Electron Spin Resonance Studies on Normal Human Uterus and Cervix and on Benign and Malignant Uterine Tumors

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ABSTRACT

Electron spin resonance (ESR) studies at $-130^\circ$ have been made on frozen samples of normal human cervix and uterus and on frozen samples of various pathological conditions of the cervix and uterus including fibroliomyma and carcinoma. Fifty-five samples of normal cervix and endometrium, 40 samples of nonmalignant disturbances, 15 benign tumor samples, and 20 malignant samples were studied.

Very strong ESR signals were seen in frozen powders and frozen intact samples of normal cervix and endometrium and in nonmalignant gynecological conditions. In many cases, the ESR signal was greatly decreased or even undetectable in cancer samples.

The substance(s) responsible for the ESR signal in frozen intact tissue ($g = 2.11$ to 2.15) is decreased in concentration when the sample is ground to powder under liquid nitrogen, and an anisotropic signal ($g = 2.002$ to 2.035) then becomes much more evident.

The ESR signals in intact and in powder samples are sensitive to temperature variations; the signals disappear around $0^\circ$, and only the intact samples show significant recovery of signal on recoiling.

The anisotropic $g$ values and temperature sensitivity in the powders may result from an organic peroxy radical that is more strongly associated with a metal ion in intact samples.

INTRODUCTION

Free radicals, as intermediates and products of metabolism, occur widely in normal tissues and are recognized to be of major importance in an increasing number of cell disturbances (33, 36). Free radicals, in general, are very reactive chemically, and several effective pathways exist for scavenging free radicals in vivo under normal conditions; moreover, their rate of formation in vivo is often rather low. These factors result in a relatively low free radical concentration in most normal tissues (21, 41).

Free radicals are usually detected and quantitatively estimated by ESR spectroscopy. This technique (24, 43) depends on the properties of the unpaired electron of the free radical and its behavior in microwave and magnetic fields.

ESR studies have been made of many human and animal tissues (42) including human uterine endometrium and uterine cervix (37). Considerable attention has been paid to variations in ESR signals during the development of chemically induced cancer in animals and to the differences in ESR signals between a multitude of normal tissues and benign and malignant tumors (40).

Cancers of the uterine endometrium and cervix are frequent and clinically important types of cancer in women (1, 8); invasive cancer of the cervix is a disease for which many factors affecting its incidence (12, 23, 48), such as age at first coitus and first marriage, numbers of partners, ethnic group, etc., are known. In the Western world, uterine cancer is a major cause of death in women even though successful treatment is available upon early diagnosis. The introduction of the Papanicolaou smear test was a major advance, and there are encouraging trends downwards in the incidence of cancer of the cervix in association with regular screening by the Papanicolaou technique (18, 19). The cytological screening process is rather costly and time consuming, however, and is subject to considerable variability in results from laboratory to laboratory (4, 13, 34). Various alternatives to the cervical smear test have been proposed in order to standardize assessments and to automate procedures (20, 25). Enzyme analysis of vaginal fluid samples (34) was an early and promising possibility but, unfortunately, the method failed to detect a proportion of the cases of carcinoma in situ. Another approach (37), ESR analysis, was tried because of the qualitative difference in the ESR spectra of various normal and malignant tissue samples reported at that time (6). It is known now, however, that those qualitative differences in ESR signals were largely artifactual and arose from degradation reactions during tissue preparation (28).

Slater and Cook (37) reported significant quantitative ESR differences between normal and malignant samples of human uterine endometrium and cervix, and the free radical signal found in normal human cervix was unexpectedly and unusually strong. Their report was restricted, however, in the analysis of the ESR spectra and in the numbers of samples used. In consequence, we decided to examine the ESR spectra of human uterine samples much more extensively in order to confirm the important differences between the ESR spectra of normal and malignant tissue samples of cervix reported by Slater and Cook (37) and to gain insight into the radical species involved.

