Progress in the Radionuclide Therapy of Cancer

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The mainstay of treatment of cancer is surgery. External beam radiotherapy has a long history, it is effective but it is local and cannot deal with the systemic nature of cancer which is being more and more appreciated. Chemotherapy is effective, is systemic, but it is not particularly selective. The therapeutic ratio is often small and adequate chemotherapy is confounded by a high level of unpleasant side effects, including marrow and immunological depression. Nuclear Medicine has a tradition of internal radiotherapy going back for forty years. The most usual approach is dependent on cell function such as the uptake of ^{131}I by thyroid cancer once all normal thyroid tissue has been ablated by surgery and ^{131}I therapy. The treatment of Polycythaemia with ^{32}P has a long history[1] but, more recently, bone metastases have been treated with Strontium 89 or Samarium 153 derivative, again dependent on the metabolic function of the bone beside the metastatic disease.

The newer approach to radionuclide therapy of nuclear medicine is dependent on tissue characterization either by using the ability of receptors present on cancer cells to bind the radionuclide bearing radiopharmaceutical, or by the use of surface antigens on the cancer cell to bind radiotherapy labelled antibodies. It is in nuclear medicine that the increasing variety of therapeutic approaches to cancer is giving a new subspecialty in this field. The treatment of thyroid cancer with Sodium ^{131}I has a long history which I will not repeat, but there are some lessons from that conventional treatment which are generally applicable to all the newer methods of therapy. First there is confirmation of the in vivo tumour uptake of the radionuclide before therapy. Secondly there is a need to avoid interfering drugs. Thirdly a long-lived beta-emitting radionuclide is used for successful therapy. Fourthly, a high activity repeated not earlier than six monthly is needed for successful therapy. Fifthly, a rapid excretion pathway to reduce normal tissue irradiation is one of the essential aspects of the success of ^{131}I therapy. Lastly, and of increasing importance though recognised for many years by Beierwaltes[2], there is an avoidance of immunosuppression when radionuclide therapy is used which allows a normal immunological response to the radiodamaged cells. Indeed, it is this retention of the host reponse that may be the most important key to the success of the radionuclide therapy. Conventional calculations of the absorbed dose from radionuclide therapy and the very slow dose rate, perhaps one or two centigray per hour, are quite different from those from external beam therapy and, indeed, it is to be wondered why radionuclide therapy is successful unless there is also an element from the host response.

BONE METASTASES

The use of bone scanning to demonstrate and follow up the progression of cancer in bone metastases from prostate cancer or breast cancer are well known. For many years ^{32}P has been explored as a method of treating bone cancer but never received

Table 1. Radiopharmaceuticals for the Therapy of Osseous Metastases

	T½	Betamax	Gamma KeV	Av. Range mm.	Pain Response
153—Samarium EDTMP[16]	46h	0.81	103 (28%)	0.8	17/26 (65%)
186—Rhenium HEDP[17]	3.8d	1.07	137 (9%)	1.0	33/44 (77%)
32—Phosphorus[18]	14.3d	1.71	–	2.5	611/766 (80%)
89—Strontium[19]	50.5d	1.46	–	2.0	395/500 (79%)

HEDP Hydroxyethylidene diphosphate
EDTMP Ethylene diamine tetra methylene phosphate
References 16–19

much popularity because of the tendency to bone marrow depression. Now there are four radionuclides which can be used for the treatment of bone metastases (Table 1). It can be seen that they range from the short-lived use of Samarium-153 with a 40h half-life to that of Strontium-89 with a 50.5 day half-life. While gamma emission may be helpful as in Samarium-153 and Rhenium-188 for confirming that there is uptake of the radionuclide therapy by the bone metastases, nevertheless this is easily demonstrated by the conventional Technetium MDP bone scan, the gamma emission raises a potential hazard to staff and visitors and may require hospital admission for radiation protection purposes. The use of the pure beta emitters such as ^{32}P and Strontium-89 do not have this disadvantage and can be used totally for outpatient therapy. Success with these techniques is generally similar with perhaps the edge on the long-lived radionuclides ^{32}P and Strontium-89 (Table 1).

