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# Transfer Rates of Gamma Globulin Between Cerebrospinal Fluid and Blood Plasma (Results Obtained on A Series of Multiple Sclerosis Patients)

**Stuart W. Lippincott, M.D., Samuel Korman, M.D., Ph.D., Louis C. Lax, M.D. and Cornelia Corcoran, A.B.**[1,2,3]

*Winston-Salem, N.C., Brooklyn, N.Y., Los Angeles, Cal. and Upton, N.Y.*

It has been known for many years (1,2) that in multiple sclerosis the gamma globulin concentration usually becomes increased in the cerebrospinal fluid as the disease develops, while it remains at a normal level in the blood. Frick and Scheid-Seydel (3) investigated the transfer of gamma globulin in a single direction from blood to cerebrospinal fluid and concluded that in multiple sclerosis a variable portion of the cerebrospinal fluid gamma globulin probably arose *de novo* in the central nervous system. Our study of the kinetics of the elevated gamma globulin in the cerebrospinal fluid in multiple sclerosis has extended the above observation by determining the transfer rates in two directions, from blood to cerebrospinal fluid and from cerebrospinal fluid to blood. To investigate these rates in patients with multiple sclerosis, $^{131}I$ labeled gamma globulin was injected intravenously, and the specific activity (the fraction of the injected dose of $^{131}I$ per mg gamma globulin) was determined on timed serial blood serum and cerebrospinal fluid samples. At another time, the experiment was performed with the same sampling procedure, except that the $^{131}I$ labeled globulin was injected intrathecally. These same specific activity versus time data were utilized

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[1]From the Department of Pathology, Bowman Gray School of Medicine of Wake Forest College, Winston-Salem, North Carolina, the Department of Medicine, Jewish Chronic Disease Hospital, Brooklyn, New York, the Departments of Surgery and Physiology, University of California School of Medicine, Los Angeles, California, and the Medical Department, Brookhaven National Laboratory, Upton, New York.

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to calculate (1) the average time a molecule of gamma globulin resided in the blood plasma and cerebrospinal fluid compartments, and (2) the rate of gamma globulin replacement in these same compartments.

## MATERIALS AND METHODS

### *Patients*

Twenty-one patients with an established diagnosis of multiple sclerosis were investigated. Both male and female patients were included in the group. The ages ranged from 29 to 66 years. No patient had had recognizable symptoms for less than five years and the maximum period was about 25 years. Immediately prior to intravenous or intrathecal injection of the labeled globulin a sample of cerebrospinal fluid was taken for a cell count, total protein concentration and electrophoresis. Similar determinations were made on postinjection cerebrospinal fluid samples. During the entire period of hospitalization the patients were carefully observed in the event that a reaction might occur with neurological manifestations. No "normal" healthy individuals were investigated because of the inability to justify asking volunteers to be injected intrathecally with $^{131}I$ labeled gamma globulin and to have one or more additional spinal taps. In addition, the primary purpose of this study was to determine rates of transfer and catabolism in multiple sclerosis, which required no other subjects.

### *Fractionation and Iodination of Gamma Globulin*

The gamma globulin was fractionated from the serum of normal donors, characterized and labeled with radioiodine as already described (4,5,6,7). The amount of $^{131}I$ gamma globulin injected intravenously varied from 1.2 to 4 mg and the radioactivity from 29.1 to 152 $\mu$C. By the intrathecal route the amount of $^{131}I$ gamma globulin injected varied from 0.5 to 2 mg and the radioactivity from 15 to 150 $\mu$C. The amount of radioactivity as the percent or fraction of the injected dose was determined for serum, urine and whole-body as in previous studies (8,9). The cerebrospinal fluid samples were weighed and counted in dried form in planchets in a Sharp low beta counter in order to minimize background counts in samples of low radioactivity. Specific activities were expressed as the fraction of the injected dose of $^{131}I$ labeled gamma globulin/mg gamma globulin in the sample.