MATERIALS AND METHODS

Tissue Samples. Samples of human uterus and cervix were obtained at operations for hysterectomy or cone biopsies at the First Clinic of Obstetrics and Gynaecology, University of Turin. The specimens were approximately 2 cm long and 0.3
were always taken by the same gynaecologist (C. Benedetto) and were immediately frozen in liquid nitrogen within a few minutes after cone biopsy or hysterectomy. Some samples were inserted directly into quartz ESR tubes (internal diameter, approximately 3 mm) prior to freezing (these were later examined by ESR) and are termed "intact samples"; other samples were first frozen in plastic tubes, later powdered under liquid nitrogen, and then transferred to quartz ESR tubes for ESR analysis; these are termed "powder samples". On many occasions, 2 separate pieces of tissue were taken from strictly neighboring sites of the same sample of uterus or cervix in order to compare closely similar samples for study as frozen powders or as frozen intact materials. Histological examination of the tissue was made using small pieces taken from a site immediately adjacent to and macroscopically similar to that used for ESR analysis. The cervical samples were always taken so as to most probably include the squamocolumnar junction, which is known to change in position with age and childbirth (7). Pieces of cervix and endometrium collected from cancer patients were taken from those who had not received previous radiotherapy or cytotoxic drug therapy.

We recorded the ESR spectra of the following human tissue samples (numbers in brackets, number of samples): normal cervix [22]; normal endometrium [33]; metaplasia of the cervix [5]; cystic glandular transformation of the exocervix [7]; parakeratosis [13]; erosions of the cervix [4]; endometrial atrophy [5]; cystic glandular hyperplasia of the endometrium [8]; carcinoma in situ of the cervix [3]; epidermal carcinoma of the cervix [5]; fibroleiomyoma [15]; adenocarcinoma of the endometrium [13]; and mesonephric carcinoma of the uterus [3]. The mean age (and range) for the normal patients and those with cancer were, respectively, 44 (38 to 66) and 53 (29 to 80) years.

Samples of cervix, uterine horn, and other tissues were also taken from adult albino rats and were immediately frozen after being placed in quartz ESR tubes.

ESR Procedures. Samples were examined either in the intact form or as powders using a Varian E-104 spectrometer with a variable-temperature cavity (at the Department of Industrial Chemistry, University of Bologna, Bologna, Italy). Usually, the cavity temperature was $-130^\circ$, the power was 10 to 50 milliwatts, the gain was approximately $10^5$, scan range was 2000 G, and modulation was 16 G. In some cases (normal tissue samples, the fibroleiomyomas, and the malignant tumor samples), the variation of the ESR signal with temperature over the range $-130^\circ$ to $0^\circ$ and with microwave power up to 200 milliwatts was studied. Variations of procedure from the above descriptions are noted at the appropriate position in the text. Diphenylpicrylhydrazyl was used as an internal and external reference standard ($g = 2.0036$).

Chemicals. Cytochrome c and catalase were obtained from Boehringer Corporation, Lewes, Sussex, United Kingdom; hemoglobin, glycerol, and diphenylpicrylhydrazyl were obtained from Sigma (London), Ltd., Poole, Dorset, United Kingdom.

RESULTS

Chart 1A shows the ESR spectra obtained from frozen powders of normal human cervix and carcinoma of the cervix; the main absorbance is close to the free electron spin position, and the associated secondary signal is about $g = 2.03$. For reasons outlined in the "Discussion," we have treated these 2 signals as the $g_s$ and $g_u$, respectively, of an anisotropic signal. The spectrum shown for the carcinoma sample in Chart 1A is considerably reduced compared to that seen generally in normal samples; in fact, a significant proportion of the carcinoma samples examined (both powdered and intact samples) gave no detectable ESR signal.

Chart 1B gives corresponding spectra for intact samples of normal human cervix and carcinoma of the cervix. The main $g$ values are clearly different from those described above for powders and lie in the region of 2.11 to 2.15 for normal tissues.

For carcinoma of the cervix, the $g$ values of the signals (where present) are somewhat higher than in normal tissue and are in the region 2.14 to 2.19.

The line widths for the major signals observed in intact and powdered samples, for both cervix and endometrial tissue, were approximately 250 and 43 G respectively.

