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Biological hazards of radiation

G. W. DOLPHIN
National Radiological Protection Board, Harwell, Didcot, Berks.

Stevenson, Bedford, Dolphin, Purrott, Lloyd, Hill, Hill, Gumpel, Williams, Scott, Ramsey, Bruckner, and Fearn (1973) reported that high chromosome aberration yields in lymphocytes were found in those patients treated with injections of ^{198}Au or ^{90}Y for rheumatoid conditions of the knee when radioactivity had leaked along the lymphatics to the inguinal lymph nodes. This leakage and the consequent high doses to the regional lymph nodes had been observed and reported earlier by Virkkunen, Krusius, and Heiskanen (1967). More recently de la Chapelle, Rekonen, and Ruotsi (1972) have shown that the leakage and the chromosome aberration yield can be reduced by immobilization of the patients after injection.

The purpose of this paper is to discuss the biological significance of the chromosome aberrations observed in lymphocytes and the significance of the radiation dose to body tissues in the patients treated with ^{198}Au or ^{90}Y as reported in the study by Stevenson and others (1973).

Selective irradiation of lymphocytes

Although details of the lymphocyte circulation in the blood and body tissues are not fully understood, there appears to be a rapid exchange from peripheral blood into the lymphatic system which probably takes place in the lymph nodes. If radioactive particulate lodges in the lymph nodes, as in the case of some patients given intra-articular injections of radio gold or radio yttrium, then the lymphocytes will be selectively irradiated as they pass through these nodes. Hence the average radiation dose to the lymphocytes indicated by the aberration yield in their chromosomes is not representative of the mean whole body dose.

Chromosome damage and its relation to radiation-induced cancer

The presence of abnormal chromosomes and aneuploidy in cells taken from solid tumours has been recognized for many years (Koller, 1972). The question of immediate interest is whether the presence of abnormal chromosomes produced by irradiation are precursors of malignant tumours which develop at some later date. For chromosome abnormalities in lymphocytes this question presumably relates to leukaemia.

The only known example of a chromosome anomaly associated with leukaemia is the Philadelphia (Ph) chromosome. This was first observed by Nowell and Hungerford (1960) in the blood cells of patients with chronic myeloid leukaemia. The Ph chromosome has now been identified as No. 22 chromosome with most of the long arm missing. By means of chromosome banding techniques, Rowley (1973) has observed that the missing part of the long arm from No. 22 chromosome has been translocated to No. 9 chromosome. Borgaonkar (1973) has suggested that, if Rowley's observation is correct, then this is the first example of a translocation of chromosome material within the genome which causes phenotypic effects. As chromosome banding techniques which enable translocation to be more easily observed have only just been developed, there may be other phenotypic effects associated with translocations which have not yet been recognized. There is little doubt that, if chromosome damage plays any part in the development of cancers, then it will be through the stable rather than the unstable aberrations.

At present, estimates of the risk of radiation-induced cancer after irradiation can be made only from radiation dose and not directly from the observed aberration yields, but only indirectly by means of calibration curves relating these yields to radiation dose.

Risk of cancer after irradiation of adults

There is considerable evidence from the study of Japanese survivors (Jablon and Kato, 1971) and of patients irradiated for medical purposes that cancer may be induced by external radiation. From these studies it is possible to obtain tentative values for a risk coefficient; usually expressed as the number of cancers per 10^6 man-rads. Values for risk co-efficients have been derived by international groups such as the

International Commission on Radiological Protection (ICRP, 1966), United Nations Scientific Committee on the Effects of Atomic Radiation (1972), and the National Academy of Sciences (1972). All these groups assumed a linear relationship between radiation dose to the whole body or to body tissues and the risk of cancer occurring in the irradiated tissues. This assumption is likely to overestimate the risk co-efficient at doses below a few tens of rads. Subjective judgements have to be made in order to obtain values from which the risk co-efficient is derived, namely the two variables, the radiation dose, and the cancer risk in the irradiated population. Consequently, many different values of risk co-efficients have been quoted in the literature. For the purpose of this paper it is proposed to use the risk co-efficients given in Table I which are essentially the same as those derived by Dolphin and Marley (1969). Jablon and Kato (1971) published more data on the cancer incidence in the irradiated Japanese population in Hiroshima and Nagasaki, but the risk co-efficients derived from these data are not significantly different from estimates made previously by Dolphin and Marley (1969). These later data from Japan focus attention on the possibility of an RBE value between 2 and 10 for fission neutrons in producing cancer. In order to avoid the problem of choosing the most appropriate value of RBE which has a critical influence on the value of the risk co-efficient, only the data from Nagasaki are used in this paper, because in this city the dose was almost entirely due to γ-radiation. My estimate of the risk co-efficient for leukaemia in survivors from Nagasaki is about thirty leukaemias per 10^6 man-rads and for all other cancers about forty per 10^6 man-rads. These values are shown in Table I together with previously derived estimates taken from Dolphin and Marley (1969). Values recommended for the calculation of cancer risks after doses of 10 rads or more at high dose rates are given in Col. 4 of the Table. Similar values for low dose rate exposures are given in the final column, and these are more appropriate for use when the irradiation results from incorporated radionuclides. The values in the final column are a factor of 3 below those in the preceding column. This factor is arbitrarily chosen; animal experiments indicate that it could be as high as 15 but human data are not available.