### *Calculations*

The tracer technique was the procedure chosen for this study chiefly because of its proven value as a physiological method wherever such quantitative measurements are to be made (10). Such a study, however, could not be carried out without the availability of a suitable tracer material, or suitable analytical and data processing methods. In all the studies to be reported in this paper, the tracer used was $^{131}I$ labeled gamma globulin. The theoretical basis for the analysis of the specific activity vs time data involved in the determination of compartmental masses and their rates was described by Wrenshall (11). This approach to the determination of transfer rates has been shown to be free of many of the

assumptions inherent in the development of similar formulations by other investigators (12,13). The technique has, furthermore, not only been tested in model systems and found to be applicable under a variety of conditions such as nonsteady states and nonuniform mixing of the labeled and unlabeled material in compartments (14,15), but has also been successfully applied in living systems to the study of multicompartmental phosphorus transfer rates with simultaneous determination of compartmental contents of this metabolite (16). The numerical techniques by which the radioisotope data were processed, fitted functions obtained, and transfer rates and compartmental masses derived have been described elsewhere (17,18).

Rates of appearance and disappearance of gamma globulin in the cerebrospinal fluid compartment were determined from specific activity vs time data collected on spinal fluid taps taken from patients with multiple sclerosis following the intrathecal administration of $^{131}I$ labeled gamma globulin. In addition, the mass of gamma globulin in the cerebrospinal fluid compartment was derived from these data by the application of the dilution principle. Serial sampling of the blood plasma in these same subjects permitted the simultaneous determination of the transfer rate of gamma globulin from the cerebrospinal fluid to the blood plasma compartment.

The entire foregoing procedures were then repeated in some of the same patients and in some additional subjects with multiple sclerosis, except that the tracer dose of $^{131}I$ labeled gamma globulin was administered intravenously instead of intrathecally. This permitted the calculation of not only the rates of appearance and disappearance of gamma globulin in the blood plasma compartment, but also the determination of the transfer rate of gamma globulin from the blood plasma to the cerebrospinal fluid compartment. The mass of gamma globulin within the blood plasma was found from these data as well.

Since all calculated rates were derived in terms of basic units, (unit mass/unit time), and since the compartmental contents of gamma globulin for both the cerebrospinal fluid and blood plasma compartment were determined as well, other modes of expressing the metabolic activities of the two compartments with respect to the replacement of gamma globulin within them could be used. For example, by dividing the rate of appearance of gamma globulin in either of these two compartments by the respective mass of gamma globulin within them, the fraction of the compartmental content of gamma globulin replaced per unit time can be found. The reciprocal of this rate gives the average time spent by a molecule of gamma globulin in the respective compartment, otherwise known as the "turnover time", as defined by Zilversmit (19).

The formulae used to calculate the rates (11) are as follows:

*Rate of appearance of gamma globulin in the cerebrospinal fluid compartment* following intrathecal injection of the $^{131}I$ gamma globulin

$$(R_{A_{csf}})_0 = \frac{(M_{csf})_0}{-(\gamma_{csf})_0} \cdot \left(\frac{d\,\gamma_{csf}}{dt}\right)_0 \qquad (1)$$

where $(R_{A_{csf}})_0$ is the rate of appearance of gamma globulin in the cerebrospinal fluid compartment (in mg/hour) at time t = 0.

$(M_{csf})_0$ is the content of gamma globulin in this compartment in mg at time t = 0.

$(\gamma_{csf})_0$ is the specific activity of the gamma globulin in the cerebrospinal fluid compartment (fraction injected dose/mg gamma globulin) at time t = 0.

$\left(\frac{d\,\gamma_{csf}}{dt}\right)_0$ is found by differentiating the fitted specific activity vs time function and setting the value of t in the derivative equal to zero. The zero subscripts denote values found by extrapolation of experimental data to time t = 0.

This formula is a special case of the general one described by Wrenshall and applies to the compartment into which the tracer is initially placed at zero time. By definition, at time t = 0 all of the tracer is in the compartment into which it was initially introduced, so that incoming gamma globulin contains none of the label. This means that the specific activity of incoming gamma globulin at time t = 0 is zero.

