Distribution of Radiolabeled Human and Mouse Monoclonal IgM Antibodies in Murine Models

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The distribution and kinetics of six human and one murine monoclonal IgM antibodies (MoAb) were studied in BALB/c mice. Labeling was with ^{111}In, ^{75}Se, and ^{125}I. The monomers and pentamers of certain MoAbs were studied. Human distribution studies were also performed. The serum containing [^{111}In]MoAb was obtained from one of the patients 24 hr after administration and injected into mice which were then killed and assayed for ^{111}In distribution. In general, the [^{75}Se] and [^{111}In]MoAbs had distribution and kinetic patterns that were similar while the ^{125}I-labeled MoAbs dehalogenated after 4 hr. Monomers and pentamers had highly similar distributions suggesting that the distribution of IgMs may be based on factors other than molecular size. The murine IgM showed a somewhat different distribution in mice than did human IgMs. Serum from the patient containing [^{111}In]MoAb had a distribution in mice similar to that of the patient with high liver and gastrointestinal uptake. The human imaging indicates that it is possible to target tumor with human IgM MoAbs, but significant problems remain in regard to their clinical use.

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The majority of monoclonal antibodies (MoAbs) studied in vivo have been murine IgG MoAbs. These MoAbs have been labeled with a variety of radionuclides and administered to both animal models and humans (*1–4*). Very little in vivo data has been published concerning radiolabeled IgM MoAbs in either mice or humans, and in these cases the radionuclide was usually radioiodine (*5,6*). Because of dehalogenation problems (*7,8*), such data are hard to interpret. We present mouse distribution data on seven IgM MoAbs labeled with three different radionuclides. In some cases, monomers of these MoAbs were also studied.

MATERIALS AND METHODS

Antibodies

Six human monoclonal IgM MoAbs were studied in this set of experiments. They are designated YBC-122, YBD-047, YBC-058, YBB-190, YBM-209, and YBY-088. One murine IgM MoAb, designated CCK-061, was also studied. The human antibodies were obtained by fusing mouse myeloma P3X63Ag8·653 to human lymphocytes obtained from regional lymph nodes draining breast cancers. The myeloma cells and the lymphocytes were fused as described by Gerhard (*9*), then transferred to appropriate media. The resultant MoAbs were tested by ELISA for reactivity with glutaraldehyde-fixed human breast tumor cell lines and other tumor cell lines. The six human antibodies reacted strongly with breast cell lines and did not bind normal fibroblasts. Subsequently, these MoAbs were tested by immunohistochemical technique on cryostat sections of tumor and nontumor human tissue and by ELISA on membrane and cytosol fractions of fresh frozen human tissue. Only three antibodies, YBB-190, YBM-209, and YBY-088 reacted in ELISA with extracts of breast tumors. The cross-reactivities of these three MoAbs with normal tissues have been described elsewhere (*10*). Briefly, the target antigens are present on a variety of normal epithelial tissues. However, the antigens cannot be detected in the sera of advanced stage breast cancer patients or on normal blood elements. Selected human IgM MoAbs were produced in vitro in stirred tank vessels in serum free medium or in RPMI 1640 media containing 10% fetal calf serum. These MoAbs were purified by concentration, sodium sulfate precipitation, and separation over Sephadex S-400 columns.

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The CCK-061 MoAb was obtained by the fusion of P3X63Ag8·653 cells with spleen cells of BALB/c mice hyperimmunized with human colon cancer cytosol. This mouse MoAb reacts strongly with colon carcinoma and normal mucosa, but does not cross react with other human organs with the exception of minor binding to normal lung and prostate.

To generate monomers, purified YBB-190 and YBM-209 were reduced with 1 m*M* dithiothreitol for 1 hr at 37°C then acetylated with 5 m*M* iodoacetamide for 0.5 hr at room temperature. Complete reduction to monomer without further reduction to heavy and light chain was obtained as verified by polyacrylamide gel electrophoresis on nonreducing gels. Monomer preparations were dialyzed overnight against phosphate buffered saline (PBS) and analyzed under reducing and nonreducing conditions by SDS polyacrylamide gel electrophoresis and high performance liquid chromatography (HPLC) on TSK-2000 and TSK-3000 columns in a series.

Indium-111 Labeling

The indium-111 (^{111}In) labeling was performed using a modification of the bifunctional chelation technique of Krejcarek and Tucker (*11*). The labeling efficiency of all of the IgMs fell into a range of 92–100%, and the specific activity was ~1 μCi/μg. The antibodies retained pentameric and monomeric form after labeling as determined by size exclusion HPLC. They also retained their ability to bind the antigen. When radiolabeled IgM was separated on Sephadex G-75 and S-400 columns, ~75% of the radiopharmaceutical adhered to the column. For this reason, in some experiments, we have administered the radiopharmaceuticals in both their immediate postlabeling form and column purified form. Unless otherwise indicated, however, the radiopharmaceuticals were administered after column purification.

RADIOIODINE LABELING

Both the pentamers and monomers of the IgMs were iodinated by the lactoperoxidase technique (*12*). The specific activity following iodination was in the range of 1 mCi/mg, and the material was administered to animals in the column purified manner. The MoAbs retained their ability to bind the antigen after the iodination process.