The value of Strontium-89 has been emphasised by multicentre studies in Canada and in Scotland. Quilty et al (1992, in press) have shown the benefit of combining external beam radiotherapy and Strontium as compared with external beam radiotherapy alone. With a combination treatment pain improved in bone metastases from prostate cancer in 56% as compared with 44% for the radiotherapy treatment of bone but, more importantly, no new sites of pain occurred in 46% with a combined treatment as compared with 23% with radiotherapy alone. Greater bone marrow depression occurred with both treatments. Platelet counts fell to, on average, half the previous value with the combined therapy as compared with two thirds of the previous value with the external beam therapy alone.

The lessons we can learn then from Strontium-89 therapy for bone metastases is that, again, a very long lived beta emitter gives good pain relief with successful therapy; that a low dose therapy acting over a long period of time is beneficial; that high specific uptake allows the even slow excretion from normal tissues to give a good therapeutic ratio with some marrow depression that is not significantly harmful to the patient, for platelet transfusions are not required; and that a pure beta emitter enables out-patient treatment.

LIVER METASTASES

There have been a number of approaches to the treatment of liver metastases from colorectal cancer and for hepatoma. Firstly, hepatic resection is used for solitary liver metastases that have been identified radiologically, but it still seems illogical that the removal of a large single metastases is not the tip of an iceberg where there are multiple small, perhaps undetected, metastases remaining in the liver and other sites. Secondary, hepatic arterial embolism of liver metastases has shown no benefit over control patients in terms of survival. Hepatic arterial chemotherapy with 5-fluorourocil and

starch microspheres has shown a marginal benefit. More successful has been hepatic arterial ^{131}I Lipiodol, particularly for primary hepatoma with a 50% survival between five and seventeen months, but it is less beneficial for colorectal metastases. Hepatic arterial glass ^{90}Y-labelled microspheres coupled with the use of angiotensin II to cause vasoconstriction of the normal hepatic circulation, thus increasing the distribution to the metastases, is showing encouraging results initially. As yet, experimental hepatic arterial infusion of ^{131}I-labelled anti-CEA antibodies for colorectal metastases has shown slight encouragement if the metastases are small. It may be that this approach should be coupled with both starch microspheres and the angiotensin II infusion to help to redirect the infused radionuclide carrying antibody to the liver metastases.

TISSUE CHARACTERIZATION

Selective receptor binding

The list of receptor binding radiopharmaceuticals that bind to benign and malignant tumours is increasing considerably (Table 2). So far, most of these are used diagnostically but, for example, Rhenium-186 has been substituted for Techetium-99m in DMSA for the proposed treatment of medullary carcinoma of the thyroid. Successful imaging of gastroendocrine tumours with ^{123}I or ^{111}In-labelled

Table 2. Receptor Binding Pharamaceuticals

I–123 MIBG	Neural crest tumours
Tc–99m. V. DMSA	Medullary carcinoma of thyroid
F–18 oestradiol	Breast cancer
I–123 hormones	
– I–123 Octreotide	Somatostatin receptors
– I–123 Insulin	Diabetes Mellitus
Prolactin	Pituitary and target organs
GHRH	Pituitary and target organs
Vasopressin	Diabetes Insipidus
– I–123 Interleukin	Autoimmune disease
– I–111 Pentreotide	Gastroendocrine tumours