It should be noted that the values of risk given in Table I stem from analysis of the small amount of human data available; consequently any conclusions which involve the use of these data must be treated with caution.

Doses and risks from intra-articular injection of radionuclides

The doses to various body tissues from intra-articular injections. 10 mCi. ^{198}Au and 5 mCi. ^{90}Y were calculated by Stevenson and others (1973) and are summarized in Table II. The highest radiation doses are to the synovium and the bones and tissue of the knee; the actual values of the doses depend critically on the assumed dosimetric model and those given in the Table are therefore indicative of the order of magnitude rather than the precise value of the dose. Presumably there is a small risk of bone cancer induced by irradiation of osteogenic cells on the surfaces of the bones in the knee region. The dose to these cells will depend on their proximity to the source of radiation. In the case of yttrium, the β-radiation will penetrate only a few millimetres, but the γ rays from ^{198}Au will deliver a dose of a 100 rads at several centimetres from the deposited radioactivity.

There have been many reports of cases of osteosarcoma following x-ray therapy, but there are few surveys of large groups of patients. Court Brown and Doll (1965), in their study of 14,554 patients treated with x rays to the spine and pelvic girdle for

Table I *Estimated and recommended values of risk co-efficients to be used in assessing risk to adults exposed to low linear energy transfer radiation, such as x or γ rays*

Cancer	*Irradiated population*	*Risk coefficients (Cancers per 10^6 man-rads)*		
		Estimated value	*Recommended value*	
			High dose rate	*Low dose rate*
Leukaemia	Nagasaki survivors	30	—	—
	Artificial menopause*	20	20	6
	Ankylosing spondylitics*	10	—	—
All other cancers	Nagasaki survivors	40	—	—
	Ankylosing spondylitics*	4 × leukaemia	80	24
	American radiologists*	4 × leukaemia	—	—
All cancers			100	30

* These estimates were made by Dolphin and Marley (1969).

ankylosing spondylitis, reported five bone cancers within the *x*-ray field when only 1·1 were expected. The average dose to the bones within the *x*-ray field was about 1,000 rads and the average follow-up time 13 years. From these data a crude risk co-efficient of 0·3 per 10^6 man-rads can be deduced. This does not allow for bone cancers which may develop later and this may double the risk co-efficient. The number of leukaemias in the same period of follow-up of these patients was sixty with 6·7 expected, that is nearly fourteen times more than the bone cancers.

Sagerman, Cassady, Tretter, and Ellsworth (1969) found nine osteosarcomas in 232 patients examined between 4 and 30 years after treatment by external beam therapy for retinoblastoma. No bone cancers were found in 121 patients who received less than 6,000 rads to the orbital bones. Although this cannot be taken to indicate a dose threshold at 6,000 rads, it is apparent that irradiation of limited volumes of bone may involve a lower risk of cancer than irradiation of the whole body.

From these two surveys it is apparent that the risk of osteosarcomas occurring in the limited volume of bone irradiated is acceptably small in the rheumatoid patients.

The dose to the inguinal lymph nodes depends on the amount of radionuclide which leaks to them from the knee up through the lymphatics. In most patients studied by Stevenson and others (1973) this was negligible, but in a few 10 per cent. or more of the activity leaked out, resulting in doses of several thousand rads to the nodes. The kinetics of cells in the lymphoid system are not well understood, but it is probable that the reticulum cells on the reticular fibres forming the structure of the node remain fixed during the irradiation but other cells, the lymphocytes, are probably in passage through the nodes. Hence the fixed cells will receive a high dose and the lymphocytes a much lower dose as indicated in Cols 4 and 5 in Table II.