*Rate of disappearance of gamma globulin from the cerebrospinal fluid compartment* following intrathecal injection of the $^{131}I$ labeled gamma globulin

$$(R_{D_{csf}})_0 = (R_{A_{csf}})_0 - \left(\frac{d\,M_{csf}}{dt}\right)_0 \tag{2}$$

where $(R_{D_{csf}})_0$ is the rate of disappearance of gamma globulin from the cerebrospinal fluid compartment (in mg/hour) at time t = 0.

and $$\left(\frac{d\,M_{csf}}{dt}\right)_0 = \frac{(M_{csf})_0}{[M_{csf}]_0} \cdot \left(\frac{d\,[M_{csf}]}{dt}\right)_0 \tag{3}$$

where $\left(\frac{d\,M_{csf}}{dt}\right)_0$ is the change/unit time in the total content of gamma globulin in the cerebrospinal fluid compartment (in mg/hour) at time t = 0.

$(M_{csf})_0$ is as defined above.

$[M_{csf}]_0$ is the concentration of gamma globulin in the cerebrospinal fluid at time t = 0.

$\left(\frac{d\,[M_{csf}]}{dt}\right)_0$ is the change/unit time in the concentration of gamma globulin in the cerebrospinal fluid compartment in mg/ml/hour at time t = 0.

*Transfer rate of gamma globulin from the cerebrospinal fluid compartment to the blood plasma* following intrathecal injection of the $^{131}I$ labeled gamma globulin

$$(R_{csf \rightarrow P})_0 = \frac{(M_P)_0}{(\gamma_{csf})_0 - (\gamma_P)_0} \cdot \left(\frac{d\,\gamma_P}{dt}\right)_0 \tag{4}$$

where $(R_{csf \rightarrow P})_0$ is the transfer rate of gamma globulin from the cerebrospinal fluid compartment to the blood plasma at time t = 0 (in mg gamma globulin/hour).

$(M_P)_0$ is the content of gamma globulin in the blood plasma compartment at time t = 0.

$(\gamma_{csf})_0$ has already been defined.

$(\gamma_P)_0$ is the specific activity of gamma globulin in the blood plasma compartment at time t = 0.

$\left(\frac{d\,\gamma_P}{dt}\right)_0$ is the change/unit time in $\gamma_P$ at time t = 0.

*Rate of appearance of gamma globulin in the blood plasma compartment* following intravenous injection of $^{131}I$ labeled gamma globulin is given by the following expression (in mg gamma globulin/hour):

$$(R_{A_P})_0 = \frac{(M_P)_0}{-(\gamma_P)_0} \cdot \left(\frac{d\,\gamma_P}{dt}\right)_0 \tag{5}$$

*Rate of disappearance of gamma globulin from the blood plasma compartment* following intravenous injection of $^{131}I$ labeled gamma globulin is given by the following expression (in mg gamma globulin/hour):

$$(R_{D_P})_0 = (R_{A_P})_0 - \left(\frac{d\,M_P}{dt}\right)_0 \tag{6}$$

$\left(\frac{d\,M_P}{dt}\right)_0$ is determined from an expression analagous to that given by equation (3).

*Transfer rate of gamma globulin from the blood plasma to the cerebrospinal fluid compartment* following intravenous injection of $^{131}I$ labeled gamma globulin is given by the following expression (in mg gamma globulin/hour):

$$(R_{P \rightarrow csf})_0 = \frac{(M_{csf})_0}{(\gamma_P)_0 - (\gamma_{csf})_0} \cdot \left(\frac{d\gamma_{csf}}{dt}\right)_0 \tag{7}$$