Endometrium. Some results for samples of human endo-

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Chart 1. ESR spectra of samples of normal human cervix and carcinoma of the cervix. A. Spectrum 1, frozen powder of normal cervix; Spectrum 2, frozen powder of carcinoma of the cervix. Spectrum 1, sample of frozen normal intact cervix; Spectrum 2 and 3, frozen intact samples of cancer of the cervix. For other details of these samples, see "Results." The conditions used were: scan range, 2000 G; power, 50 milliwatts; gain, $6.3 \times 10^5$; cavity temperature, $-130^\circ$; field setting for A, 3350 G; field setting for B, 3230 G. Arrows, $g$ value for the diphenylpicrylhydrazyl standard.

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Chart 2. ESR spectra of normal human endometrium, fibroleiomyoma, and adenocarcinoma of the endometrium. A. Spectra 1, 2, and 3, results for frozen powders of normal endometrium, fibroleiomyoma, and adenocarcinoma, respectively. B. Spectra 7 to 3, results for frozen intact samples of normal endometrium, fibroleiomyoma, and adenocarcinoma, respectively. For other details of the samples, see "Results." The conditions used were: scan range, 2000 G; power, 50 milliwatts; gain, $6.3 \times 10^5$; cavity temperature, $-130^\circ$; field setting for A, 3350 G; field setting for B, 3230 G. Arrows, $g$ value for the diphenylpicrylhydrazyl standard.
metrium are shown in Chart 2. Spectra obtained from frozen powder samples of normal endometrium, fibroleiomyoma, and adenocarcinoma of the endometrium are shown in Chart 2A, and the corresponding spectra from frozen intact samples are shown in Chart 2B. As with cervix powders, the main signals in powders of endometrium, fibroleiomyoma, and adenocarcinoma (where present at all in the latter case) were at \( g = 2.002 \) with a secondary signal at \( g = 2.03 \). With intact samples, the main signals were at \( g = 2.11 \) to 2.15 in normal endometrium and fibroleiomyoma; normal endometrium also had a strong additional asymmetrical signal at \( g = 2.01 \) to 2.08 in some cases.

Table 1 gives information on the relative ESR signal intensities obtained with normal and tumor tissue samples. The signal heights are in arbitrary units (all measured under the same spectrometer conditions) and are for purposes of comparison only. It was not always possible to perform the ESR analysis on corresponding intact and powdered samples from the same patient, so that the number of patients involved in these studies (already listed in “Materials and Methods”) is necessarily different from the sum of intact and powdered samples shown in Table 1. In Table 1, we have grouped all conditions of the cervix (other than invasive cancers and carcinoma in situ) together as “normal” cases; similarly, with endometrium, we have included endometrial atrophy and cystic glandular hyperplasia samples with the “normal” group. It can be seen in Table 1 that there is an obvious difference in the percentage of negative responses in the malignant samples compared to the normal tissue; these differences are collated at the bottom of Table 1 where normal cervix and endometrium samples are contrasted to the results obtained from all of the cancer samples. Although there is a clear difference in the percentage of negative responses between normal and cancer samples, it is evident from Table 1 that a proportion of cancer samples give signals well within the normal range of intensity.

With both intact and powdered samples of normal and cancerous cervix and endometrium, there were often several other signals present in addition to the main signals discussed above. Of importance to note is that some intact samples of normal cervix and endometrium also had a signal in the same position as the main signal normally seen in powder (\( g \) approximately 2.002) while some powder samples sometimes had signals in the same region as normally seen with intact samples (\( g = 2.11 \) to 2.15). Examples of these spectra are shown in Chart 3.

An important general observation with samples from cervix and endometrium (normal and malignant) was that, when frozen powders and frozen intact tissue from immediately adjacent sites of the same tissue sample were examined, a good correlation was observed between the intensity of the signal in the intact piece of tissue (at \( g \) around 2.14) and the signal in the powdered sample (\( g \) around 2.002).

**Rat Tissues.** A signal similar to that reported for powdered samples of human cervix and endometrium was observed in powdered samples of rat cervix, rat seminal vesicles and, to a small extent, rat lung but not in other rat tissues examined (liver, kidney, spleen, heart, intestine, ovary).

