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A Review of Low Angle Fibre Diffraction in the Diagnosis of Disease

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Author's contribution

The author designed the study, checked the beam, performed or oversaw the loading of samples, the collection of data, the statistical analysis, wrote the protocol, and wrote the manuscript. All samples were collected at institutions where ethics approvals had been approved. The samples were delivered to me under number only and I at no time knew the identity of the patient unless they wished to discuss the results, at which time they approached the surgeon and obtained the number that the surgeon had given their sample and then informed me of that number. Ethics were granted at the synchrotrons where the samples were viewed.

Review Article

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ABSTRACT

More than ever, unlocking the secrets of cancer in the 21st century is a collaborative exercise between medical science and a greater use of all available forms of technology. Peeling away the layers that surround cancer diagnoses reveals a deeper understanding about the nature of cancer conditions. The use of technology thus may aid the process of early diagnosis. The information gained by each successful step in turn adds to our existing understanding and helps to direct the course of improved treatment protocols. Treatment protocols resulting from our greater understanding of the cancers bring us one step closer to our ultimate goal of better interventions for all patients suffering from a range of cancer conditions. One such method of investigation has been the use of low angle fibre diffraction techniques in the analysis of body tissues, including skin, hair and nails. The results obtained produce characteristic diffraction patterns which are distinctive and reproducible for a number of cancers including breast cancer, prostate cancer and melanoma. These patterns may be used as a means of early detection of some of the most commonly occurring cancers, or, alternatively, as an indicator that cancers which have previously been diagnosed for particular patients have been cured

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and no trace of the disease remains in the patient's body.

Keywords: Low angle fibre diffraction; cancer.

1. REVIEW

Whilst the literature is littered with papers relating tumour metastases and connective tissue, low angle fibre diffraction studies clearly indicate that changes in the fibre diffraction patterns (FDP) vary both with the type of cancer and also the method of transfer of this signal at a distance from the tumour location. Hair, nails and skin samples all show changes for breast and colon cancers. However, whilst prostate, melanoma, ovarian, bowel, liver and lung cancers do not show any change in the FDP of hair and nails, most of these cancers do show changes in FDP of skin samples, Fig. 1. Non-metastatic cancers such as basal skin carcinoma show no changes at all in the diffraction patterns.

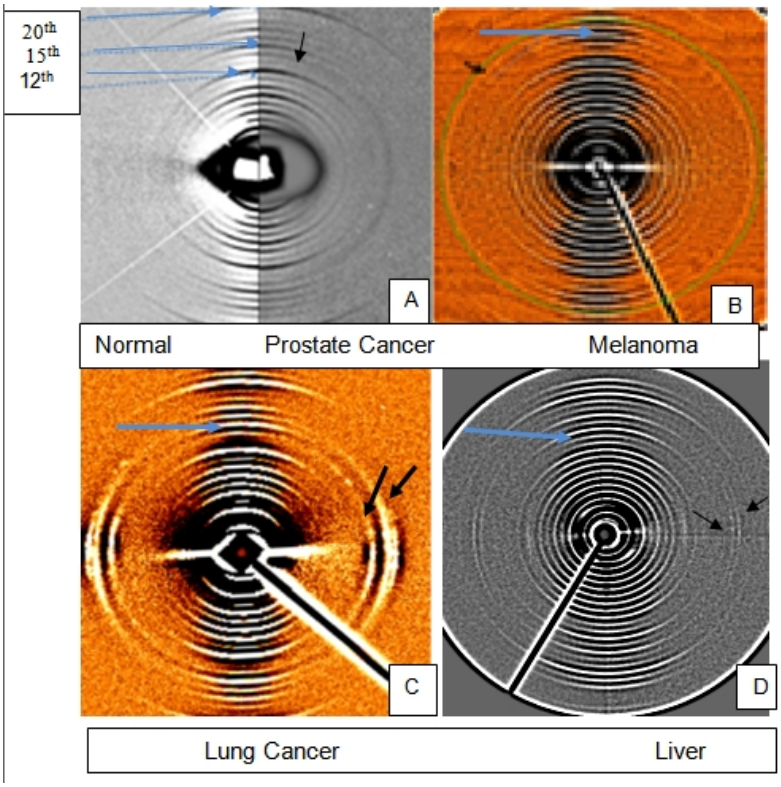

Fig. 1.

A. Extra ring or rings between 13th and 14th orders of skin FDP (D spacing of skin collagen pattern is 65.2nm) for prostate cancer; B. extra ring on 16th order of skin FDP for melanoma but stronger in equatorial; C. rings, on 14th and 16th orders of skin FDP for bowel cancer but much stronger in equatorial (unpublished data); D. thin rings on 17th and 18th of skin FDP orders in liver cancer (unpublished data) shown by black arrows. Blue arrows indicate the strong 15th meridional order of the skin collagen pattern.