There is no relevant human experience of the effects of radiation on lymph nodes which can be used to assess the risks of cancer at these doses. When the question of high localized doses was discussed by an ICRP Task Group on Radiosensitivity and Spatial Distribution of Doses (ICRP, 1969), it was concluded that human experience showed local irradiation of small volumes to be relatively innocuous at doses below 1,000 rads. If more than 2 or 3 per cent. of the radionuclide leaks from the knee then the doses to the lymph nodes do not come into this innocuous category referred to by ICRP. Leakage of this amount or more should be avoided if possible, especially as irradiation of this tissue is of no benefit to the patient in the treatment of the rheumatoid disease, which in itself is not a terminal condition.

The biological significance of the mean dose to the lymphocytes of 100 rads which results from a 10 per cent. escape of radionuclide is difficult to assess. This dose is of the same order as that received by the lymphocytes in patients given 80 mCi. ^{131}I for treatment of thyroid cancer, but here the condition under treatment is more acutely serious. On the basis of integral dose (gramme × rads), the significance of this irradiation is about the same as that to the inguinal lymph nodes where the mass is much lower but the dose is higher. It would therefore be reasonable to regard the significance of the dose to the lymphocytes in the same manner as that to the lymph nodes, which is that leakage of more than 2 or 3 per cent. of the injected activity should be avoided.

In Table II the possible movement of 1 per cent. of the radionuclide into the liver is shown to give rise to a relatively low dose of a few rads which is acceptable, for it is lower than the dose limit set by ICRP (1966) for radiation workers which is 15 rads per year.

In the final column of Table II, a notational radiation dose to the whole body is calculated on the assumption of a uniform distribution of the radionuclide throughout the body tissues—a useful concept but a most unlikely circumstance. This notational dose is 13 rads for both the radionuclides. From Table I the risk of cancer is given per rad dose to the whole body, so that for these patients the risk may be written as $30 \times 13/10^6$ *i.e.* ~400 per 10^6 patients treated. This is a very crude estimate of cancer risk. It may be compared with the natural risk of cancer in England and Wales which, during a period of 10 years, is about 31,000 per million for a 50-year-old person and 860 per million for a 10-year-old. Hence a whole body dose of about 10 rads significantly increases the chance of cancer in a child but not in a 50-year-old adult.

Table II *Mean radiation doses in rads to body tissues of patients given intra-articular injections of 10 mCi. ^{198}Au or 5 mCi. ^{90}Y*

Amount injected	*Estimated treatment dose to synovium*	*100 per cent. retained in knee (300 g.)*	*10 per cent. movement to regional lymph nodes*		*1 per cent. in liver (1,700 g.)*	*Dose averaged whole body (70,000 g.)*
			Dose to lymph node (10 g.)	*Dose to lymphocytes*		
10 mCi.^{198}Au	6,300	2,380	6,380	100	4·5	13
5 mCi.^{90}Y	7,200	3,100	9,100	—	5·4	13

In patients treated with ^{198}Au, the radiation dose to the gonads could be a few tens of rads from γ-radiation emitted by activity in the inguinal lymph nodes. The risk of genetic damage in any offspring produced after the treatment could be increased up to double the natural risk for doses of this order. It would be prudent to advise males to avoid procreation for about 3 months after a treatment if appreciable leakage of radiogold to the inguinal nodes occurred. This time lapse would allow sperms which were in meiosis or later stages of maturation during irradiation to pass out of the body. Progeny of radiation-damaged primary spermatocytes is selectively eliminated during meiosis, consequently sperm from these cells, which take 3 months to mature, are less likely to carry genetic damage than sperm irradiated as sperm. In a female, the only precaution possible is to avoid irradiation of a newly fertilized ovum. In treatments with ^{90}Y the gonad dose would be insignificant.

Conclusion

The whole body dose concept might be the best criterion for judging the risk of treatment, particularly if γ rays are emitted by the radionuclide as is the case for ^{198}Au. It may therefore be argued that the treatment should normally be reserved for older patients unless no alternative is available. The leakage of radioactivity from the knee should be avoided or kept down to 2 or 3 per cent. of the injected amount, as the radiation dose to the lymphocytes and lymph nodes from larger leakages may have a biological significance. This leads to the conclusion that ^{90}Y should be preferred to ^{198}Au because it has no γ-emission and some method of administration or postinjection regime must be devised to reduce leakage to a minimum.

Summary

The risk of cancer after the treatment of rheumatic conditions of the knee by radioactive colloids is considered, and the significance of the finding of large numbers of lymphocytes with chromosome aberrations in a few patients treated with ^{198}Au and ^{90}Y is discussed. It is concluded that ^{90}Y is to be preferred to ^{198}Au, and that methods of reducing the leakage of activity from the knee into the inguinal lymph nodes should be developed.