**Temperature Variation.** The effects of varying the ESR cavity temperature on the main signal (\( g = 2.002 \)) of powders of cervix and endometrium (normal tissue, fibroleiomyoma, and tumors possessing an appropriate signal) are shown in Chart 4. It can be seen that the intensity of the main signal decreases in all cases as the temperature rises; the decrease in signal intensity is particularly marked when the temperature increases above \(-80^\circ\). On recoiling samples from \( 0^\circ \) to \(-130^\circ\), no significant recovery of the signal was observed in powders, indicating that a reactive species has been irreversibly destroyed by warming. This temperature sensitivity of the species observed in cervix and uterus probably accounts for the occasional failure to detect strong signals in normal tissue samples (in approximately 9% of normal powders examined); accidental “warming up” (to temperatures above \(-60^\circ\)) during sample handling may have occurred on some occasions.

Increasing the temperature from \(-130^\circ\) to \( 0^\circ\) also caused a loss of signal in solid samples of cervix and endometrium. The
Chart 3. ESR spectra: Spectrum 1, frozen powder of normal cervix; Spectrum 2, frozen powder of fibroleiomyoma; Spectrum 3, frozen intact normal endometrium that show both types of major signal in the regions near $g = 2.14$ and $g = 2.002$. The conditions used are: Spectrum 1, power, 50 milliwatts; gain, $6.3 \times 10^2$; field setting, 3350 G; Spectrum 2, power, 50 milliwatts; gain, $8 \times 10^2$; field setting, 3230 G; Spectrum 3, power, 20 milliwatts; gain, $2 \times 10^3$; field setting, 3100 G. The cavity temperature and scan range were $-130^\circ$ and 2000 G, respectively, in all cases. Arrow, $g$ value for the diphenylpicrylhydrazyl standard.

Chart 4. Effects of temperature on the major ESR signal ($g = 2.002$) seen in frozen powdered samples of cervix, cancer of the cervix, endometrium, fibroleiomyoma, and adenocarcinoma of the endometrium. A, 3 samples of frozen powders of normal cervix (C, O, X) and for 2 samples of frozen powder of detailed situation was more complex, however, than with powders; in the intact samples, there was often a significant change in $g$ value when the temperature was increased above about $-80^\circ$. This indicates an interconversion of substances responsible for the ESR signals that is temperature dependent. An example of this temperature-induced $g$ value splitting is shown in Chart 5. Unlike the case for powdered samples, a significant recovery of signal was found on recooling the intact samples from $0^\circ$ to $-130^\circ$, especially in the presence of glycerol (added to the original fresh tissue before initial freezing). The beneficial effect of glycerol in helping to recover the signal on recooling intact samples may be due to the inhibition by glycerol of ice crystal formation during rapid freezing.

Power Saturation. Chart 6 gives the results obtained from varying the microwave power in relation to the signal intensity of the main signals in normal and malignant cervix (Chart 6A) and in fibroleiomyoma and in normal and malignant endometrium (Chart 6B). Generally, the same behavior was observed with normal as with malignant samples. There were marked differences, however, between the power saturation behavior in powders compared to intact samples. It can be seen that intact samples show a linear response to increasing microwave power, and there is no evidence of a power saturation effect. Powdered samples, however, show an increasing saturation effect with microwave powers greater than about 10 milliwatts.
In all samples of cervix and endometrium examined (including those tumor samples that possessed a signal), an appreciable fine structure was apparent in the main signal between $g = 2.00$ and $g = 2.03$ with low microwave powers. This fine structure (see Chart 7) was very easily saturated with increasing microwave power. High concentrations of a number of iron proteins (catalase, hemoglobin, and cytochrome c) were examined under the same conditions as used for human uterus and cervix; the ESR response was insignificant in the $g$ regions discussed above.

**DISCUSSION**

The results of this study are consistent with the previous work of Slater and Cook (37), who reported that powdered samples of normal human cervix gave a strong ESR signal that was much reduced or absent in samples obtained from cases of cancer. This difference possibly reflects a major metabolic difference between the normal tissue and cancer samples. However, it is important to note that samples of normal cervix and endometrium are histologically quite different from samples taken from patients with overt cancer; the inflammatory reaction to a tumor is an additional factor to be considered here. In consequence, it is impossible to be sure whether the ESR changes found arise from a metabolic disturbance directly related to cancer or from a change in cell type and arrangement.