Selenium-75 Labeling

Selenium-75 (^{75}Se) labeling of the protein was performed as previously described (*13*). Basically, the hybridoma was starved for methionine for 30 min by administering only 1/100 normal levels of methionine. Following this, the cells were fed [^{75}Se]methionine (Amersham Searle, Arlington Heights, IL; specific activity 183 mCi/mg) for 24 hr. The [^{75}Se] MoAb was then isolated from the tissue culture supernate by concentration, salt cut and standard sizing chromatography over Sephacryl S-200. The elution profile of labeled MoAb over the sizing column assured that the [^{75}Se]MoAb was intact pentamer. A specific activity of 1-5 mCi/mg was estimated.

Endogenously-Labeled Antibodies

Two experiments were performed with ^{75}Se endogenously labeled MoAbs as baseline work for other studies. In the first experiment, between 850,000 and 1.25 million cpm of ^{75}Se-labeled YBC-122, YBD-047, and YBC-058 were administered i.v. in 200 λ of solution. This represented ~1 μg of antibody. The mice were killed 4 hr postadministration by cardiac exsanguination and cervical fracture. Blood, bone, heart, kidney, lung, liver, muscle, skin, spleen, and intestine were taken, the tissues washed twice in water, blotted dry, and wet-weighed on an analytical balance. The samples were counted on an autogamma well counter, along with standards prepared from the injected material. The organs in their entirety were counted when possible. The data are presented as % dose/organ. In the case of the heart, kidney, lung, liver, spleen, and intestine, each organ was weighed and counted in its entirety. The data for blood, bone, muscle, and skin were computed from the total weight of the mouse by assuming that the blood was 7% of the body weight, the bones 15% of the body weight, and the muscle 40% of the body weight. Urine and feces were separated from one another and counted by the same technique.

In the experiment using YBB-190, the MoAb was studied as both the monomer and pentamer in parallel groups of animals. The total volume of solution administered per mouse was 50λ, the total counts varying from 750,000 to 1.2 million cpm. The protein mass was ~1 μg. These animals were killed in groups of four at 4, 24, and 48 hr after injection and their tissues processed as indicated in the first experiment. Urine and feces were collected at the 24- and 48-hr time periods.

Exogenously-Labeled Studies

The distribution of iodine-125 (^{125}I) and ^{111}In YBM-209, both the pentamer and monomer, were studied in normal BALB/c mice. In the ^{111}In portion of the experiment, the animals were administered ~4 μCi (1 μg) of intact YBM-209 i.v. and another group of mice received ^{125}I-labeled YBM-209 monomers (8 μCi; ~0.2 μg). All groups were killed at 4 and 24 hr and the tissues processed as described earlier. The thyroid glands of the mice were blocked by adding a saturated solution of potassium iodide to their drinking water 3 days before the radiopharmaceutical was administered. Urine and feces were collected for the 24-hr time point.

In the mouse IgM experiment ~1 μCi (1 μg) of CCK-061 was administered i.v. and the animals killed at 4 and 24 hr. Urine and feces were taken at the 24-hr time point. The tissues were processed as described earlier.

Effect of Column Purification and "Patient Filtration" on ^{111}In IgM MoAb Kinetics

In the process of working with the ^{111}In-labeled human IgM MoAbs, we observed that a large percentage of the dose was removed in passage over G-75 and S-400 Sephadex columns despite the fact that HPLC indicated that the material remained as a pentamer after labeling. The pre- and post-column material were identical by analytical HPLC on TSK-2000 and TSK-3000 columns, SDS-reduced and nonreduced gels and had similar specific activities. The nature of the IgM fractions was studied in the following experiment using the YBY-088 MoAb.

The [^{111}In]YBY-088 was prepared using 1 mg MoAb. An aliquot of this material was removed prior to its S-400 column purification for animal work. A portion of the column purified material was also saved for animal studies. For human studies, 19 mg of purified unlabeled (unconjugated) YBY-088 was administered i.v. followed by 1.7 mCi ^{111}In on 1 mg of column

purified antibody. The MoAb was infused into the patient over a 2-hr period and 24 hr later, blood was obtained for animal work. Approximately 10 μCi (1 μg) of YBY-088 was administered to six mice without benefit of column purification. In a parallel group of animals, the mice received ~ 1 μCi of column purified [^{111}In]YBY-088. A third group of mice received 200λ of serum from a patient (~24 hr after injection) that had received the column purified material. It is estimated that the μCi dose in the serum injected was between 0.05 and 0.1 μCi. The quantity of protein associated with the activity was unknown. All the mice were killed 24 hr postadministration and processed as previously described.

After administration of the antibody to the patient, scanning was performed at 30 min, 24 hr, 48 hr, 72 hr, and 144 hr. Blood was drawn at the end of infusion, at 30 min, 60 min, 2 hr, 3 hr, 6 hr, 24 hr, 48 hr, and 72 hr postinjection. Scanning was performed on a gamma camera (General Electric 400AT, General Electric, Milwaukee, WI) using both the 173 and 243 keV photopeaks. A 20% window and medium-energy collimation was used. Prior to the 144-hr scan, the patient was administered cathartics.