All metastatic cancers show extra rings superimposed on the normal tissue pattern in diffraction patterns taken from hair, nail or skin samples. The diameters of these superimposed rings are specific to the type of cancer. In the case of breast cancer, the circumference of the first order of the diffuse ring is located just outside the 10th order of the 46.7nm lattice of the keratin pattern [1], therefore the diameter of this ring must be less than 4.67nm [2]. In the place of this normal diffuse breast cancer FDP ring, Fig. 2B, the patterns obtained for BRCA positive persons do not have additional diffuse rings but additional very sharp rings which are preceded in teenage years by incomplete dotted rings, Fig. 2A. Fibre diffraction could replace the very costly blood tests presently in use for this gene test.

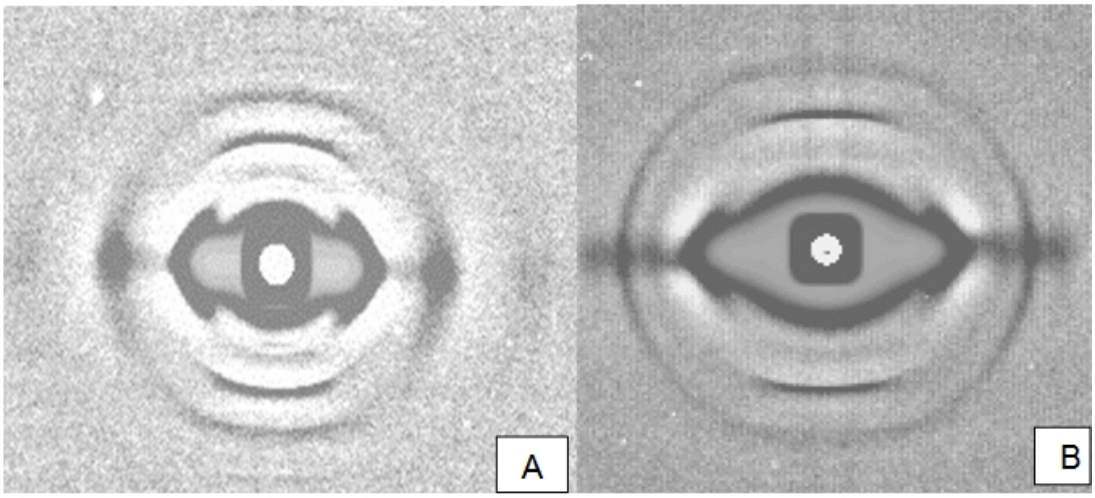

Fig. 2.

A. The diffraction pattern of hair from a breast cancer patient who does not have a family history of breast cancer and therefore has a weak diffuse ring of change.

B. The diffraction pattern of a breast cancer patient who has a positive BRCA gene and therefore a superimposed sharp ring of change (unpublished data).

Our earlier study in which a human breast cancer was grown on the back of a nude mouse [3] indicated that the ring associated with breast cancer appeared the moment the blood from the mouse started to flow through the implanted cancer. A study of a human hair from a woman showed positive for each of the two years before her breast cancer showed up in a mammogram in the third year. Unfortunately the diffraction results in both of these years were marked as false positives. She died 6 months after the mammogram finally showed breast cancer. Mammograms were taken at the same time as the annual diffraction test hair was taken. Her third FDP also showed positive. She was not told the results of the FDP tests as this was part of the ethics requirements though her surgeon requested the mammograms be rechecked in the two earlier years, no change was recorded. These results indicate that the diffraction change was visible at least 2 years before the cancer was detected by mammography.

This FDP breast cancer change was also seen in the FDP of hair, skin or nails from every woman and man studied, who had breast cancer. The 4000+ double-blinded samples, obtained at 5 locations in Europe, 4 in North America, and 8 in Australasia, where ethics approvals had been granted, were studied by my protocol. In addition, all experimental procedures were approved by the ethics committees at synchrotrons used in the USA,

Japan, and Australia. No false negatives were recorded and many of the so-called false positives have since been shown to be positive [4], giving a sensitivity of 100% and specificity of 99.1%. The same superimposed ring was visible in the diffraction pattern of a hair sample taken from a dog that had a mammary tumour.

2. DEVELOPMENTS SINCE THE ORIGINAL REPORT

The original report in Nature [2] was very brief in keeping with that journal's requirements. Many important details were omitted. Researchers subsequently attempting to replicate my results then faced often unappreciated problems despite my efforts to disseminate details personally, through other papers and conference presentations (e.g. NSLS Keynote Address 1999) and many correspondences.

Fibre diffraction analysis of hair involves three distinct technical stages: mounting the specimen; configuring the synchrotron; and fine tuning for image sharpness. Each presents characteristic needs.

- **Mounting:** Hair is fine and a suitably taut mounting of a clear specimen ideally around 0.5 cm is needed. Tying at both ends has in my experience produced the best results. Problems can be expected if the hair is glued or shampooed (contamination occurs), split, desiccated, curled or slack (inadequate focal object with poor signal and excessive noise), subject to changes in humidity post-mounting (retensioning needed) or other actions such as twisting, stretching, teasing or backcombing which add disorder rings in the area of interest of the breast cancer ring, [5].