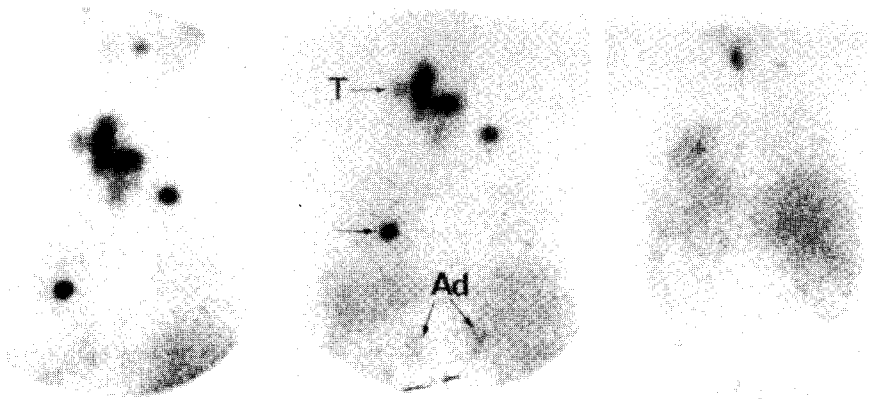

Fig. 1. I-131 MIBG Therapy in malignant paraganglioma. Images of the anterior chest: left, before the therapy widespread focal areas of increased uptake are seen in the upper mediastinum and lungs. Biochemistry was grossly abnormal and patient was unable to work. Centre, one year later after 300 mCi of I-131 MIBG (T, Tumour; arrow, lung deposit, Ad, normal adrenal uptake). Left five years later after 1 curie of therapy. The resolution of the tumour is evident. There is still some mediastinal uptake in perhaps sterile tumour. Biochemistry is now normal. Patient is back at work and has fathered three children.

Octreotide[3] is leading to the potential use of ^{131}I or ^{90}Y-labelled Octreotide as a therapeutic agent, but there is a concern that significant irradiation of the normal pituitary may be detrimental. ^{123}I MIBG has become the established technique for demonstrating neural crest tumours, malignant phaeochromocytoma and malignant paraganglioma, and the therapeutic use of ^{131}I MIBG is now also established. The results of imaging with ^{123}I MIBG and of therapy with ^{131}I MIBG are shown in Table 3 together with an example of the improvement in the treatment of a malignant paraganglioma in a patient over 7 years using ^{131}I MIBG (Fig. 1).

Lessons that can be learned from ^{131}I MIBG therapy or malignant phaeochromocytoma and paraganglioma are almost the same as those for ^{131}I therapy of thyroid cancer. Confirmation of in vivo tumour uptake first before therapy using ^{123}I MIBG, avoidance of interfering drugs including nose drops, ear drops, various drugs for asthma, antidepressants including Reserpine and Adrenaline and Noradrenaline-like drugs. Again, a long-lived beta emitter is used for radionuclide therapy, and a high activity is repeated not earlier than six-monthly. There is again rapid excretion of ^{131}I MIBG through the kidney to reduce normal tissue irradiation and avoidance of immunosuppression which allows a normal immunological response to develop against the malignant tissue. While such therapy is not curative in this group, nevertheless significant benefit and partial remission and indeed, sterilisation or apparent sterilisation of the tumour, although able to continue to take up the radiopharmaceutical, has been demonstrated.

The following scheme is used in our hospital for ^{131}I MIBG therapy of childhood neuroblastoma. The patient is selected by the paediatric oncologist; a full explanation to the parents, who must understand exactly what the therapy involves from the point of view of their child, themselves and their other children, is given; informed signed consent is obtained and their cooperation in the management of the child during this period of isolation is essential. Interfering drugs that I have indicated previously are stopped for at least two days. A diagnostic study with ^{123}I or ^{131}I MIBG is made after the completion of the chemotherapy and not during chemotherapy, to confirm in vivo tumour uptake. If ^{131}I MIBG is used for imaging (not recommended) then an estimate of the dosimetry may be obtained. There is now a formula for relating the child's body weight and the required dose to give a maximum whole body irradiation of 2 to 2.5 Gray. Dose in GBq=0.55 kg−1.79. This allows one to estimate an appropriate dose, usually of the order of 11 GBq (300 mCi) millicuries ^{131}I MIBG in a four year old child.

The haematological status is important. The ^{123}I MIBG scan will have shown the extent of bone marrow involvement and this may be a contraindication to therapy if bone marrow involvement is extensive. Alternatively, bone marrow salvage can be undertaken with cleansing of the bone marrow using an anti-neuroblastoma antibody, so that clean bone marrow is available for reinfusion should significant marrow depression occur. That significant marrow depression does occur is a consequence of the previous extensive chemotherapy in combination with the additional MIBG therapy in many cases. Thyroid blockade is essential with Potassium Iodide or Potassium Iodate starting the day before and continuing for at least three weeks during therapy, Potassium Iodide 60 mg bd is appropriate. When the ^{131}I MIBG is ordered, it is important at the time of therapy to check a small sample for its chromatographic purity. At least in the early days, and still, some manufacturers allow far too much free ^{131}I to be present in their so-called pure ^{131}I MIBG. Some claim on the manufacturer can then be made if an unacceptable level of ^{131}I contamination is found.