RESULTS

Figure 1 shows the mouse distribution of three ^{75}Se-labeled human IgM MoAbs 4 hr following their i.v. administration. The three MoAbs have virtually identical distribution with the exception of the liver in those animals receiving YBC-058, which shows greater ^{75}Se uptake than with the other MoAbs. Significantly, the blood levels of all three MoAbs are in the vicinity of 10% of the injected dose/organ while 20% of the injected dose has already been accumulated by the intestine.

Figure 2A shows the distribution of ^{75}Se-labeled YBB-190 pentamer and Figure 2B its monomer at 4, 24, and 48 hr. The general distribution of YBB-190 at 4 hr is very similar to that of the three previous MoAbs. From 4 hr onward the only tissue that changes significantly is the liver which decreases by half. Nearly 30% of the material was excreted in the feces by 48 hr. The monomer left the vascular compartment at approximately the same rate and was extracted by the liver to a lesser extent than the pentamer. Intestinal concentration was similar for both proteins; however, fecal excretion of the monomer was slightly less over 48 hr. The monomer appeared to enter muscle and skin tissue more rapidly and perhaps in a greater degree than the pentamer.

Figure 3 shows the 4- and 24-hr mouse distribution data for the [^{111}In]YBM-209 preparation. The blood levels decrease rapidly with marked liver uptake and rapid gastrointestinal concentration. By 24 hr, over one-half of the ^{111}In has been excreted in the feces with ~10% cleared into the urine.

Figure 4 shows the results of administration of a ^{125}I-YBM-209 pentamer and monomer preparation in parallel groups of BALB/c mice. The data was similar for pentamer and monomer in all tissues. The route of excretion was primarily by the kidney with 90% of the pentamer and 64% of the monomer excreted by that route in 24 hr. Less than 10% of the iodinated pentamer and monomer was excreted in the feces.

Figure 5 shows a distribution of ^{111}In-labeled YBY-088, 24-hr after its administration to BALB/c mice. Three preparations were administered: the first being the material immediately after its preparation; the second after column purification; and the third was the ^{111}In-labeled material remaining in the patient's serum 24 hr after administration of the column purified prep-

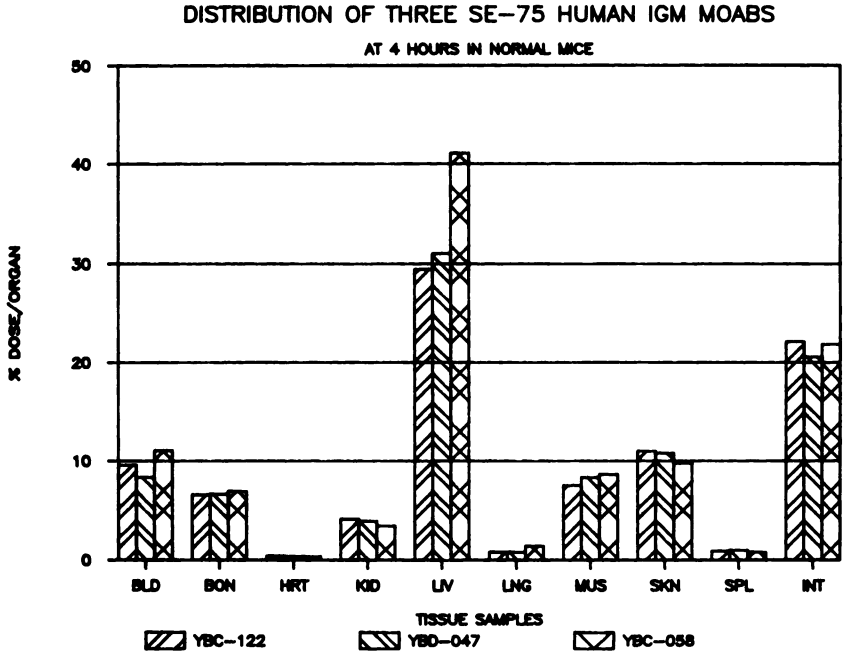

FIGURE 1
The above pentameric IgM MoAbs are endogenously labeled and thus do not contain material that might possibly be damaged in the exogenous labeling process. Note the high liver uptake of all three antibodies and the high intestinal uptake. Only 10% remains in the vascular compartment 4 hr after administration. Five mice/data point with standard deviations for most tissues ~15% of the mean.