- **Configuring:** Synchrotrons have idiosyncrasies which can markedly affect image capture. Such things as detector placement and width of beam at the sample need to be varied in setup of an unfamiliar machine. They may also need to be rechecked if drift occurs during operation. The ideal length of the sample to detector varies with the strength and focused size of the beam. We used 200, 400, 600 and 1000mm sample to detector distances at synchrotrons and 250mm on rotating anodes. Unless a full keratin pattern can be obtained out to and including the strong 38^{th} order of keratin for a human or animal hair (d-spacing for hair 46.7nm), the set-up is not adequate for this work. Fig. 3A is a diffraction pattern of a pig's hair showing these 3 strong peaks in the inner section of the hair pattern. The top section of a hair pattern obtained from a cat's whisker extending beyond the 5.15 nm reflections, the 91st order of the 46.7 nm keratin lattice, is given in Fig. 3B.

- **Tuning:** Images from synchrotrons are highly processed outputs from particle diffraction experiments. The original particle patterns are captured electronically and analysed using software that seeks regularities and coherences "after the (diffraction) event". My preferred software, IRAF and SAO [6-8], were sourced from astronomy. These programmes were designed by the Smithsonian astronomers to search for dark stars by continuously wiping out the brighter stars and looking at successively weaker stars. These programs are therefore very useful for searching for weaker and weaker reflections in the extremely wide dynamic range of the fibre diffraction patterns of hair. These programs also have excellent graphical capabilities for plotting 1D and 3D intensity distributions in any linear, circular or elliptical direction across the fibre diffraction pattern.

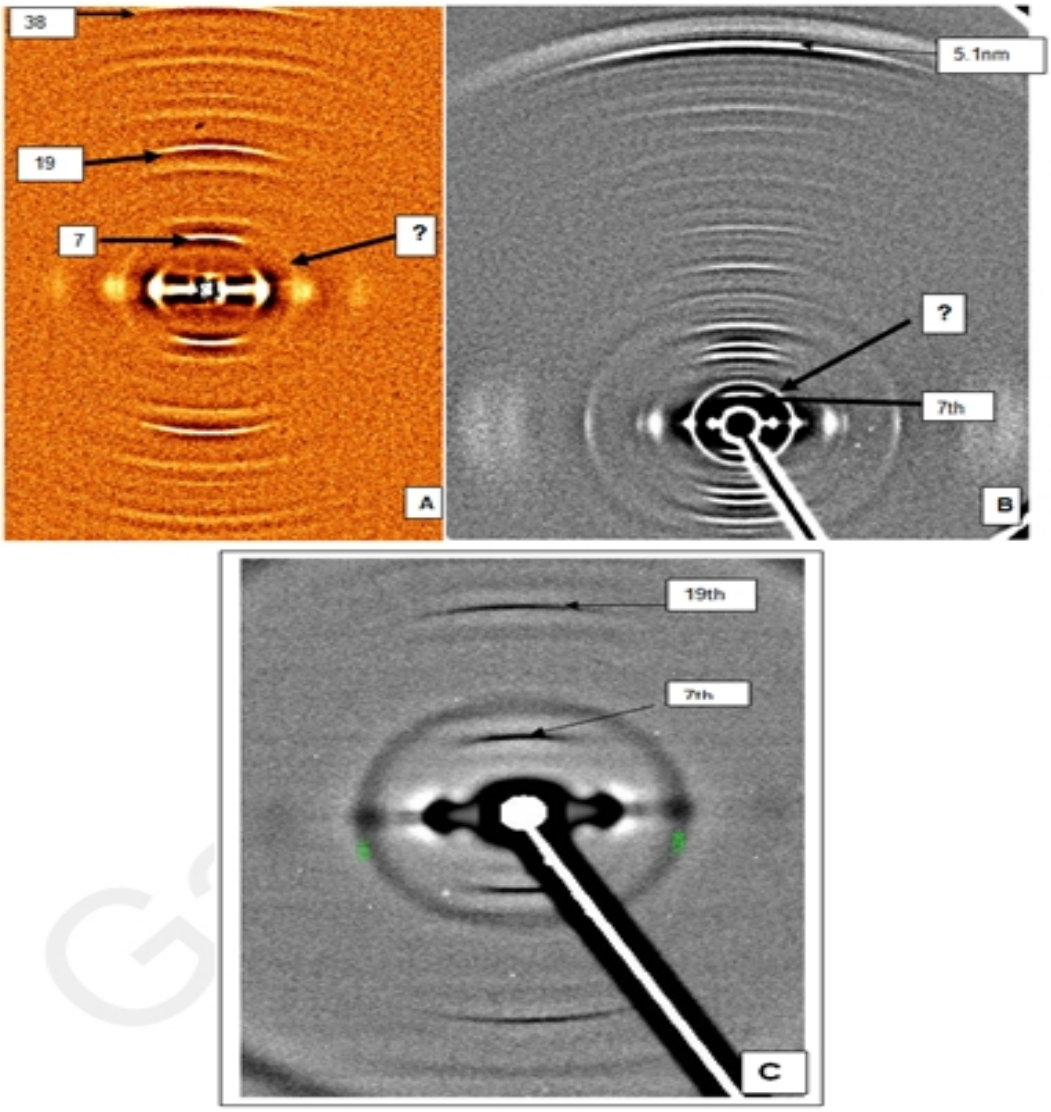

Fig. 3.

