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 CARCINOMA[1]

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-

[1] From the Departments of Biochemistry, Medicine, Radiology and Surgery, College of Physicians and Surgeons, Columbia University. This investigation was aided by a grant from the Josiah Macy, Jr. Foundation.

stasis in the femur had fixed such a large proportion of the material. Accordingly a therapeutic dose of 10 millicuries of radioactive iodine, mainly of the 12.6 hour period, was given. The femoral metastasis took up about 30 per cent. and the thyroid gland about 6 per cent. of the total amount administered. Radioautographs of the femoral metastasis were made by placing a film on the patient's thigh and allowing the radiation from the radioactive iodine to darken the film. The position of this metastasis as shown by the Geiger counter and by the radioautographs agreed well with the area of bone destruction shown in the x-ray plates.

About three weeks after the therapeutic dose the metastasis had lost about 85 per cent. of the radioactive iodine, while the thyroid still contained about the same amount as that originally taken up. A tracer dose given a few days after this finding showed prompt uptake by the thyroid gland, but no appreciable uptake by the femoral metastasis. This would suggest that at least the thyroid-like function of the metastasis had been impaired.

The patient is still under observation and a complete report will be made later.

The radioactive iodine was supplied to us through the kindness of Professor E. O. Lawrence, of the University of California, and Professor R. H. Evans, of the Massachusetts Institute of Technology.

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SCIENTIFIC APPARATUS AND LABORATORY METHODS

A SENSITIVE CHECK VALVE

BEFORE carrying out electrophoresis or diffusion experiments by methods involving the study of a boundary between solvent and solution, it is necessary to bring a small volume of the colloidal solution under consideration into ionic equilibrium with the solvent, usually a dilute buffered salt solution. Although this can be accomplished by simple stationary dialysis if sufficient time is allowed, it was thought likely that the equilibrium could be attained much more rapidly if some such device as the rocking dialyzer of Kunitz and Simms[1] were used. All that was required was some means of causing the buffer solution to circulate constantly past the dialyzing membrane. As was first pointed out to the author by Dr. D. A. MacInnes, the necessary energy for such circulation can be derived from the rocking motion of the dialyzer. A well-built rocker with a reliable source of power,[2] a small reservoir attached to one end of the table of the rocker, a larger reservoir to hold the bulk of the liquid, some rubber tubing and two check valves to render flow unidirectional constitute all the essential features of the set-up used in our laboratory to obtain the desired circulation. A diagrammatic representation of the assembly is shown in Fig. 1. In order to make the apparatus work, the level of the liquid in the larger reservoir must be intermediate between the upper and lower positions of the smaller reservoir and the check valves must be sufficiently sensitive to be opened and closed by small pressure gradients. A very simple and highly sensitive check valve suitable for such purposes

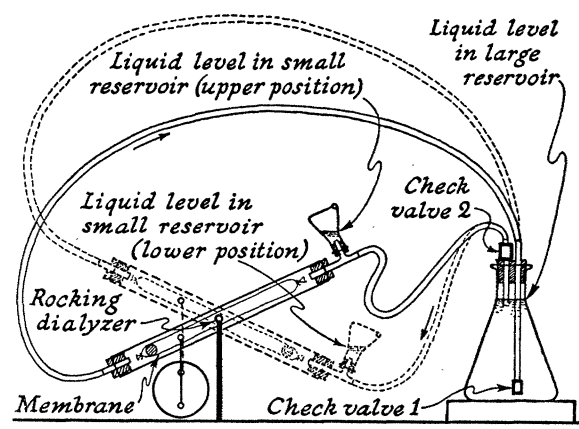

FIG. 1. Diagrammatic representation of assembly for rocking circulating dialysis.

was designed and constructed with the aid of Mr. William Duthie, machinist in our laboratory. Because of the satisfactory service the check valve has given, it was thought desirable to publish a description of it.

The valve consists of nothing more than a very thin sheet of rubber resting against the opening of a hole drilled into a "lucite" rod. A slight pressure tending to cause a liquid to flow out of the hole pushes the rubber film away, but an equally small pressure in the opposite direction causes it to cover the opening securely, preventing the flow of liquid in that direction. As is illustrated in Fig. 2, two modifications of the valve were constructed. The simpler of the two, No. 1, was cut from a 2-inch section of a $\frac{3}{4}$-inch "lucite" rod. After drilling a 3/16-inch hole (a) through the center of the rod from one end to within 3/16 inch of the opposite end, hereafter designated as the head, a $\frac{1}{8}$-inch hole (b) was drilled diagonally

[1] M. Kunitz and H. S. Simms, *Jour. Gen. Physiol.*, 11: 641, 1928.

[2] A 1/80 HP universal motor with a 1: 595 reduction gear manufactured by Bodine Electric Company of Chicago may be used for this purpose.