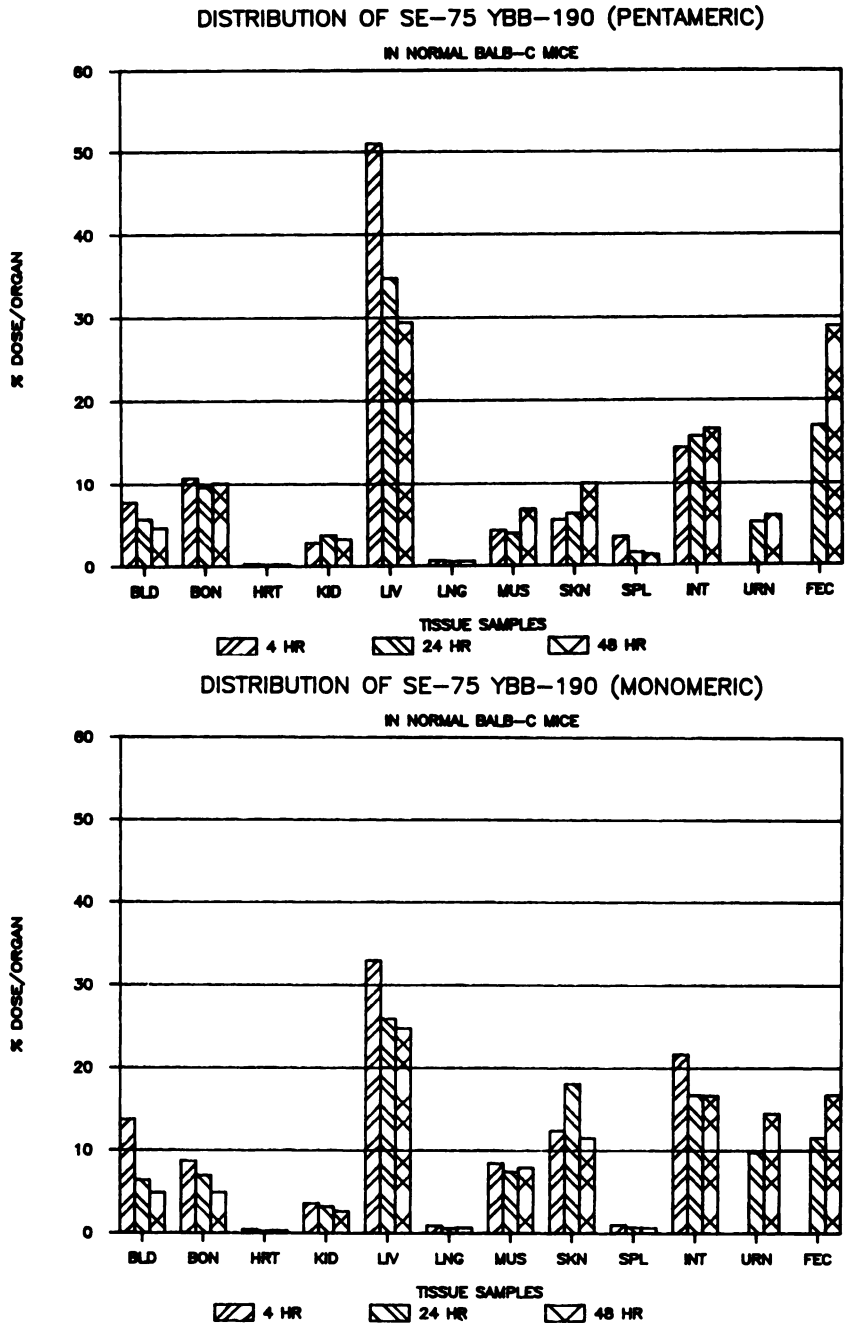

FIGURE 2
A: The distribution of this endogenously labeled pentameric IgM was followed over a 48-hr period. Again, the high liver and intestinal uptake is noted and marked fecal excretion occurs. Blood levels are relatively low at 4 hr but do not decrease much after 4 hr. Four mice/data point with standard deviations at ~10% of mean. B: The monomer of the endogenously labeled IgM antibody has a very similar distribution to the pentamer shown in A. Fecal excretion may be somewhat less than the pentameric form and urinary excretion slightly higher. Four mice/data point. Standard deviations were ~10% of the mean.

aration. The distribution of all three compounds was similar. The major difference in the preparations is that approximately half as much of the serum ^{111}In appeared in the mouse's liver as was noted in the original preparation administered to the patient.

Figure 6 shows the results of the administration of a [^{111}In]IgM murine MoAb in normal BALB/c mice. The animals were killed at 4 and 24 hr. Sixty percent of the radioactivity was present in the vascular compartment at 4 hr and over 20% at 24 hr. The liver acquired over 20% of the dose by 4 hr and has nearly 30% of the dose by 24 hr. Fecal and urinary excretion at 24 hr was ~5%.

Figure 7 shows the 48-hr scan of the patient. Tumor is obviously present in the left posterior chest (arrows). Note the intense liver and colon activity. The colon was cleansed with laxatives and at 144 hr was free of ^{111}In, indicating that this activity was not in the bowel wall. The blood disappearance of the [^{111}In]IgM MoAb in the patient was slower than observed in the mouse with ~40% of the ^{111}In left in the patient's vascular compartment at 24 hr. About 5% remained in the vascular compartment of the mice at 24 hr. As in the mouse, high liver uptake was observed with this organ being very radioactive immediately postinfusion. A large amount of ^{111}In was present in the large bowel at 24, 48, and 72 hr.