A. Diffraction pattern of a pig's hair showing the three strong reflections required for patterns suitable for these studies.
B. Full diffraction pattern of a cat's whisker showing the full range of reflections.
Both A and B show disorder rings (?) as they cannot be properly aligned because of their natural stiffness. Similar disorder rings found in loose hair and curly hair if sample is too long
C. Human hair showing disorder ring resulting from brushing, 5cms from follicle.

Unfortunately a complex experiment looked simple. No details learned over 15 years of experimental trials typically involving highly skilled researchers from various relevant specialities were able to be included [in2]. As scientists from many disciplines rushed to synchrotrons and X-ray sources to carry out tests, many were apparently blind to significant details or even unaware of key features of the field.

One skilful team [8] did replicate the essential result: that the presence of cancer in a body affects hair in ways that are observable through fibre diffraction. Briki et al. [8], had great experience in the diffraction of hair. However, their imaging details differed so they queried the absence of the broad disorder ring which they had in all their patterns, the intensity of which was always lower when breast cancer was present. These broad rings were a result of the hair being attached at only one end and, through Nature, I related that these rings could be easily removed by attaching the hair at both ends, thus keeping it taut.

Other teams appear to have failed due to inadequate understanding of the area or inappropriate experimental set ups. Some, for example, had no knowledge of what the keratin pattern for hair should look like and this is obvious from patterns they presented [10-14]. Visits to the laboratories of two teams [13, 14] verified problems with camera arrangements and duration of experiments. The samples used in [14] were sent to me as a blinded set of samples and after the code was broken, my results were correct as reported in [15]. While a number of papers [5, 16, 18] were written in response to explain problems with protocols used, no teams (to my knowledge) have attempted to repeat the experiment or to acknowledge why experiments failed. Indeed many “footloose” researchers moved rapidly onto other areas, possibly discouraged by patents or commercial considerations but also probably chasing the “next big thing” for their organisation or team.

Reflecting further on patterns Figs. 3A and 3B, both of these patterns also contain a spurious sharp ring marked (?), in the area of interest for a breast cancer ring. These are disorder rings resulting from the inherent stiffness in these samples. Neither are true breast cancer rings and nor is the broad diffuse ring in Fig. 3C, due to the section of hair used in this sample (viz. 5cm from follicle) this diffuse ring is clearly a disorder ring from normal brushing which may or may not occlude the presence of a real breast cancer ring. Such problems in these diffraction patterns have been discussed in detail along with those from samples that have been back-combed, curled, twisted, stretched, brushed or teased either in situ or in mounting [5] but completely misunderstood by subsequent teams [17,19,20], who have little or no experience in loading hair samples or analysing keratinous diffraction patterns.

The relative intensities of the normal keratin pattern to those of additional rings must also be strictly observed. The beam should be focused to fit entirely in the hair as the beam glancing off the scales on the surface of the hair can cause further problems.

Whilst low angle fibre diffraction patterns, (FDP), provides an early diagnostic tool for breast cancer[2], colon cancer [21], prostate cancer [22,23], liver cancer[unpublished-data], bowel cancer[unpublished data] and melanoma [24] using changes in the diffraction patterns for skin, hair or nail samples, these changes are introduced by the presence of the cancer cells in the body and are totally removed if all such cells are removed in treatments [5]. This means that FDP can also diagnose the complete cure of a patient and thus answer the question, “Was my cancer cured?” with absolute certainty. During my breast cancer studies, nine patients were followed for up to 7 years after mastectomies. Only one of these patients still showed the breast cancer change on FDP examination during this time. Subsequently she was shown to still have breast cancer [unpublished data]. It was hoped to continue this study to 14 years post operation.

The results in Fig. 4 were obtained for a 50 year-old breast cancer patient. She was very concerned that if she had chemotherapy following her lumpectomy her hair would fall out and was reluctant to have this treatment but on advice went ahead and had it anyway. She was deeply disappointed when her hair fell out after chemotherapy. The FDP patterns shown

in Fig. 4 confirm that this patient was cured of breast cancer by the lumpectomy and has had no reoccurrence of this cancer in the years since. In fact, she need never have endured chemotherapy if this test had been available to her at the time.

From Fig. 4, it is also clear that the change in the FDP of hair associated with breast cancer does not alter the intensities of the reflections in the FDP of the hair itself which remains the same whether or not the breast cancer ring is superimposed onto it. This clearly indicates that the additional material arising from the cancer does not bind to the keratin helical structure itself [25,26]. Although the FDP ring can be "washed out" of the FDP pattern by immersion of the sample in formic acid, all possible chemical tests of the substrate have failed to find any trace of it. We can only surmise that the molecules that create the ring have been broken into smaller molecules by the formic acid and these smaller molecules are scattered within the hair structure, and are so small that they are not visible in the low angle diffraction patterns. These molecules could be located at points inside or outside the helical arrangement of the 8 tetramer intermediate filaments, as formic acid is capable of opening up the helical arrangements of the tetramers [1,26], in the non-helical tails, in the membranes or other material in the outer layers of the hair.