If a child is under $2^1/_2$ or if incontinent, it is essential to catheterise the child. Because of the high urinary excretion of ^{131}I MIBG, contaminated

nappies or bed linen represent major radioactive spills and are a hazard. The therapy is carried out in the special therapy side ward with a contained shower and toilet which should be in the paediatric ward. We have built and designed such a ward for this therapy since treating young children in an adult therapy ward was found to be very unsatisfactory. The cooperation of the nursing staff, the radiation physicist and the parents is essential.

An automated infusion system is used for the ^{131}I MIBG which is infused over 60 minutes under distant supervision. The blood pressure is monitored but in fact we have found this to be unnecessary if the infusion is given over this time with no hypertension or hypotension being recorded. However, an automatic blood pressure monitor would save irradiation to nursing staff. The child is monitored in the ward for three days and then comes down to the department for a whole body monitor using a shadow shield counter for profile and for imaging the areas of high uptake using a heavily collimated gamma camera. This is repeated at 5 to 7 days and at 2 weeks and 4 weeks so that the total body dose and the dose to the tumour can be obtained retrospectively although this is at best a very inaccurate measure. The child is not allowed home until there is less than one millicurie of therapy remaining and it may take two weeks for this to be achieved. This is particularly essential if there are young children at the home. It may be that the child undergoing treatment, or these other children, are sent to relatives to stay for the first week after the treated child leaves hospital if it is essential to get him or her home earlier. During the follow-up period, weekly full blood counts are undertaken for at least six weeks and then consideration is given to repeating the therapy, usually not earlier than six weeks, although some workers recommend repeat treatment as early as two weeks. Hofnagel summarised the benefits of diagnosis and treatment of neuroblastoma with radioiodine labelled MIBG at a meeting in Rome. Of 127 patients imaged with ^{123}I MIBG, the true positive rate was 106, true negative 16, false positive 0 (sensitivity 100%) false negatives 5 (specificity 76%) possibly related to unsuspected interfering medication. ^{131}I MIBG therapy in 273 patients gave an objective partial remission in 35%. It must be remembered here that all these patients were endstage neuroblastoma patients after completion of full surgery, external beam therapy and chemotherapy courses. Höfnagel[4] has recommended and undertaken the much earlier introduction of ^{131}I MIBG in therapy in fact, even before surgery, to cause the shrinkage of the tumour to make it operable, previously undertaken by chemotherapy. While many may not go along with this very early use, at least in my view, ^{131}I MIBG therapy should be

Table 3. Radioiodine MIBG Imaging and Therapy

123—I MIBG Imaging	Total	True Positive	True Negative	False Positive	False Negative
Paraganglioma	136	59	72	1	4
Neuroblastoma	127	106	16	0	5
131—I—MIBG Therapy					
	Complete Remission	Partial Remission	Biochem Response	Stabilisation	Progression
Malignant paraganglioma	3%	35%	24%	13%	25%
Neuroblastoma		35%			65%

Report of the International Meeting on MIBG Rome, 1991
(Ackery & Höfnagel personal communications)

introduced immediately after the first course of chemotherapy when the tumour has an intact MIBG transport system and before it becomes progressively less organised with each recurrence. In this situation complete remissions of neuroblastoma should be expected. A problem here then becomes obtaining appropriate patients for such studies since the chemotherapy manufacturers are encouraging all neuroblastoma children to enter their chemotherapy trials making them thus unavailable for ^{131}I MIBG therapy trials.