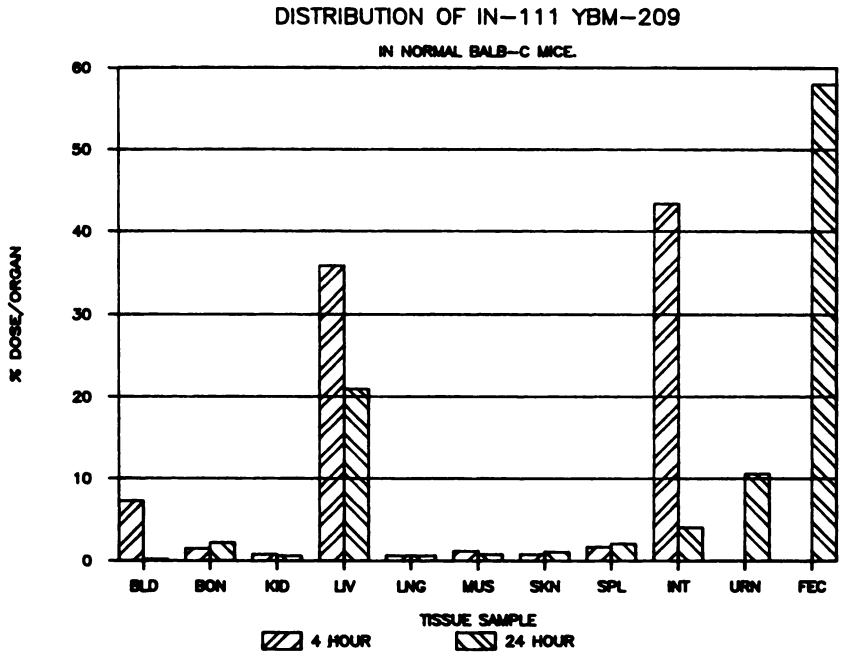

FIGURE 3
The 4- and 24-hr mouse distribution data from a [^{111}In]YBM-209 pentameric preparation is shown above. The blood levels decrease rapidly with marked liver uptake and rapid gastrointestinal concentration. By 24 hr over half of the ^{111}In has been excreted in the feces with ~10% cleared into the urine. Four mice/data point. Standard deviations for most organs range from 10–20% of the mean.

DISCUSSION

Human MoAbs offer theoretical advantages as radiopharmaceuticals for radioimmunoimaging. As proteins of human origin, they should be less immunogenic in humans than murine MoAbs which would allow repeated administration to patients with less danger of anaphylaxis or serum sickness. It is also reasonable to expect less cross-reactivity with normal tissue than occurs with polyclonal or monoclonal antibodies of animal origin. The first human MoAbs available to our group that exhibited tumor affinity were IgM. Little is known about the kinetics, body distribution, or excretion of this class of MoAbs in animal models or humans. Since a human radioimmunoimaging program was in place at our institution, it allowed for a comparison of the radiopharmaceutical in mice and humans. It was also possible to do mouse distribution studies of the radiolabeled material remaining in the patient's vascular compartment following its administration. There are a variety of interesting observations in these data.

There is a definite difference in the in vivo distribution of ^{111}In-labeled murine monoclonal IgG that we have studied in the past, and the ^{111}In-labeled human or murine IgM MoAbs used in these experiments. These

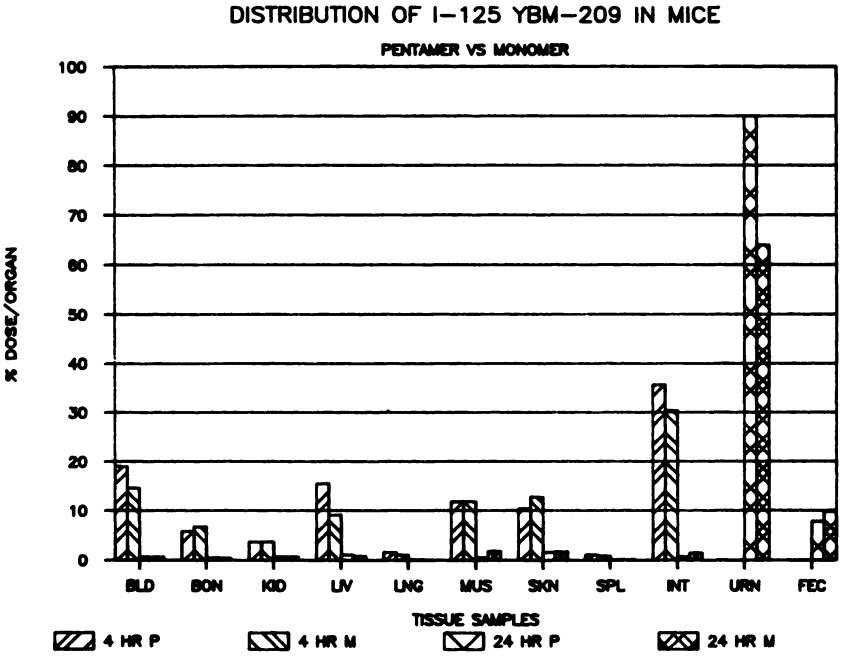

FIGURE 4
Results following the administration of a ^{125}I YBM-209 pentamer and monomer preparation to parallel groups of mice. The blood disappearance of the two species was similar. The data was similar for pentamer and monomer in all the tissues. The route of excretion was predominantly by the kidney with 90% of the pentamer and 64% of the monomer excreted by that route in 24 hr. Four mice/data point. Standard deviations of 4-hr data <10% of mean, slightly wider at 24-hr time period.