Discussion (after Papers 7 and 8)

DR. SCOTT I should like first of all to re-inforce what Dr. Stevenson has said. We need to find out the clinical significance of what we are doing in terms of possible toxicity. We have already held the Stoke Mandeville meeting and now we have this meeting today, and it would be quite inexcusable if information was not forthcoming by means of these proformas, so I hope we all can collaborate in this way. Before embarking on any general questions or discussions we ought to find out from Dr. Andrews why he is doing less damage than the rest of us. You will remember the number of dicentrics in Dr. Andrews' patients, although the numbers were small, but he was, I think, giving a higher dosage.

DR. ANDREWS I was surprised when Dr. Stevenson wrote to me and told me these figures. Our treatment was not in any way pre-planned in terms of special precautions. Perhaps I ought to say, because it is rather illustrative of the terrible mistakes that can so easily be made in administering radioactive isotopes, why we deal with our patients as we do at present. About 4 years ago we gave some ^{90}Y to a patient with rheumatoid disease in one knee. This was done by myself, the day before I went on holiday, and he was an out-patient. The following evening he presented in Casualty with a very smart reaction to the yttrium resin and a very high temperature, and an enthusiastic Casualty Officer put a needle into the knee, took out all the fluid and put it straight down the drains. We were very unpopular with the local Medical Officer of Health. Now, it was for this reason that we decided that in future all our patients should be admitted and kept at rest in bed for 24 hours before the yttrium was given, and that they should stay in hospital for 48 hours after it was given, at rest in bed but not splinted.

DR. SCOTT I am not sure that this is the whole explanation because, speaking for my own group, these measures were also carried out with our own patients, and I think with others as well.

MR. A. R. TAYLOR I should like to know from the people who are using radioactive material injected into the knee, whether they take any precautions as regards the clinical or radiological diagnosis of the popliteal cysts or communications that exist in probably some 40 per cent. of patients with a normal bursa at the back of the knee. It seems to me important that one should determine whether such a cyst is present or not. Probably the only definite way of doing this is by arthrography, and I wonder whether Mr. Fearn has been lucky and has ten patients who have not had popliteal cysts or bursae at the back of the knee.

MR. FEARN Could I comment on a point which came up. Working on some of the patients that Dr. Stevenson has discussed from the group of yttrium and gold patients principally treated around Oxford, I made an assessment of the relationship between joint damage and the amount of chromosome damage. If you look at the left hand column (see Fearn: p.34, Table II), there are a number of damaged lymphocytes per hundred cells, and this is the data which Dr. Stevenson has supplied. I then assessed the state of the knee radiologically to find out whether it was an early case of rheumatoid disease, that means minimal narrowing of the joint space and damage to the articular cartilage, as opposed to late, with considerable narrowing and damage to the joint, destruction of cartilage and bone, and often a considerable amount of cyst formation. In the late case there will be a different bone-synovial interface. Where there are cysts full of synovial tissue there will be a readier exchange between

the cancellous bone and the synovium. Chromosome damage at the top of the chart occurs mostly in patients with early changes in the knee joint who have had a higher dosage. If you follow the chart down, the patients with larger numbers of damaged lymphocytes per hundred cells counted tend to be late cases, although there are two early cases in which there had been a much larger dosage of radioactivity given, for instance in the eight and the tens, these are patients who had 30 and 46 mCi, not all at once, but over the course of several years. So, I would suggest, as a useful measurement to take when assessing chromosome damage, that one should examine the state of the joint radiologically, and find out whether there is an early or a late amount of damage. In the late case there may be a much more rapid dispersal of radioactivity from the injured joint.

DR. SCOTT The popliteal cyst patients which Dr. Grahame and I looked at tended to be fairly early cases, because these are the patients who formed Baker's cysts, and yet they had chromosomal damage; this may be an explanation, but it is uncertain.

DR. ROBERTS I should like to compliment Dr. Stevenson on his work on chromosome damage. I wanted to get things into perspective, by referring to work not presented here by Dr. Stevenson, about the amount of chromosome damage which occurs in patients treated with phenylbutazone. I find it very difficult to absorb the figures. Could you relate the amount of damage that you are seeing here in a way that I can understand, for example to the amount of damage you get with phenylbutazone as you have done so very clearly with ^{131}I.