RADIOIMMUNOTHERAPY

The diagnostic use of radiolabelled monoclonal antibodies has been well recognised. With the introduction of stable simple Technetium-99m labelling of monoclonal antibodies this diagnostic approach to cancer has become routine in several centres around the world. The application of radionuclide labelled monoclonal antibodies for therapy is much more difficult. First, for diagnostic imaging only small amount of the antibody need be taken up since, if only the outer cells of the tumour are labelled still the tumour is identified for diagnostic purposes. For therapy, penetration of the whole tumour by antibody-carrying radionuclide is required. Secondly, the residence time of the antibody for a diagnosis need only be twenty-four hours whereas for therapy, particularly with long-lived beta emitters, then a much longer residence time for the antibody on the tumor is required. That this is reasonable has been shown by Martin et al[5] who have used ^{125}I labelled antibodies for intraoperative probe guided diagnosis. Here, they inject an ^{122}I-labelled antibody up to 30 days before operation and still demonstrate specific uptake on tumour as compared with the non-tumour or normal tissues using probes at operation. Thirdly, and most importantly, it does not matter for imaging if there is a high background provided that there is a good signal such as that given by ^{99m}Tc, whereas for therapy this is a real problem. At present a typical

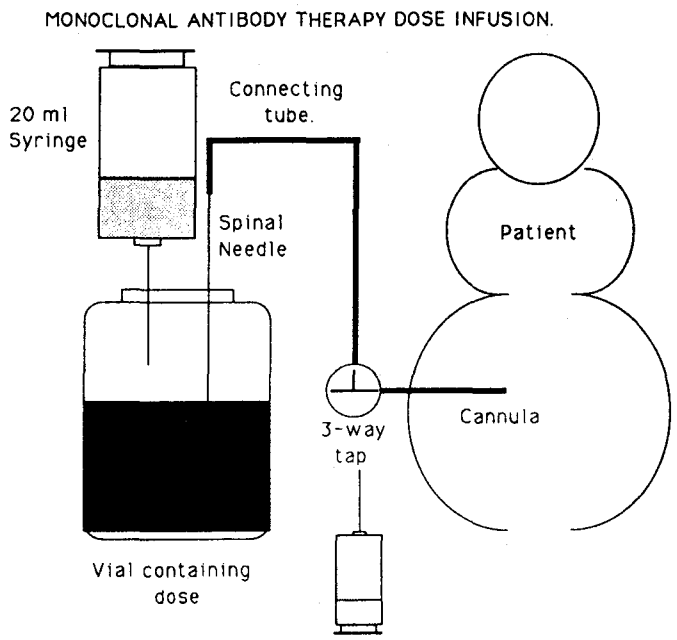

Fig. 2. Diagram of the apparatus for intraperitoneal radioimmunotherapy.

tumour may take up between 1~3% of the injected radionuclide antibody, meaning that there is 97% plus remaining in the whole body and of which half perhaps will be excreted through the kidneys. Thus the therapeutic ratio is grossly detrimental to the treatment of tumour by a simple intravenous systemic injection.

To overcome this problem various forms of regional or intracavity approach have been used. First, the intracavity treatment of malignant ascites using infusion of ^{131}I or ^{90}Y-labelled antibodies was proposed by Epenetos et al[6]. The set up is shown diagramatically in Fig. 2 and the steps in Table 4. An image of the distribution of the uptake after intraperitoneal refusion is shown in Fig. 3. It should be noted that, in spite of Potassium Iodide for thyroid suppression, there is uptake in the thyroid since the ^{131}I labelled antibody is metabolized by the presence of deiodinases in the liver and kidneys.

The results can be summarised as generally unsuccessful. Solid tumours, even under two centimetres in diameter, showed little or no response but malignant ascites could be treated successfully with relief of recurrence of ascites for up to four months as compared with, usually, three to four weeks in the untreated patient[7]. In view of these results, it was felt that an alternative radionuclide such as Yttrium-90 should be used. This has a half-life of 64 hours, beta energy 2.2 MeV with a range of 2.3 mm on average, maximum 11 mm. This is conjugated to the antibody using DTPA[8]. Infusion intraperitoneally of ^{90}Y-labelled antibody had a problem in that the ^{90}Y would leach off the antibody and have a maximum uptake in the blood by about 50 hours. Then the

Table 4. Steps in Intraperitoneal Radioimmunotherapy

1. Insert flexible cannula into patient's abdomen under local anaesthetic and draw off ascites. Replace with 1.5 litres of dialysis fluid.
2. Connect vial to patient via sterile needle, an infusion extension line, a three way tap and the cannula.
3. Connect 10 ml syringe to three way tap, and with tube to dose vial closed, inject 10 ml saline into patient, to check line is free of obstruction.
4. Insert syringe containing 20 ml saline into top of vial, ensure pathway to patient is open and slowly inject saline into vial. The pressure forces the dose into the patient.
5. Switch three way tap off in the direction of the patient. Draw up syringe full of air and insert into vial.
6. Reopen tap and inject air into vial. Air will force remaining liquid into the patient. Turn off tap.
7. Remove cannula ensuring no leaks.