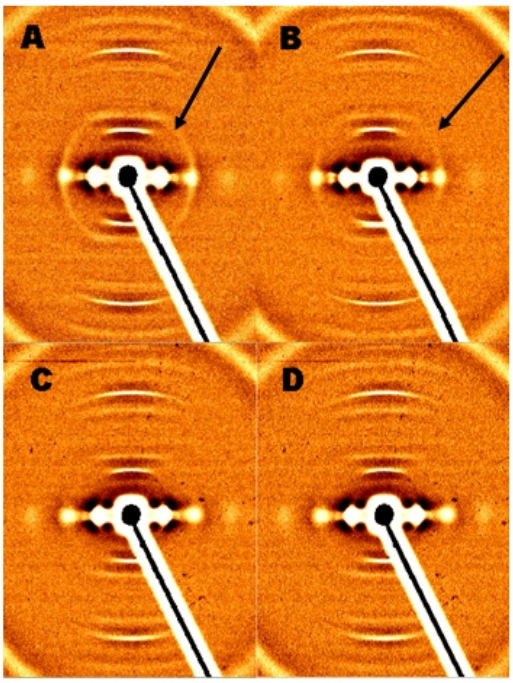

Fig. 4.
All four diffraction pictures here are FDP's of hair
A. Section of Hair from 2 days before lumpectomy, arrow showing breast cancer ring of change.
B. Section of Hair from 8 days after lumpectomy. Note the much weaker ring of change indicated.
C. Section of Hair from 18 days after lumpectomy, a week before chemotherapy commenced. No breast cancer ring of change in C.
D. Section of Hair from 38 days after lumpectomy. No breast cancer ring of change in D.

For the cancers and diseases that travel via collagenous tissue with superimposed rings showing in FDP of skin (Collagen Types I, III, V d-spacing 62.6nm [27,28]), breast tissue

[29], colon tissue [18], or chordae tendineae, the changes in the FDP also disappear when the cancer is cured. An example of this in the case of prostate cancer is given in Fig. 5. Results have been obtained for men suffering from prostate cancer where after treatment some, but not all, have been found to have no change from normal in the diffraction pattern (Fig. 5A), that is they have been cured by the treatments received. Changes in the diffraction patterns for patients with prostate cancer are given in Fig. 5B and those for patients with benign prostate hypertrophy are given in Fig. 5C. Other changes noticed are under review.

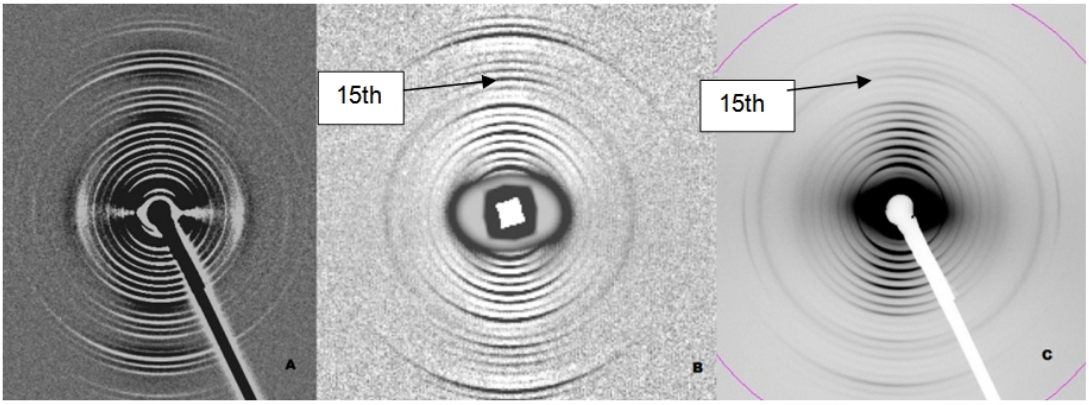

Fig. 5.

Fig. 5A Diffraction Pattern of skin biopsy from patient after extensive radiation and hormone treatment shows this patient is cured as no prostate ring is present. FDP of patient with prostate cancer is shown in Fig. 5B showing added Prostate Cancer ring between 13th and 14th meridional orders of skin collagen and in Fig. 5C, a FDP for a patient with Benign Prostate Hypotrophy showing extra but different ring, superimposed on skin diffraction pattern between 15th and 16th orders.

Details of medical treatment for one such “cured” patient, whose prostate before diagnosis was very enlarged, hard and nodular, were:-

- 13 separate biopsies were taken and all showed positive with most giving a score of 7-9 and the lowest 3.

- March, 2011: Diagnosed by truss biopsy, followed by scan and x-ray to check for secondaries - negative.

- End March, 2011: First injection of hormone Lucrin depot 22.5 mg and to continue at 3 monthly injections until April 2013. Commenced 1 month of hormone tablets Cyproterene 100 mg daily. June: Start of radiotherapy consisting of 40 treatments of the highest dose attacking 7 sites in the prostate. The PSA before treatment was 3.8, and immediately after the radiotherapy finished it was 0.01.