DR. STEVENSON The damage from either ^{198}Au or ^{90}Y or ^{131}I per treated patient on average is about ten times as much as in patients taking phenylbutazone. I should like to refer to another interesting series of patients which I did not mention, a series treated by Dr. Wiernik with, on average, 140 mCi of yttrium resin colloid for multiple papillomata of the bladder. This radio-isotope is introduced and the bladder is left filled for 2 to 3 hours, aiming to give a surface dosage of yttrium of some 2 to 4,000 rads, or even higher; the yttrium is then washed out and counted, and they reckon they are losing less than 1 per cent. We have analysed 200 cells in each of ten patients treated in this way, and have not found a single dicentric and no increase even in minor chromosome damage. One last point—I am now scraping the bottom of the barrel of my experience—I studied two patients each treated with 140 mCi ^{198}Au for malignant effusions, and they had rather more, almost one dicentric per mCi per 100 cells which is high, which suggests to me that the colloidal gold is absorbed fairly rapidly in the very efficient drainage system of the gut.

MR. TAYLOR Just one question, can one normally see these dicentric cells?

DR. STEVENSON I cannot remember the figure off-hand. In our experience it is certainly less than 1:3,000, but various other people estimate from about 1:1,000 to 1:10,000. I do not know what figure you usually use here normally.

DR. DOLPHIN At the N.R.P.B. we are, of course, interested in the background of dicentrics and chromosome anomalies in normal adults, and we have been surveying new workers coming onto the Harwell site. We score 50 cells from each individual, and at the moment are running, I think, around eight dicentrics per thousand cells which is considerably higher than anyone else has reported. Values given in the literature are less than 1 per 3,000 cells.

DR. STEVENSON Our controls are really pretty extensive now, both in terms of numbers of patients and the number of cells, and we certainly do not approach the 1:3,000 level. This is an extraordinary experience. Of course, there is an awful lot of radioactive waste dropped around Harwell!

PROF. INGRAND Just a few comments. First Dr. Stevenson's results support the fact that it is very important not to use the therapy in children; not to use γ emitters; to prevent leakage by all means; and to reduce the injected activity. This is especially important with gold in patients. One more point, Dr. Stevenson presents his results in percentages of cells damaged per mCi. administered, not taking into account the activity which has possibly escaped. Since this phenomenon exists, it may explain the difference in statistics in the two series with ^{90}Y. My last question is whether Dr. Stevenson performed any experiments in patients after the injection of a placebo and what number of dicentric cells is found in normals? Again, this work with abnormalities occurring after the use of radioisotopes is very interesting, but there are large numbers of patients undergoing x-ray diagnostic procedures or x-ray therapy, and I wonder if Dr. Stevenson has studied any of these patients to provide a wider base to his statistics.

DR. SCOTT Professor Ingrand, you have a much wider clinical experience in France than we have in this country. Is there any clinical evidence from the French studies of a significant risk of malignant disease or leukaemia?

PROF. INGRAND We have been using this therapy for only 6 years, and I suppose that we cannot make any definite statement until 20 years have elapsed. To my knowledge, 20 years after the start of ^{131}I therapy for hyperthyroidism, no case of leukaemia has been reported. We use 5 or 10 mCi. of a β^-- or γ-emitter, and at least one-third of the administered dose leaves the thyroid to irradiate the whole body. I suppose that the therapeutic risk in the field of rheumatology is considerably less.

DR. DOLPHIN Leukaemias have been reported after radioiodine treatment of thyroid carcinoma. Pochin (1961) studied about 200 patients treated with radioiodine for inoperable carcinoma and found an increased incidence of leukaemia. Later he reported an increased incidence of breast cancer in a group of patients treated with radioiodine.

Information about the rate at which cancers occur following radiation exposure is given by Court-Brown and Doll (1965) in their report on ankylosing spondylitics treated with external radiation. Their observations show that leukaemias turn up within a few years of irradiation and reach a peak incidence after about 10 years. The solid tumours in these patients occur later and a peak in incidence has not yet been reached after 20 years. Data from the studies of cancer mortality in Japanese survivors of the atomic bombs (Jablon and Kato, 1971) support the observations of Court-Brown and Doll. Most of the

leukaemias appear to have occurred among the Japanese survivors whereas there is still an increase in solid tumour incidence 20 years after exposure.

DR. STEVENSON Yes, there is of course a great deal of information on patients treated with external radiation, but one thing perhaps which may re-assure you is this: I have quitc a series of patients who were treated by external radiation of the knee and hip joints for arthritis in what were considered to be therapeutically effective doses. The amount of lymphocyte damage in these patients was very very much greater, an order of magnitude at least greater than in the patients treated presumably to the same point of therapeutic efficiency by injection of isotopes.