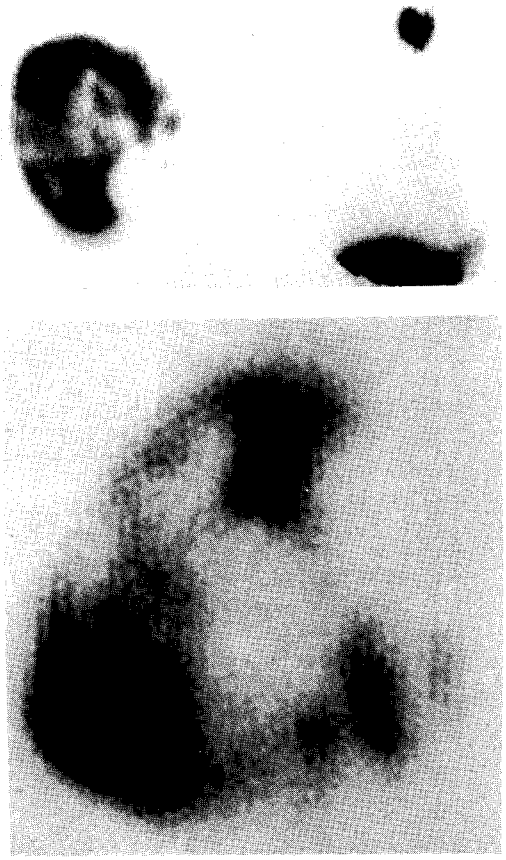

Fig. 3. I-131-HMFG2 monoclonal antibody. Bottom, anterior abdominal images at 24 hours after infusion for therapy (100 mCi) showing the irregular, but specific, uptake in the abdomen at tumour sites. Top left, Right lateral view of abdomen; Top right, anterior chest, uptake in the thyroid although 'suppressed' by Potassium Iodide and Potassium Perchlorate.

blood level would remain high causing a high marrow uptake since ^{90}Y is a bone seeker. There was up to Grade 4 myelotoxicity, even from, on average, 30 millicuries. Stewart et al[9] showed that by infusing EDTA to chelate the free ^{90}Y leading to its renal excretion, a doubling of the administrated dose could be obtained with a halving of the myelotoxicity. Nevertheless, in solid tumour and small tumours intraperitoneally no benefit was demonstrated. However, there was a dramatic benefit to be found in patients who had no evidence of intraperitoneal disease at the time of the infusion. In this adjuvant role, ^{90}Y-labelled monoclonal antibody showed a five-year survival in 14 patients of over 90% whereas a contemporaneous clinical trial without such treatment showed that the usual five-year survival for similarly graded patients with ovarian cancer would be 25% (Epenetos, Personal Communication).

This dramatic improvement needs to be explained. It is difficult to conceive that a small dose of ^{90}Y can have caused such benefit and it appears more likely that two things have happened. First that the damaged ovarian cancer cells have become recognised as foreign by the host and the immune response activated, and at the same time the idiotype system has been activated. The antibodies of murine origin and anti-idiotype 1 reaction leads to an anti-idiotype 2 reaction in the human. In this way, an antibody is produced by the host which recognises the tumour surface antigens. Evidence for such an approach has been obtained both by the demonstration of idiotype 2 antibodies even after infusion of diagnostic doses of antibodies by Oehr in Bonn[10] and activation of T-lymphocytes in response to antibody infusion has also been demonstrated. Thus the importance of the host response is again emphasised.