The prostate after completion of radiotherapy had returned to normal size and texture. FDD was carried out at the end of January, 2012 at the Australian synchrotron. The cancer was shown by FDD as totally removed at this stage, Fig. 5A, as only the skin collagen pattern is seen in the FDP. The prostate ring (Fig. 5B) is not present. This patient’s cancer has been cured.

All the collagen in the entire body shows the superimposed ring in Fig. 5B if the person or animal has prostate cancer. So the ring associated with prostate cancer can be seen in the FDP of tendon taken from the tip of the tail of a 3 week old tramp mouse, indicated by black arrows on right hand side of Fig. 6.

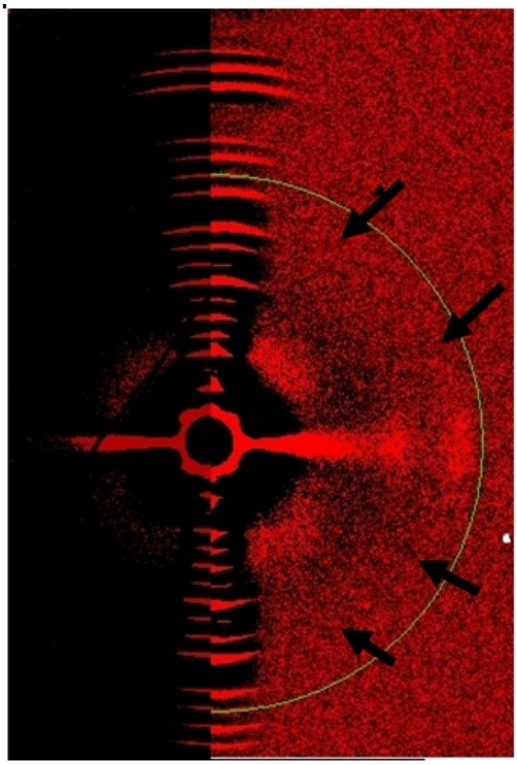

Fig. 6.
This composite diffraction pattern of tendons pulled from the tips of 3 week-old mice shows the difference between the pattern of the control mouse on the left hand side and that of a TRAMP mouse on the right hand side where the weak ring of change is indicated by black arrows. (Green ring indicates the 15th order of collagen Type 1 d-spacing 67nm.)

FDP from breast ducts show changes in superimposing rings as you move along the duct from normal breast tissue towards the tumour, Fig. 7. Fig. 7(1) is the FDP taken from collagen near the duct that from pathology is normal, hence the presence of an additional broad weak “fat” ring superimposed on the collagen pattern. Since the fat is removed from the area as you move closer to the tumour into the “elastotic tissue”, Fig. 7(2), there is collagen with no “fat” ring. This tissue is extremely dense collagen (not elastin) from which all fat has been excluded, so dense in fact that a hypodermic needle will bend rather than go into it. Then, as you move further along the duct towards the tumour, the first superimposed ring appears, (D spacing 43.8±0.5 nm), Fig. 7(3). Finally in Fig. 7(4) two rings appear superimposing the collagen pattern denoting the presence of foetal tissue adjacent to the tumour itself, (D spacing of these two rings are 43.8±0.5 nm and 32.1±0.5nm) [29], (insert foetal pattern [30]). Fig. 8 is the pathology slide of a frozen section of breast tissue taken with a polarising microscope which shows the cancer as green**,** the fat shows as luminescent yellow and the elastotic tissue as flat reddish-brown surrounding the duct, indicated by bent

white arrow. Such a flat area gives an indication to the pathologist that a cancer is probably somewhere near.

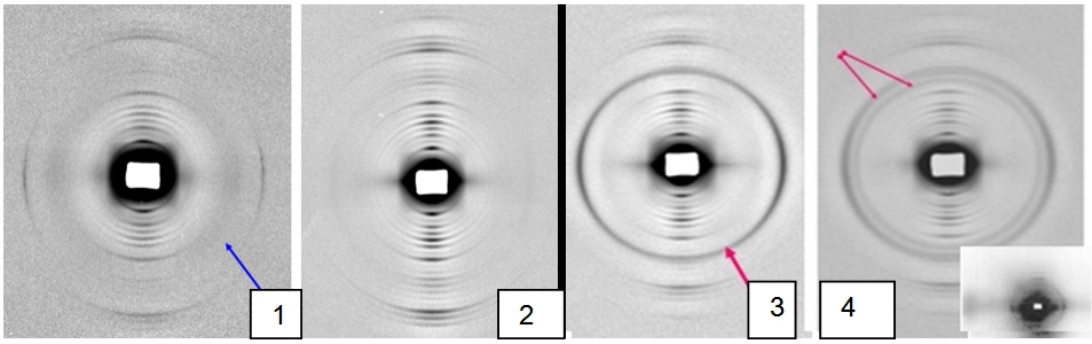

Fig. 7.