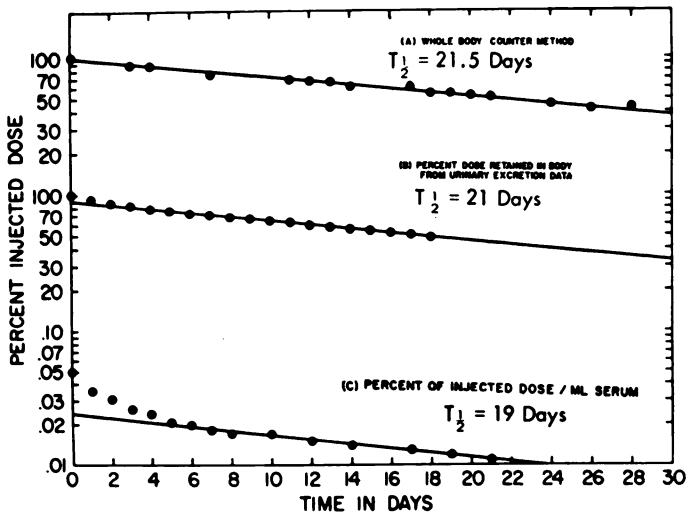



Figure 1 Biological Half-Life ($T_{\frac{1}{2}}$) of Intravenously Injected $I^{131}$-Labeled Gamma Globulin Determined from Whole-Body, Serum and Daily Urine Counts in a Patient with Multiple Sclerosis.

## RESULTS

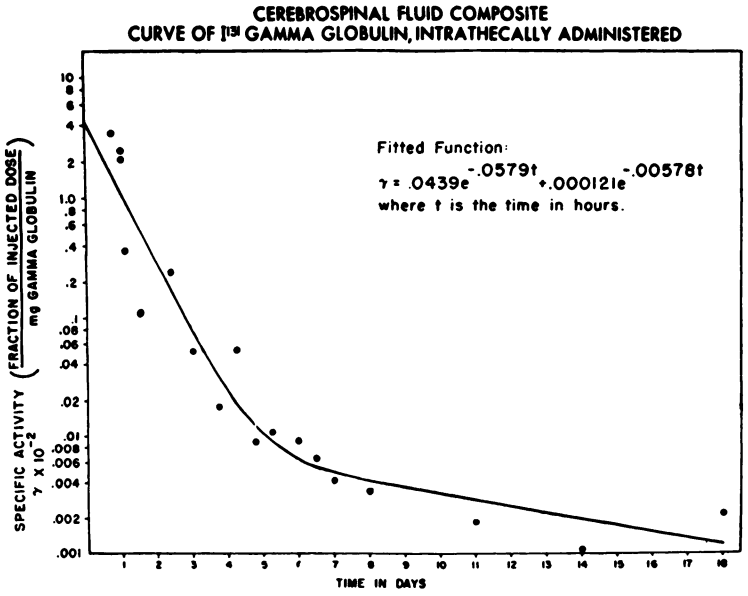
An important requirement in using a radioactively labeled protein such as gamma globulin in a tracer study is that the protein should not be degraded during the fractionation nor during the iodination. Figure 1 contains data compiled from patient C. This ambulatory patient still retained control of his urinary bladder and so was a suitable subject. He received an intravenous injection of 142 $\mu$C of $^{131}$I labeled globulin (3 mg) and the biological half-life was determined to be 21.5 days when he was counted in the whole-body gamma spectrometer, 21 days by counting 24 hour urinary collections in the same device, and 19 days by counting samples of sera. These findings are in good agreement, and the globulin preparation used was considered to be biochemically suitable for this series of studies.

The response of the cerebrospinal fluid concentration of gamma globulin and total protein to intravenous and intrathecal injection of tracer amounts of $^{131}$I gamma globulin was determined in the patients with multiple sclerosis (Tables I, II). It appeared desirable, as a part of this overall study, to establish how sensitive such a response, if it occurred, might be as a basic observation in a disease that may be associated with an autoimmune process. At periods varying from six hours to 22 days, following intravenous injection of $^{131}$I gamma globulin, there was no statistically significant change in the concentration of total protein in the cerebrospinal fluid before and after the injection of the tracer material. At periods varying from six hours to 19 days, following intrathecal injection of $^{131}$I gamma globulin, there was a statistically significant rise in the total protein concentration of cerebrospinal fluid as compared to the preinjection concentration. Seventeen of the twenty-one patients injected intrathecally with $^{131}$I gamma globulin had negligible clinical reactions, while four had severe headache and two of them had nuchal rigidity. It is possible that these reactions were due to the spinal tap alone but it is also conceivable that they were associated with the response to the injections of a presumed "tracer" amount of gamma globulin.