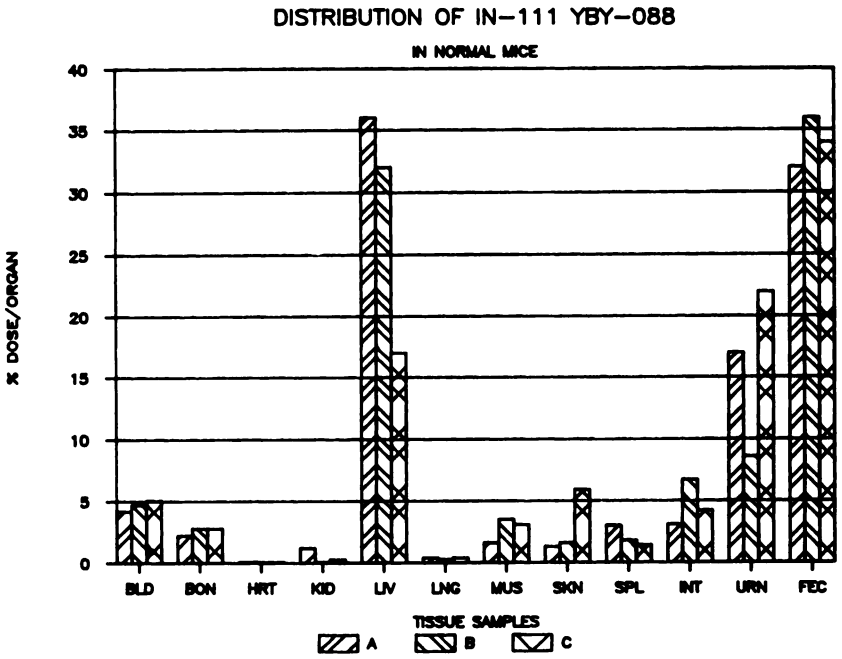

FIGURE 5
Distribution of the pentameric IgM [^{111}In]MoAb (A) prior to column purification (B), after column purification and (C), the material remaining in the patient's serum 24 hr after administration of the isotope. The mice were killed at 4 hr postinjection. The only major differences occur in C where less of the ^{111}In compound was acquired by the animal's liver. Five mice/data point at group A, six/data point in groups B and C. Standard deviations are ~20% for each group.

differences were obvious in both mice (*1,7,8,13*) and humans (*14–16*). Murine IgG MoAb exhibits a slower disappearance from the serum, less liver uptake and less gut and fecal excretion in the mouse than did human IgMs in the same model. This is in keeping with earlier data concerning IgM antibodies which indicate a shortened serum half-time vis-a-vis IgG antibodies (*5*). The rapid and marked uptake of [^{111}In]IgM MoAbs by the liver was also observed by Buchsbaum (*5*) who did not see this when ^{131}I was employed as the label. Our data indicates the liver uptake occurs with both endogenous ^{75}Se and exogenous ^{111}In-labeled material. This suggests that IgM MoAbs are rapidly acquired by the liver, a fact not obvious when ^{131}I is the label due to the dehalogenation. Further, the human IgM MoAbs cleared significantly from the liver and were excreted into the gut unlike IgG MoAbs which tended to remain at steady amounts in liver tissue over similar time periods. Interestingly, the distribution and kinetics of murine IgM and IgG in our studies were similar with the exception that the liver uptake of the IgM was three times that of the IgG. Very little of the mouse IgM was excreted from the liver into the gut, however, and the feces contained only ~6% of the injected dose of ^{111}In at 24 hr.

Our studies indicate that, while there may be some differences between the distribution and kinetics of endogenously labeled pentamers and monomers, the

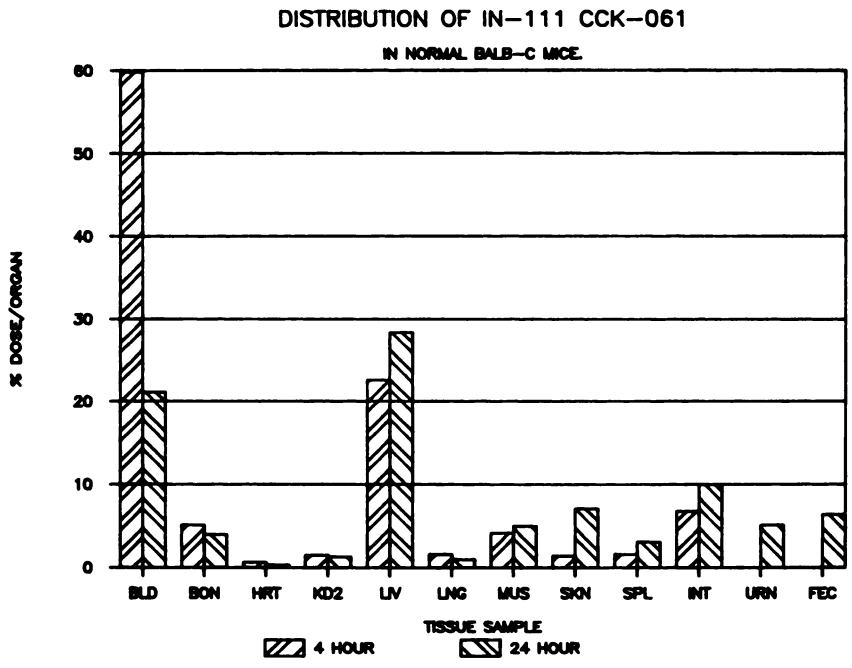

FIGURE 6
Distribution of a ^{111}In-labeled pentameric murine IgM. The blood levels remain higher for longer periods of time than occurred with human IgMs in the mouse, and there was less ^{111}In excretion in the feces. Six mice were used per data point with standard deviations ~10% of mean.