In this investigation, we have examined many samples of normal human cervix and endometrium, both in intact and powdered forms, and have found strong ESR signals in the region of $g = 2.14$ for intact samples and very strong signals in the region of $g = 2.002$ for powdered samples. The signals in powdered samples are particularly strong for biological material, and we have seen comparable responses only in powdered samples of rat cervix and rat seminal vesicles; other rat tissues examined (after grinding to powder under liquid nitrogen) did not produce large signals of the type studied here. Liver, for example, is rich in cytochromes, non-heme iron, various transitional metals including copper, and flavines and gives a complex ESR spectrum very different (5) from that observed in cervix and endometrium.

Some characteristics of the ESR signals found in powders of cervix and endometrium that we have reported in "Results" (variation in signal intensity with temperature and microwave power) show that the species responsible for the signal is chemically reactive and not easily saturated by increasing the incident microwave power. The shape, anisotropic character, and temperature sensitivity of the signals in the range $g = 2.00$ to 2.035 in powdered samples are indicative of organic peroxy radicals that are known to show nonisotropic signals in the frozen state (9, 26, 49). Moreover, peroxy radicals most likely to occur in biological materials, such as polyunsaturated fatty acid peroxy radicals involved in lipid peroxidation (10) and prostaglandin biosynthesis (32), are known to be rather reactive chemically (16). In this context, uterine tissue can undergo lipid peroxidation (14) and is active in prostaglandin synthesis (11, 35).

The pathways of lipid peroxidation and prostaglandin synthesis are known to involve (or to be stimulated by) non-heme iron (17, 31, 47). If the free radicals observed here in powdered normal cervix and endometrium result from peroxy radicals, as seems to us very likely, then a close spatial relationship of the peroxy radical-metal complex on an enzyme site may be the reason for several of the major features described here: power saturation; difference between powder and intact tissue signals; high intensity of an anisotropic signal in the $g = 2.002$ to 2.035 region.

Intact samples of normal cervix and endometrium gave major signals between $g = 2.11$ and 2.20 $g$ (with some secondary signals at higher $g$ values) and showed a complete lack of power saturation over the power range 1 to 200 milliwatts tested; in addition, the major signal in intact tissue, although...
decreasing markedly in intensity as the temperature increased from \(-130^\circ\) to \(0^\circ\), was substantially recovered on recooling. These data show clearly that the major types of substance present in intact tissue, and which are responsible for the main ESR signals observed, are different quantitatively and perhaps qualitatively from those seen in powdered samples. As shown in Chart 3, some samples of intact tissue and some samples of powdered material gave signals in the normal range for both intact samples (g about 2.14) and powdered samples (g about 2.002). One possibility, therefore, for the 2 types of signal is that the species present in intact samples is substantially converted by grinding under liquid nitrogen to the species responsible for the major signal in powders. Another possibility is that the mechanical grinding process resulted in a more or less total loss of the \(g = 2.14\) species with the artifactual production of a new peroxo species giving the \(g = 2.002\) signal. Mechanical grinding (in this study done manually by the same person, T. F. Slater, throughout) is known to result in bond fission and some free radical production (45). However, because of the observations illustrated in Chart 3 that both types of signal may occur in both intact and powdered samples, we prefer the first of the above possibilities as the major mechanism for a working hypothesis. This view is strengthened, in our opinion, by the correlation reported in "Results" between the intensities of the signals observed in neighboring pieces of tissue from the same clinical sample which were used for both frozen intact and frozen powder studies. It appears plausible that we that in the intact state an unsaturated fatty acid oxygen and an iron-dependent enzyme (e.g., cyclooxygenase or lipoxygenase) react together to produce the major species observed by ESR with the free electron spin being mainly associated with the metal. On grinding, a change in protein conformation and in the relative interaction of the fatty acid (peroxy) radical with iron could lead to the changes in ESR signal observed. A change in the spin state of the iron could also be a contribution to the difference between intact and powdered samples; a marked temperature dependence has been observed for some iron spin state changes (29).