These diffraction patterns were taken from a breast duct that leads to a tumour, this duct had been identified by the insertion of blue dye through the nipple prior to the total mastectomy. The first picture is from an area of normal tissue, the arrow pointing to the broad diffuse fat ring still present in the tissue. This 'fat' ring has gone in the 2nd pattern as we move along the duct towards the tumour. The third pattern shows a single ring spacing 43.8nm and close to the tumour a second ring, spacing31.1nm is added bringing the tissue to that of foetal skin (insertion) [26].

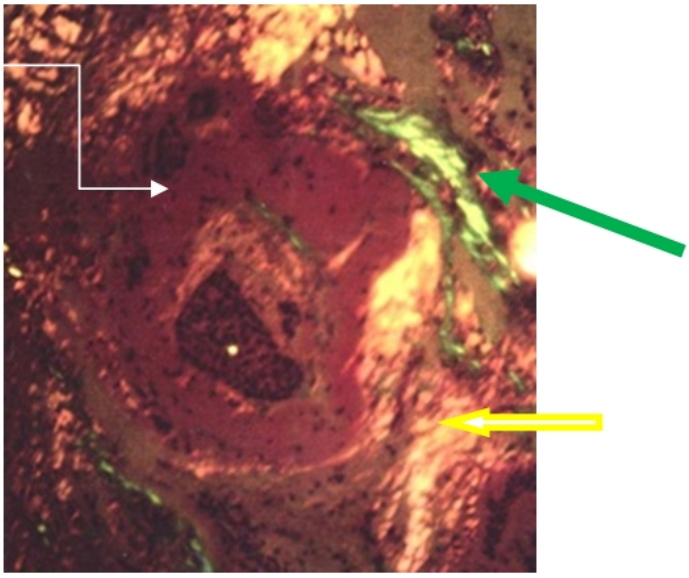

Fig. 8.

This pathology slide of a frozen section of breast tissue shows the cancer as green, the fat shows as luminescent yellow and the elastotic tissue as flat reddish-brown surrounding the duct indicated by bent white arrow. Such a flat area gives an indication to the pathologist that a cancer is probably somewhere near.

Added rings in FDP of chordae tendineae also mirror the advance of myxomatous heart conditions which most surgeons relate to the “elastotic” tissue found in the breast surrounding breast cancer. Fig. 9, d-spacing 43.8 nm of superimposed ring.

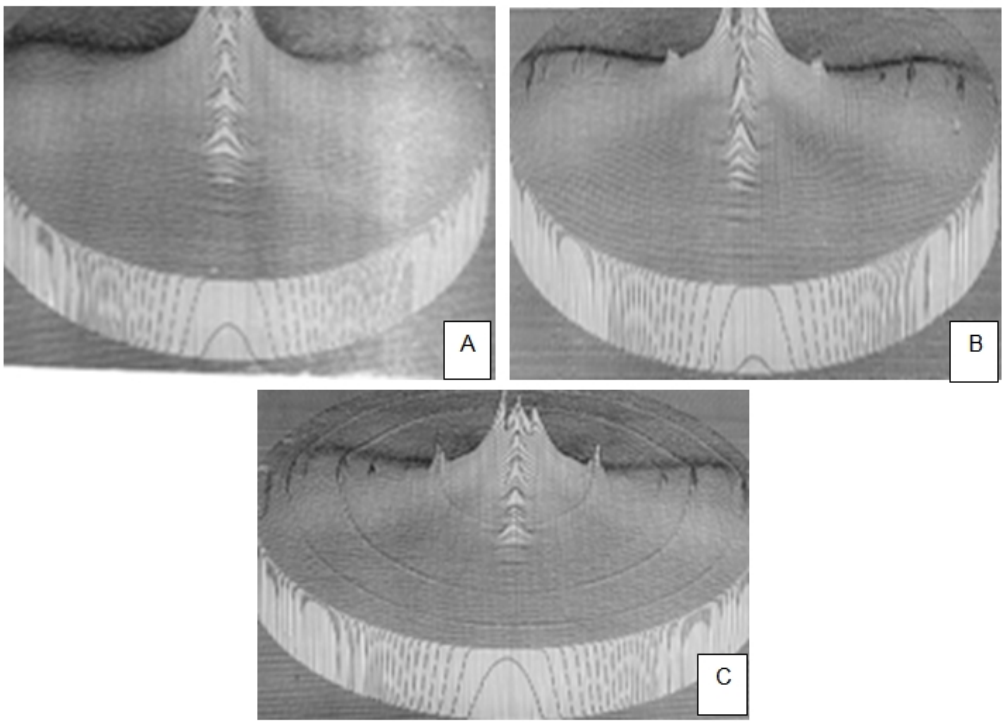

Fig. 9.

Fig. 9A is the pattern obtained from the chordae tendineae of a patient with a normal heart. Fig. 9B is the pattern from a person who has a mild myxomatous heart valve condition which along with the meridional reflections of 9A has an additional set of equatorial reflections superimposed on the normal FDP. Fig. 9C is the pattern from the chordae tendineae of a patient whose myxomatous heart valve is at the breaking point. In this case the extra equatorial arcs have become the centre point of a series of rings, d-spacing 43.8nm.