In multiple sclerosis it has been previously reported that during the course of the disease the concentration of the serum gamma globulin may be within the range for normal subjects while the concentration in the cerebrospinal fluid is greater than normal. Although it was anticipated that this also would be true in our patients, it was thought that it would be best to establish the fact, since it was desirable to compare the rate of gamma globulin replacement in serum and in cerebrospinal fluid. In eight patients the serum gamma globulin concentration determined at two intervals from three to twenty-four months apart showed no significant difference. In nine patients the serum gamma globulin content measured as a percent of total protein concentration was compared with that in the cerebrospinal fluid. Both sets of values were obtained from chemical determinations and paper electrophoretic values. In seven of the nine patients the content of gamma globulin, expressed as a percent of the total protein concentration, was higher in cerebrospinal fluid than in the serum. In one patient the value was the same and in another the cerebrospinal fluid value was four percent less than the serum gamma globulin.

A plot of the specific activity vs time for the cerebrospinal fluid following intrathecal injection of the $^{131}I$ labeled gamma globulin is shown in Fig. 2. This is a composite curve made up of 18 points, for which specific activities were determined by using the fraction of the injected dose at the time of spinal tap, divided by the content of gamma globulin in the same sample, with each point being obtained on a different individual. The solid line curve is given by the exponential function which was fitted by least squares iterative procedure programmed for the IBM 7090 in the FORTRAN language (18,20). This program not only obtains the least squares fit to the given data in the form of a sum of exponential terms, but it also calculates the mass of the compartment, the rate of appearance of the given metabolic factor within the compartment, and after an elaborate calculation involving the inversion of the final matrix, which is used

Figure 2




to fit the parameters in the exponential expression, it computes the standard deviation of the rate of appearance. By means of equation (1), the overall transfer rate of gamma globulin into the cerebrospinal fluid compartment (or the rate of appearance) and its standard deviation as determined by means of extrapolated values derived from the fitted function (11) was found to be 1.31 ± 0.91 mg gamma globulin/hour, or 31.2 mg/day. The rate of disappearance was calculated from the rate of appearance and the rate of change in the concentration of gamma globulin in the cerebrospinal fluid compartment (16). It was found to be equal to 1.28 mg gamma globulin/hour, or 30.7 mg/day. Since the rate of change in the content of gamma globulin in the cerebrospinal fluid was found not to differ significantly by Student's t-test from zero, the rate of appearance can be considered to equal the rate of disappearance of gamma globulin from

the cerebrospinal fluid compartment, *i.e.* a dynamic steady state can be presumed to exist. The content of gamma globulin in the cerebrospinal fluid compartment was also determined from the fitted specific activity vs time function using a value found by extrapolation to time t = 0 and applying the dilution principle (11,16). It was found to be equal to 22.7 mg gamma globulin.

If the rate of appearance of gamma globulin in the cerebrospinal fluid compartment is divided by the content of gamma globulin in this compartment, the fraction of the compartmental content of gamma globulin that is replaced per unit time can be calculated. This was found to be .0577 mg gamma globulin/hr/mg gamma globulin in the compartment or hour$^{-1}$. The reciprocal of this value, 17.3 hour is the average time spent in the cerebrospinal fluid by a molecule of this protein.