Our results discussed above are consistent with the possibility that the species seen in powdered samples may also occur to a limited extent in frozen intact samples and that mechanical grinding of the intact material produces a marked increase in the radical species normally observed as the major signal in powders.

Although the discussion above is centered around an involvement of iron in the intact samples, another possibility would be a copper protein. These metalloproteins give signals in the \(g\) regions observed here (15). However, the general association of iron with lipoxygenase and cyclooxygenase enzymes and the close similarity of the signals in the powders with peroxy-radicals lends us to favour iron as the most likely metal to be involved in the intact tissue signals in a major sense. Of course, the signals seen in both intact and powdered samples are necessarily composite signals from more than one species of free radical. The powder samples, for example, show an easily saturated component (Chart 7; "Results") together with the main component at \(g = 2.002\) that is not readily saturated.

The signals seen in intact endometrium were overall similar to those in intact cervix, although the \(g\) values were somewhat changed, especially with high microwave powers. No significant change was seen in the signals in relation to the state of the menstrual cycle of the patients; as far as could be ascertained, the patients were not using steroid contraceptives and, as already mentioned, had not received prior radiotherapy or cytotoxic chemotherapy. In related studies with female rats, marked changes in ESR signals were observed over the estrus cycle using intact samples of rat cervix and uterus; these data show that such signals reflect, at least in part, endogenous physiological events.

With nonmalignant pathological conditions of the cervix and endometrium, we saw no significant differences in ESR behavior compared to normal samples.

Although few in number, our results with carcinoma in situ are of intrinsic interest. Of the 3 samples examined, 2 did not give any signal. In view of the fact that macroscopic samples of carcinoma in situ inevitably contain a large proportion of normal tissue (see below) which gives a high ESR signal, these results suggest that a small tumor cell population may affect neighboring normal cells to reduce the paramagnetic and/or free radical content. Tumor cells often have a high antioxidant content (2, 27), and tumor cells in liver have been shown to affect neighboring normal liver cells with respect to the cytochrome P-450-metabolizing system (38).

One technical problem with these studies on cancer samples (especially with small lesions such as carcinoma in situ) is the impossibility of obtaining tumor material substantially free of normal tissue. Since normal cervix and endometrium gives strong ESR signals, the above difficulty probably accounts for the marked variation of signal seen in cancer samples ranging from total absence of signal to signals of normal intensity. Because of this intrinsic difficulty of obtaining samples of cancer tissue essentially free of neighboring normal tissue, the mean signal intensities (Table 1) for cancer samples must be viewed cautiously in relation to direct comparisons with the corresponding normal tissue. In our view, a more useful quantitative indicator of the difference in ESR behavior between normal and malignant samples is the percentage of samples that gave no detectable ESR signal. With the latter indicator, there is a clear difference in ESR response between normal and malignant tumor samples (Table 1).

While bearing in mind the above-mentioned reservation about the experimental reliability of measuring differences in signal intensities between the normal and malignant samples, the results obtained for signal intensities (Table 1) are in agreement with many other studies showing that, in general, there is a smaller ESR signal(s) in tumor samples than in corresponding normal tissue (39). In this context, it is interesting to note that cancer tissue generally has a much decreased rate of lipid peroxidation (e.g., in mitochondria or in microsomes (2, 3, 27, 44, 46) while generally having an increased production of prostaglandins (22). If these general observations apply also to normal and malignant cervix and endometrium, then it seems that the main signal seen around \(g = 2.14\) in intact samples (and which decreases in cancer) is more likely to be associated with lipoxygenase than with prostaglandin synthesis. However, the production of prostaglandins is associated with rather low concentrations of end products, and the ESR technique itself is not very sensitive. Considerable changes in prostaglandin production may occur, therefore, without overmuch affecting the main ESR signals observed.

\footnote{C. Benedetto, T. F. Slater, and A. Tomasi, unpublished experiments.}
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We are hopeful that our future studies using spin traps and prostaglandin estimations will allow us to draw unequivocal conclusions about the biological significance of the ESR changes reported here.

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