolonging the duration of treatment. Conversely, on any schedule of injections, the shorter the total time period over which the treatment is administered, the lower is the margin of safety afforded.

Thus, (1) on six weekly injections the total tolerated dose (60 mg per kg) was 7.5 times the minimal curative dose (8 mg per kg), as compared with a margin of 1.4 for a single injection. Moreover, the margin of safety afforded by 30 weekly injections would probably be not far from 30. (2) When the injections were given three times weekly for four weeks, the chemotherapeutic index was 12: and it is estimated that the index on a similar eight-week schedule would be about 24. (3) With four consecutive daily injections, the margin of safety was approximately 6; and it is estimated that 12 daily injections will provide a margin of approximately 10. (4) Multiple daily injections over a four-day period gave a safety factor of approximately 10; and an intravenous drip for the same period provided a margin of safety of only 4. In both cases, a shorter time period (1 or 2 days' treatment) gave an even lower chemotherapeutic index; while a longer treatment period would presumably have resulted in a correspondingly wider margin of safety.

D. CLINICAL IMPLICATIONS

In the absence of evidence to the contrary, we must assume that these same considerations apply in human beings. Indeed, such data as are available from the clinic are in accord with the dual thesis that the total curative dose of Mapharsen varies only slightly with the frequency and total duration of treatment, while the total tolerated dose varies directly with the time period over which the arsenical is administered.

The implications with respect to the treatment of human syphilis are clear. On any schedule of injections, any desired margin of safety can apparently be achieved by suitable prolongation of the treatment period. Some compromise between the vexatious 18-month schedule, as now employed, and the dangerous 5-day schedule is clearly possible. Current clinic practice calls for approximately 40 injections of 60 mg each of Mapharsen and 40 injections of bismuth over an 18-month period. If we omit from consideration the role of bismuth, which is probably of secondary importance as compared with the arsenical, and if we take due cognizance of the fact that relatively few patients in the average clinic actually complete this treatment schedule, the desideratum appears to be an intensive treatment schedule as effective as 20 to 30 weekly injections of 60 mg (1 mg per kg) Mapharsen, and providing a comparable margin of safety.

On the basis of our animal results to date, those requirements would be at least approximated by (a), injections of 20 mg Mapharsen (0.3 mg per kg) repeated twice daily for 4 to 8 weeks; (b), daily injections of 30 mg Mapharsen (0.5 mg per kg), continued for 5 to 10 weeks; or (c), injections of 60 mg Mapharsen (1 mg per kg) repeated three times weekly for 5 to 10 weeks. Probably dozens of schedules could be elaborated, both safe and effective, the only choice between which would be that of convenience to the patient and to the physician.

For purposes of orientation, a clinical study has been organized in twelve cooperating clinics, in which the following three schedules are being used for the treatment of early syphilis: (a) Injections 3 times weekly for 4 weeks. (b) Injections 3 times weekly for 6 weeks. (c) Injections 3 times weekly for 8 weeks. On the last two schedules, some of the patients are being given concomitant weekly injections of bismuth. The results to date with respect to toxicity are encouraging. Further modification may, however, prove desirable in the light of continuing clinical experience, and particularly, in the light of end-results.

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STORAGE OF RADIOACTIVE IODINE IN A METASTASIS FROM THYROID CARCINOMA¹

A PATIENT with metastatic thyroid carcinoma was studied from the standpoint of storage of radioactive iodine. The carcinoma was of the adenoma malignum type with widespread bone metastases showing colloid follicles, and with no evidence of recurrence of the primary growth removed thirty-five years previously from the thyroid.

A tracer dose of radioactive iodine was given by mouth, and field plots of its distribution were determined by means of a Geiger-Müller counter. The Geiger counts indicated that more of the radioactive substance had been taken up by a metastasis in the right lower femur than by the thyroid gland itself. Other metastases, which, as a therapeutic measure, had been irradiated previously with deep x-ray, failed to take up the radioactive iodine in appreciable amount. The material present in the femoral metastasis and in the thyroid gland could not be washed out of these tissues by the administration of 54 mgm of potassium iodide, which indicates that the radioactive iodine was fixed in both these tissues.

The possibility of the use of radioactive iodine as a therapeutic agent was suggested because the meta-

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