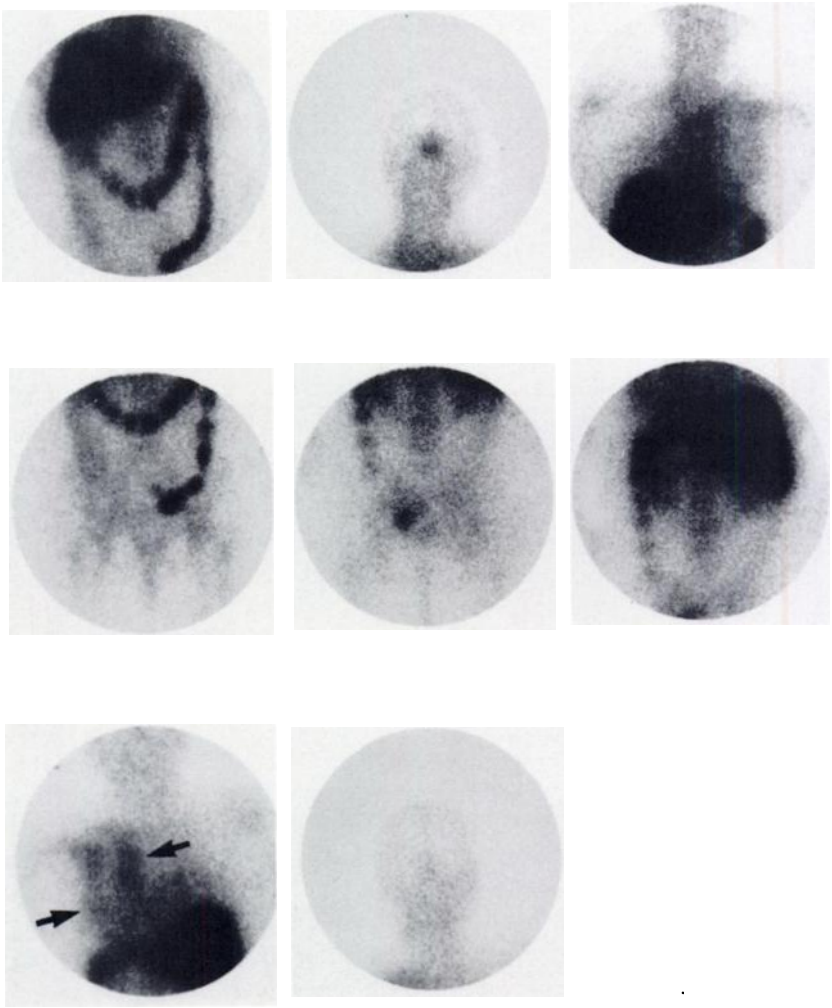

FIGURE 7
Scans of a patient with breast carcinoma 48 hr after receiving pentameric [^{111}In]YBY-088. The mouse distribution of this material is shown in Figure 5. Note the high liver uptake and the bowel uptake. Lesions (arrows) are present in the left lung.

distribution of the monomer (180,000 D) resembles that of the pentameric IgM MoAbs (~900,000 D) more than it does a murine IgG MoAb (150,000 D). In short, size of the molecule may not be the determining factor (or the only factor) in the human IgM distribution in the mouse model. The reasons for the above observations could be due to a difference in the quantities of carbohydrate present on the IgM and IgG molecules. Carbohydrates constitute at least 7–11% (*17*) of the intact IgM molecules but <5% of IgG (*18*). It is also known that carbohydrate receptors exist in the liver and can be found on both hepatocytes and reticuloendothelial components (*19,20*). Why or how the human IgM molecule is so rapidly excreted from the liver into the gut is unknown. In general, large molecules are not excreted through the biliary system. That this did not occur with murine IgM in the same mouse model is even more difficult to explain.

Another observation of note from this study is the difference between the overall kinetics and distribution of the IgM species based on radiolabels. While the general distribution of ^{111}In-labeled MoAb is similar to the endogenously labeled IgMs with rapid liver uptake and gastrointestinal excretion of the label, somewhat less of the ^{111}In remains in the bone, kidney, muscle, and skin at both 4 and 24 hr than is observed with the ^{75}Se label. This is different than what was observed when the same experiment was performed in IgG studies. There the ^{111}In data was highly similar to the ^{75}Se protein (*13*).