BRAIN TUMOURS

For a long time, intracystic therapy with ^{32}P Chromic phosphate has been used for cystic gliomas of the brain with some benefit. Recently, Coakham et al[11] have shown that cerebral malignant meningitis can be treated effectively by the infusion into the cerebro spinal fluid of ^{131}I-labelled appropriate monoclonal antibody such as UJ13A reacting with medulloblastoma or pinealoblastoma. They have demonstrated that, in a selected series of patients, a 62% response rate was found with survivals up to two years compared with the mean survival of a patient with cerebral malignant meningitis of about three months. Thus it can be seen that the intracavity approach has benefits when the cavity is closed and when a host reponse to the tumour after the radioimmunotherapy can be mounted.

1. Systemic Radioimmunotherapy

While intracavity and intraarterial radioimmunotherapy may have benefit in special cases and systemic therapy may have benefit in lymphoma or other malignancies where there is good blood access, the major cancer problem is that of solid tumours and a new approach is required. Time factors are the key to radioimmunotherapy[12,13]. For any given antibody the residence time in the blood determines the supply to the tumor and the radiation dose to the critical organ. For any given activity taken up, the residence time in the tumour determines the radiation dose to the tumour. For any given uptake the ratio of the residence times in the tumour to the residence time in the critical normal organ will determine the therapeutic ratio. Therefore a long lived therapy radionuclide with a half life of weeks may be more effective than a short lived one whose therapeutic radio dependes primarily on relative uptake. If the non tumour radionuclide can be rapidly excreted and the tumour radionuclide can be retained for a considerable length of time, then it is the differential biological half life that will give the good therapeutic ratio. Since this cannot be achieved by a single systemic injection, it is clear that a two or

three stage approach must be used. The first of these was to make use of the avidin-biotin system. The avidin-biotin system has a very high binding constant, 10^{15} litres per mole, and streptavidin or avidin has four binding sites for biotin. Biotin is linked to the antibody then injected. Avidin is given three days later to bind to the antibody bound to the tumour and to bind to the antibody that is circulating and clear it to the liver and reticuloendothelial system. Then the radionuclide label attached to another biotin can be infused as a third stage and target the avidin bound to the biotinylated antibody, bound to the tumour. If a small radionuclide ligand such as radiolabelled biotin is used, then renal excretion will clear it from the body and thus give the good therapeutic ratio that is required. Such an approach has been developed successfully by Paganelli (1992) who demonstrated that this sandwich technique works in man, at least initially for imaging, and that the third stage of ^{111}In-labelled biotin led to high quality images of tumour within an hour of the administration. Problems with this approach include the development of antibodies against avidin and the fact that the radionuclide biotin is taken up by the kidney which is avid for biotin rather than just being excreted.

An alternative approach is to use a bifunctional antibody, an antibody that is bispecific with one specificity for the cancer antigen, one specificity for the radionuclide labelled ligand. In such an approach the bifunctional antibody would be administered first. A period of two or three days wait would then follow. During this time the antibody targets the tumour and clears from non-tumour tissue by the reticuloendothelial system. Then the ligand labelled radionuclide is administered and targets to the antibody. Bispecific antibodies may be made by the quadroma technique where two hybridomas, each with the appropriate specificity, are fused together: or by chemical linkage of two Fab'$_2$ or Fab or Fv pairs, each with appropriate specificity; or else, to improve valency, a triplet with one Fv specific for the radiotherapy ligand and two Fvs specific for the cancer antigen so that higher avidity of the complex is ensured. Alternatively, linked, genetically engineered single chain antibodies could be used or else molecules mimicking antibodies, so-called mimic molecules, may be synthesized. In such a two-stage approach, an appreciation of the list of possible radionuclides for therapy indicated that those that are short-lived would then not be used. Only those such as ^{114m}In with a 60 day half life, a 2MeV beta with 80% abundance and a weak gamma energy would be used, or ^{32}P with a 14-day half-life, 1.7 MeV beta emission with 100% abundance with a mean beta range of 2 mm and a maximum of 8 mm.