Other diseases such as insulin dependent diabetes mellitus (IDDM) [31] do change the structure of both the collagen in skin and the keratin in hair. These changes are illustrated in the graphical plots of the meridional intensities in the FDP of hair for IDDM patients and controls, Fig. 10. The IDDM pattern shows the 19^{th} and 38^{th} orders have almost the same intensities whereas for the control the 38^{th} order is much less intense. In addition the presence of the much more intense reflection indicated by wide arrow in the IDDM hair and narrow arrow in the control, a reflection which confirmed the 62.6 nm lattice in hair [1] suggests the bonding position of the additional material could be associated with that lattice. These changes indicate that the glucose bi-products are bound to the keratin in the hair for persons with IDDM. Similar changes have been observed for cats, baboons and orang-utans with IDDM. No added rings occur with IDDM but unlike the superimposed rings in the cancer FDPs where extra material does not bind to and alter the collagen or keratin, the glucose bi-products do.

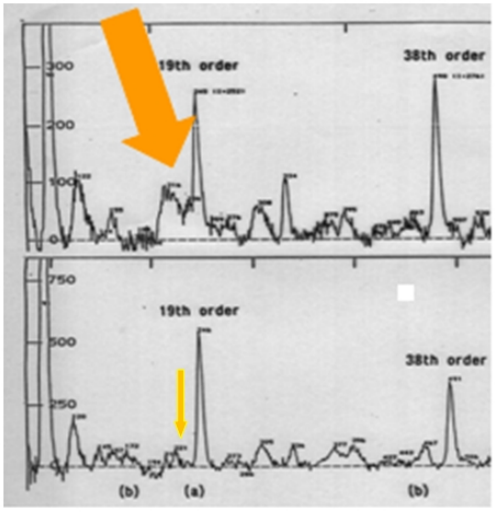

Fig. 10.

These are partial IRAF graphs of the intensities of the meridional pattern for hair; the upper graph is for a patient with insulin dependent diabetes, the lower for an age-matched control. The relative intensities of the 19th and 38th orders are almost the same in the diabetic sample compared with a much lower 38th order in the normal. The increased reflection marked with yellow arrow gives confirmation for the 62.6nm lattice.

In the case of Alzheimer's disease [32], although the bi-products of beta amyloid do not bind to the keratin of the hair, they produce spot-like reflections in the same position in the FDP of hair for all humans and also for all horses and dogs suffering from this condition, Fig. 11. Again there are no added rings for this disease, only spot reflections located in a 7º arc in a position of the keratin FDP that is usually blank, as indicated by arrows in Fig. 11, Changes were observed in the hair and whiskers of transgenic Alzheimer's mice visible from 2 months that may be related to changes in the brain of similar mice, observed by Richardson et al, 6 months before beta-amyloid deposition [33]. The FDP patterns correctly identified the transgenic mice from the controls. The presence of beta-amyloid plaques were established by pathology [32] after mice were sacrificed.

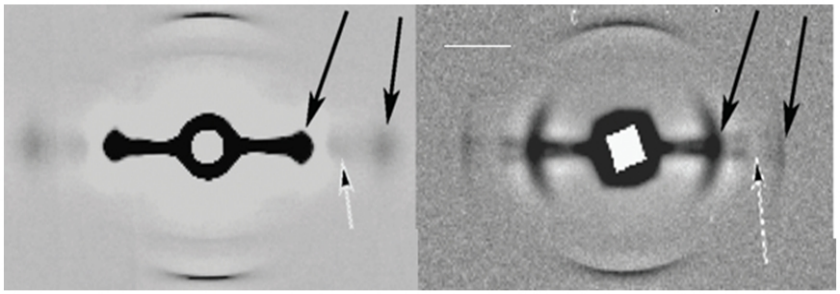

Fig. 11.

These are plots of right hand side intensities of the central sections of the diffraction patterns for hair. The left hand pattern is from control hair, the right hand pattern is a pattern of hair from an Alzheimer's patient. The arrows indicate the pattern changes found in all positive patients.

3. CONCLUSION

This paper lists the additional rings that have been identified for the presence of various cancers by low angle fibre diffraction and contrasts these changes with other alterations to the FDPs by diseases such as insulin dependent diabetes and Alzheimer's disease. Whilst X-ray diffraction pictures taken by Roslyn Franklin and her student, Raymond Gosling, were responsible for the structure of DNA, this same technique has a much wider usage in the diagnosis of cancers, stage of myxomatous heart valves and other diseases in humans and animals. All samples were collected with ethical approval of the host institution whether they were in Europe, USA, or Australasia and also by the ethics approval teams at the synchrotrons where the studies were carried out. A sensitivity of 100% (no false negatives) and a specificity of 99.1% in over 4500 samples for cancer diagnosis should be sufficient to prove this technique works, if my experimental protocol for sample choice, sample loading and data collection and analysis are followed exactly.

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CONSENT

The author declares that 'written informed consent was obtained from the patient for publication of this case report and accompanying images.

ETHICAL APPROVAL

I hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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