The radioiodinated IgMs, in contrast, show an early (4 hr) distribution slightly more in keeping with the distribution of the endogenously labeled IgM than does the ^{111}In label. However, by 24 hr the pattern radioiodinated MoAb exhibits is very confusing. The ^{125}I observed in the gastrointestinal tract, which should have been excreted through the feces, is predominantly excreted through the kidney. This probably represents free iodine since the ^{75}Se and ^{111}In labels that enter the gastrointestinal tract were not reabsorbed but eliminated in the feces. Free iodine is rapidly absorbed in the small bowel, then excreted in the urine if the thyroid gland is blocked, as it was in this experiment by the addition of potassium iodide to the drinking water for

3 days prior to the study. When the iodinated data from our study is compared with that from Buchsbaum et al. (*5*), Ballou et al. (*21*) and Pimm and Baldwin (*22*), the problems associated with interpreting in vivo studies performed with iodinated proteins become obvious. This is especially true of anything which is acquired by the liver since dehalogenation by this organ occurs relatively rapidly. If IgM antibodies are to be used in clinical studies, these data strongly indicate that isotopes other than iodine should be used as a radiolabel, or new methods of iodination should be used.

A comparison of the distribution and kinetics of the ^{111}In-labeled murine monoclonal IgM and human monoclonal IgM in the mouse model suggests there may be differences in the handling of the two molecules in the mouse. Ballou et al. (*21*) found a 24-hr blood disappearance of intact murine IgM that was less than for our murine MoAb; however, this could be due to differences in the particular MoAbs that were used in these experiments. While dehalogenation can account for the differences in the solid tissues, our data with murine IgG suggests that dehalogenation is not aggressive in the vascular compartment. Interestingly, while we did not find any large differences between the distribution of an intact pentamer and its monomer component, Ballou's group (*21*) found a very significant difference between the half-times of intact murine IgM and a labeled $F(ab')_{2\mu}$, with the pentamer remaining in the animals much longer than the fragment. Again, this could be due to individual MoAb differences, or in this case, to species differences, as our monomers were derived from human IgM. Another factor that might be important in the rapid disappearance of the IgM fragment is a further splitting of the molecule to a Fab' species, a phenomenon we have observed for $F(ab')_2$ derived from murine IgG (*23*). Why such changes occur, and why it is more or less characteristic for each particular MoAb is obscure.

While Pimm and Baldwin were unable to target tumor in a murine system using a radioiodinated IgM, their data indicates extremely rapid dehalogenation in the manner noted by Ballou et al. (*21*). We did not have an animal tumor model for this work, yet we did have human subjects and were able to image tumor in humans with at least two IgM MoAbs. While the first author agrees with Pimm and Baldwin (*22*) that size does effect entrance of MoAb into tumor with the smaller fragments entering faster than the larger molecules (*24,25*), our data indicate that an IgM can penetrate the capillaries and enter the tumor and result in tumor targeting as shown in Figure 7, and in other patients studied in our laboratory (*26*). Blood levels remain much higher and liver levels lower when murine IgMs are administered to a mouse than when human IgMs are administered. Furthermore, the excretion patterns are different for the two. Whether this is unique to the particular murine IgM MoAb that we have chosen to study or whether we are looking at a true species difference, is impossible to say since we have data on only one murine IgM MoAb.

Compartmentalization is a problem with murine IgGs in humans (*15*), and it is frequently necessary to "saturate" some of these unknown "binding sites" with unlabeled MoAb (*16*). This is accomplished by increasing the MoAb mass. In fact, we found that this was still necessary in the IgM studies performed in humans employing YBM-209 and YBY-088 (These data will be the subject of a separate communication) (*26*). The distribution of the ^{111}In IgM antibodies in the human resembles that of the mouse with high liver uptake and in some cases dramatic excretion into the feces. In fact, the excretion from the biliary system in one patient was so rapid that it caused the gallbladder to visualize. HPLC analysis of serum from the patient on TSK-2000 and TSK-3000 indicated that the ^{111}In labeled materials remained attached to a pentameric size molecule 24 hr after administration. This ^{111}In species had a distribution in mice similar to both the column purified and noncolumn purified material with the exception that the uptake in the liver was less than for the native materials. At the time of this writing, the reason for this phenomenon is unknown; however, it could represent aggregates of damaged MoAb (but not apparently so) or less likely some form of colloidal indium. Similarly, it has not been possible to identify what IgM species adheres to the G-75 and S-400 column. The bound fraction cannot be eluted under nondenaturing conditions, and pre- and post-column radiolabeled antibody is identical in specific activity, charge and molecular weight. Most IgM antibodies show nonspecific binding to a variety of solid phases including glass and plastic. Thus, we believe the presence of a fraction of the radiolabeled antibody which binds Sephadex columns is an inherent property of IgM molecules, possibly due to large size, extensive glycosolation, and poor solubility. These properties may be useful in triggering in vivo immunological properties associated with IgM antibodies such as agglutination and complement fixation.

In summary, human IgM MoAbs appear to have unique properties in vivo as compared to murine IgG MoAbs. The monomeric derivatives are similar to the pentamers in distribution. High liver uptake and fecal excretion characterizes these species when labeled endogenously with [^{75}Se]methionine or exogenously with ^{111}In. Iodination of IgM MoAbs led to rapid dehalogenation in vivo. Early evidence suggests that tumor can be targeted with labeled IgM MoAbs but obvious problems remain in their use.

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