Figure 3

SPECIFIC ACTIVITY OF SERUM I$^{131}$ GAMMA GLOBULIN AFTER INTRATHECAL INJECTION

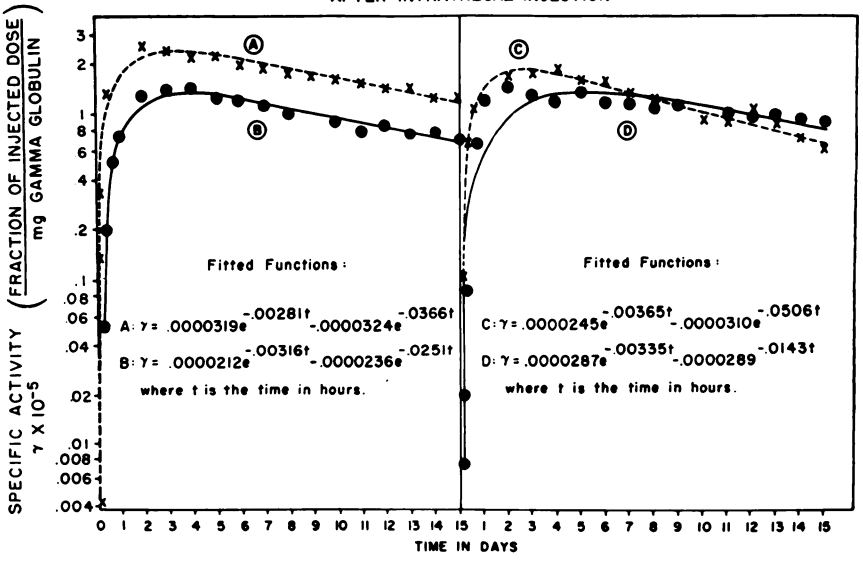



Figure 3 shows the specific activity vs time data for the sera of four patients following intrathecal injection of the $^{131}$I labeled gamma globulin. Similar data were also obtained on a fifth subject. The transfer rate of gamma globulin from the cerebrospinal fluid to the blood plasma compartment was calculated from the data in Figs. 2 and 3 and was found to be 0.425 mg ± 0.208 (S.D.) gamma globulin/hour.

The four patients represented in Fig. 3 were also studied, together with four more patients, by means of the intravenous injections with subsequent serial blood samples. The average rate of appearance of gamma globulin in the blood plasma compartment was determined as 312 ± 103 (S.D.) mg gamma globulin/hour. Since the serum gamma globulin concentration did not change significantly (by Student's t-test) throughout this study, the rate of disappearance of

gamma globulin from the blood plasma compartment is assumed to equal the rate of appearance, *i.e.* a dynamic steady state can be said to exist. From data on eight patients, the mean content of gamma globulin in the plasma compartment was calculated to be 22.5 ± 3.6 (S.D.) gms. The mean value for the fraction of the gamma globulin content of the blood plasma being renewed per unit time is equal to $\frac{312}{22{,}500}$ *i.e.* 0.0138 mg gamma globulin/hour/mg gamma globulin in the compartment of $hr^{-1}$. The reciprocal of this value gives the average time spent by a molecule of gamma globulin in the blood plasma compartment as 72.4 hours. This has also been termed the "turnover time" (19).

It is of interest to compare the rate at which gamma globulin is being replaced in the blood plasma compartment with that at which it is being replaced in the cerebrospinal fluid compartment. This can be done by means of the rate figures which deal with the fraction of the compartment being replaced per unit

TABLE I. TOTAL PROTEIN CONCENTRATION IN CEREBROSPINAL FLUID PRIOR TO AND FOLLOWING INTRAVENOUS INJECTION OF $^{131}I$ GAMMA GLOBULIN IN PATIENTS WITH MULTIPLE SCLEROSIS

| *Number* | *Patient Code* | *Mg Injected $^{131}I$ Labeled Gamma Globulin* | *Radioactivity Microcuries* | *Pretracer Injection CSF* | *Posttracer Injection CSF* | |
|---|---|---|---|---|---|---|
| | | | | *Total Protein Concentration mg/100 ml* | *Elapsed Time from Injection* | *Total Protein Concentration mg/100 ml* |
| 1 | F | 4.0 | 57.8 | 39.8 | 6 hours | 39.7 |
| 2 | R | 2.6 | 152.0 | 68.5 | 24 hours | 67.8 |
| 3 | S* | 2.8 | 98.8 | 27.0 | 24 hours | 23.7 |
| | | 2.0 | 100.0 | | 60 hours | 23.6 |
| 4 | M* | 4.0 | 106.0 | 39.2 | 24 hours | 36.2 |
| | | 3.0 | 142.0 | | 13 days | 40.0 |
| | | 2.0 | 131.3 | | 22 days | 41.8 |
| 5 | A | 0.5 | 15.0 | 66.1 | 8 days | 68.3 |
| 6 | G | 4.0 | 104.0 | 28.0 | 4 days | 25.9 |
| 7 | H | 1.2 | 29.1 | 50.9 | 13 days | 44.6 |
| 8 | B* | 4.0 | 104.0 | 19.8 | 17 days | 23.8 |
| | | 3.0 | 142.0 | | 19 days | 18.3 |
| 9 | C | 3.0 | 142.0 | 28.2 | 19 days | 22.6 |
| 10 | E | 4.0 | 104.0 | 37.1 | 20 days | 34.1 |
| | | 2.0 | 131.3 | | 4 days | 33.7 |
| 11 | T | 1.5 | 142.0 | 38.5 | 22 days | 35.5 |

