METABOLISM OF HUMAN GAMMA GLOBULIN IN NORMAL SUBJECTS*

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The fraction of human serum protein which has the slowest electrophoretic mobility at alkaline pH is referred to as gamma globulin. Several techniques, including electrophoresis, ultracentrifugation, and chromatography, as well as immunological methods, indicate that gamma globulin consists of a wide spectrum of related but dissimilar molecules. Despite this known heterogeneity, however, turnover studies based on plasma-elimination curves have suggested that all gamma-globulin molecules have a uniform metabolic fate in healthy subjects.[1-3]

In assessing metabolic homogeneity of plasma-protein fractions, radio-active iodine undoubtedly offers advantages over other forms of labelling. It is now known that the iodine label attached under defined conditions can be used as a reliable indicator of the metabolic behaviour of unlabelled protein molecules; in addition, the iodine label liberated during protein catabolism is quantitatively excreted in the urine provided that thyroid uptake is inhibited by administration of adequate amounts of inactive iodide.[4] Daily turnover rates can therefore be calculated by expressing urinary radio-activity as a fraction of the labelled protein remaining in the plasma.[5]

The turnover rate of albumin measured by this method remained constant during 4 weeks of observation in healthy human subjects. On the other hand, gamma globulin prepared by zone electrophoresis appeared to be metabolically heterogeneous since the turnover rate fell progressively during the first 7 - 13 days after injection. Such gamma-globulin preparations were found to contain 5 - 10% of macroglobulin ($S_{20,w}=19$) when examined in the ultracentrifuge.

An attempt was made to isolate metabolically homogeneous subfractions of gamma globulin having different turnover rates. Human serum was fractionated by anion exchange chromatography on columns of diethylaminoethyl cellulose.[6] Three subfractions of gamma globulin having increasing electrophoretic mobility and hexosamine content were prepared. All were free of macroglobulin and had similar sedimentation coefficients ($S_{20,w}=6{\cdot}10$ - $6{\cdot}62$). These fractions together comprised about 90% of the total gamma globulin. Each was found to be metabolically homogeneous, but by means of a double labelling technique, all were shown to be identical in regard to distribution and turnover. The half-life of this gamma globulin was 21 - 26 days (mean 23 days), the extra- to intra-vascular mass ratio was $0{\cdot}6$ - $1{\cdot}1$ (mean $1{\cdot}0$) and the exchange rate between intra- and extra-vascular pools was equivalent to 19 - 33% (mean 25%) of the circulating gamma globulin per day. The turnover rate was $4{\cdot}0$ - $6{\cdot}8$% of the intravascular gamma pool per day and the absolute turnover rate was $1{\cdot}5$ - $2{\cdot}5$ g. per day (mean $2{\cdot}1$ g. per day).

The chromatographic subfractions were all free of gamma macroglobulin which is known to be a normal constituent of human serum. This protein was therefore isolated by preparative ultracentrifugation followed by zone electrophoresis. When labelled by radio-active iodine, the turnover rate of the macroglobulin was found to be at least 3 times more rapid than the ordinary molecular weight gamma and, in contrast to the latter, it did not equilibrate with an extra-vascular pool.

These findings indicate that normal gamma globulin contains 2 metabolically distinct groups of molecules which differ in regard to their turnover rate and distribution between intra- and extra-vascular pools.

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