If such an approach to cancer is used, then one needs to reconsider the basic radiobiology of this approach. Traditionally, the radiobiology of external beam radiation has been extrapolated from a high dose, short-lived burst of energy to the low dose long-lived effects of radionuclide therapy and there is also a tendency to extrapolate the concepts of DNA double strand breakage and repair from high dose external beam therapy to low dose radionuclide therapy. Indeed, this may be totally inappropriate since the dose from radionuclide therapy is, usually, of the order of 2 centigray per hour over several days or weeks as compared with hundreds of centigray per minute over a hort time period. Rather than blasting DNA strands as for external beam therapy, this internal irradiation may well be disrupting the transfer of information from the cell surface to the cell nucleus and distorting the cell surface membrane proteins so that they are recognised as foreign by the host. The internal radionuclide therapy appears to be subverting cellular repair rather than breaking DNA strands. The higher the frequency of the elemental doses and the longer the repetition, provided this frequency is much greater than the repair frequency of about 4 hours per cell, then the internal radiotherapy would be effective. Another

advantage is that long-lived radiation doses may mean that the cells of the tumour will be likely to enter the more radiosensitive G2 part of the cycle during an irradiation time lasting weeks rather than a few minutes. For example, a typical turnover rate of 12 days for a stem clonogenic cell would be dealt with using a radionuclide with a half life of 14 days, which may be much more effective than a radionuclide with a half life of two to three days that many are recommending. The advantages of ^{32}P radioimmunotherapy in this context can then be summarised. It has a long half life of 14.3 days. Its moderately high beta energy of 1.171 MeV gives a tumour penetration cross fire of up to 8 mm. The lack of gamma emission allows for simple radiation protection of the staff and family. There is a pro-drug effect. When the ^{32}P-labelled antibody is metabolized, the ^{32}P Phosphate will be freely diffusible at the site of the tumour and be taken into the tumour and incorporated in the tumour RNA and DNA and, from this fixed site, be able to continue the irradiation of the tumour. At equivalent administered dose it has been shown that ^{32}P is twice as effective as ^{90}Y[14]. Oral effervescent sodium phosphate may be used to dilute the effects of radiophosphate on normal tissues. There is a long established clinical usage of ^{32}P for Polycythaemia and intracavity treatment of cancer so problems with regulatory authorities may be lessened.

^{32}P is suitable for two or three stage immunotherapy. ^{32}P may be linked to an antibody through the Kemptide sequence. This is a naturally occurring amino acid sequence of seven amino acids which binds phosphate in a stable way. ^{32}P Phosphate is introduced by a phosphokinase using AT^{32}P although simpler methods are being developed[15]. We have started to use ^{32}P-labelled antibodies in this way in a phase-1 trial in Polycythaemia where its likely marrow side effects would have a potentially beneficial effect.

The scheme for two stage bifunctional radioimmunotherapy then is as follows: Firstly, the preparation of the bifunctional antibody which should include a site for binding Technetium so that Technetium-labelled bifunctional antibody can be administered and in vivo uptake of the antibody by the tumour confirmed. Then a wait of three days is made. Then the ^{32}P Kemptide ligand is injected and binds to the bispecific antibody. The ^{32}P ligand that is unbound is cleared through the kidneys, thus giving a good therapeutic ratio. In conclusion, using a conventional approach, the percentage of the injected dose taken up is still too low and the therapeutic ratio is consequently much too low. Intracavity therapy is a possible method for a closed cavity such as cerebral malignant meningitis, and in microscopic residual disease, malignant ascites and as an adjuvant approach. It seems likely that ^{131}I will not be used as the radionuclide of choice because of the difficulties in patient management due to the high gamma emission and it is likely that alpha emitters which are short-lived will also not be appropriate since a one to one antibody to cancer cell uptake has to be fulfilled. The accumulation of antibody in the tumour will not be greatly improved, for the best cytokine stimulation of tumour uptake experimentally appears to increase antibody uptake by not more than two-fold. The sandwich technique has been shown to work in vivo. Thus a two or three stage approach to radioimmunotherapy with a long lived pure beta emitting radionuclide such as ^{32}P will be the most appropriate. Genetically engineered bispecific CDR grafted designer molecules incorporating specific radiolabelling site for imaging with ^{99m}Tc, a therapy ligand binding site and a tumour specific binding site of improved affinity should be successful. There is real progress in the radionuclide therapy of cancer.

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