*In patients S and B intravenous injections were given in two separate studies, in patient M in three studies, while in the rest a single study was made.

time. From these values it can be seen that, on the average, the gamma globulin in the cerebrospinal fluid is being replaced $\frac{0.0577}{0.0138} = 4.18$ times as fast as it is in the plasma.

A composite plot was made of the specific activity vs time in the cerebrospinal fluid of eight subjects with multiple sclerosis in whom $^{131}I$ labeled gamma globulin was injected intravenously followed by a spinal tap. The function for the fitted curve was obtained by the same techniques as already described. The data from the composite plot, together with that for the specific activity vs time in the blood plasma, were used to determine the transfer rats of gamma globulin from the blood plasma to the cerebrospinal fluid compartment. The mean value

TABLE II. TOTAL PROTEIN CONCENTRATION IN CEREBROSPINAL FLUID PRIOR TO AND FOLLOWING INTRATHECAL INJECTION OF $^{131}I$ GAMMA GLOBULIN IN PATIENTS WITH MULTIPLE SCLEROSIS

| *Number* | *Patient Code* | *Mg Injected $^{131}I$ Labeled Gamma Globulin* | *Radioactivity Microcuries* | *Pretracer Injection CSF* | *Posttracer Injection CSF* | |
|---|---|---|---|---|---|---|
| | | | | *Total Protein Concentration mg/100 ml* | *Elapsed Time from Injection* | *Total Protein Concentration mg/100 ml* |
| 1 | A* | 0.5 | 15.0 | 57.0 | 6 hours | 66.1 |
| | | 1.0 | 75.0 | 60.0 | 11 days | 72.4 |
| 2 | B* | 1.0 | 46.0 | 19.8 | 18 hours | 60.0 |
| | | 1.0 | 65.7 | 18.5 | 24 hours | 40.5 |
| 3 | C* | 1.0 | 57.8 | 28.2 | 26 hours | 85.8 |
| | | 1.4 | 105.0 | 28.9 | 18 days | 44.6 |
| 4 | D | 1.0 | 65.7 | 45.3 | 36 hours | 49.3 |
| 5 | E | 0.8 | 46.0 | 32.5 | 48 hours | 51.9 |
| 6 | F | 1.0 | 57.8 | 39.8 | 72 hours | 45.4 |
| 7 | G | 1.0 | 57.8 | 28.0 | 4 days | 65.9 |
| 8 | H | 1.0 | 57.8 | 50.9 | 113 hours | 104.0 |
| 9 | I | 1.0 | 57.8 | 36.7 | 172 hours | 57.3 |
| 10 | J | 2.0 | 150.0 | 64.7 | 8 days | 141.3 |
| 11 | K | 2.0 | 150.0 | 60.5 | 12 days | 97.0 |
| 12 | L | 1.0 | 75.0 | 50.0 | 4 days | 85.0 |
| 13 | M | 0.8 | 46.8 | 39.2 | 24 hours | 25.4 |
| 14 | N | 1.0 | 65.7 | 36.7 | 102 hours | 20.5 |
| 15 | O | 1.0 | 65.7 | 70.3 | 126 hours | 55.8 |
| 16 | P | 1.0 | 65.7 | 42.0 | 144 hours | 34.3 |
| 17 | Q | 1.0 | 65.7 | 58.8 | 156 hours | 35.7 |

*In patients A, B, and C intrathecal injections were given in two separate studies, while in the remainder of the patients a single study was made.

found in eight subjects for this transfer rats was .0367 mg gamma globulin/hour. The transfer rate of gamma globulin from the cerebrospinal fluid to the blood plasma was $\frac{0.425}{0.0367}$ or 11.6 times as rapid as from the blood plasma to the cerebrospinal fluid compartment.

## DISCUSSION

Some of the properties of gamma globulin present in the cerebrospinal fluid of patients with multiple sclerosis have been reported recently. MacPherson and Cosgrove (21) identified two immunologically different gamma globulins in "normal" and multiple sclerosis cerebrospinal fluids by immunoelectrophoretic analyses employing rabbit antisera prepared against "normal" and multiple sclerosis cerebrospinal fluids. The major gamma globulin of cerebrospinal fluid was shown to be immunologically identical with the single gamma globulin of human serum, but the minor gamma globulin of cerebrospinal fluid was identified only in the latter. The major and minor gamma globulins of normal cerebrospinal fluid could not be distinguished from those of multiple sclerosis cerebrospinal fluid. These investigators felt that the presence of the gamma globulin peculiar to cerobrospinal fluid confirmed the suggestion of Kabat, Freedman, Murray and Kraub (1) that central nervous system tissue is capable of forming gamma globulin. They also thought it would be of interest to find out whether any of these particular gamma globulins function as an antibody.

Tourtellotte, Parker, Haerer, Harrell, Haerer, Gustafson and DeJong (22) raised the question in their study as to whether an elevation of a specific antibody could be the reason for the increase in gamma$_2$ globulin in the cerebrospinal fluid of patients with multiple sclerosis. They applied an ion exchange cellulose chromatography technique to the cerebrospinal fluid from 30 normal individuals, 40 patients with multiple sclerosis, and 6 patients with neurosyphillis. A distinct gamma globulin fraction found in the cerebrospinal fluid of seventy-five percent of the patients was named by them CM-11. The finding of this fraction (gamma globulin) suggested to them that it might be related to the etiology of multiple sclerosis. Following the work of these two groups another study was reported by Caspary (23) who undertook a comparison of immunological specificity of gamma globulin in the cerebrospinal fluid in normal and multiple sclerosis subjects. The conclusion reached were contrary to those of MacPherson and Cosgrove. Caspary stated that antibodies prepared against the proteins of normal serum, and those of normal and multiple sclerotic cerebrospinal fluids indicated the immune identity of gamma globulin from all three sources.

In a pioneering study with radioisotopes, Frick and Scheid-Seydel (13) injected intravenously (but not intrathecally) $^{131}$I gamma globulin into 28 patients with various neurological disorders. Three to four days, or occasionally later, after injection the specific activity was determined in samples of cerebrospinal fluid and blood. On the basis of this single route of exchange, in patients with multiple sclerosis, it was concluded that a variable portion of the cerebrospinal fluid gamma globulin did not come from blood. The authors stated that this assumption was based upon the fact that the specific activity was lower in the

cerebrospinal fluid than in the blood. Sites of production for the gamma globulin not entering the cerebrospinal fluid from the blood were regarded as the meninges and the mesenchymal tissues of the central nervous system. Our transfer rate studies indicate that the total amount of gamma globulin present in the cerebrospinal fluid could not be accounted for solely as a result of physical transfer from the blood.

## SUMMARY

$^{131}$I gamma globulin was injected both intravenously and intrathecally into patients with multiple sclerosis with subsequent sampling of blood and cerebrospinal fluid. Specific activity versus time curves were constructed from the data obtained from these samples. The transfer rate of gamma globulin from the cerebrospinal fluid to the blood plasma was 11.6 times as rapid as from the blood plasma to the cerebrospinal fluid compartment. The average time a molecule of gamma globulin spent in the cerebrospinal fluid compartment was 17.3 hours; whereas, in the blood plasma compartment it was 72.4 hours. The gamma globulin in the cerebrospinal fluid compartment was found to be replaced 4.2 times as fast as it was in the blood plasma compartment.

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