



Report on the Anglo-Israeli Workshop on the Genetic Risk of Breast Cancer*

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In April 2006 I had the privilege of organizing an Anglo-Israeli workshop on the genetic risk of breast cancer that was held in Tel Aviv. Thanks to the generosity of the academic study group for Israel and the Middle East that covered all the travel costs, and Mr. David Lewis of Isrotels who provided the conference facility and much of the accommodation, I was able to bring about a dozen British scientists to meet with a similar group of Israeli medical scientists. Of incidental interest was the fact that the majority of my British colleagues had never visited Israel before and I had the particular pleasure of seeing Israel through the eyes of strangers to the land. The program itself and the associated fieldwork were organized by Miri Ziv of the Israel Cancer Association and the meeting was co-chaired by Prof. Gad Rennert, professor of epidemiology at Haifa University. As it turned out, the meeting exceeded my expectations and ended up as a journey through the land of Israel, the history of the Jewish people, our genealogy and genetic anthropology, as well as a consideration of the mutations that predispose to breast cancer. However, before we get down to the main subject of the conference, a short digression is necessary to understand what is meant by the genealogy of the Jewish people, as illustrated through genetic anthropology.

My son-in-law is a “Cohen” and I am proud of this fact that my daughter has married into this princely and scholarly lineage. My son-in-law’s father is Rabbi Dr. Jeffrey Cohen, and through the oral tradition they can trace their routes back to the *Cohanim* (priests) of the Temple in Jerusalem. We now know that this oral tradition has been scientifically confirmed by studying the Y chromosome of *Cohanim*. The Y chromosome is associated with the male sex and handed down through the generations from father to son. The Y chromosome of the *Cohanim* has certain characteristics that are common to all the *Cohanim* in the world, confirming the veracity of the oral tradition.

Perhaps more remarkable and certainly more relevant to our discussions is the tradition that our ethnicity is handed down through the maternal line. Every cell in the human body has two sources of DNA. The major source is within the nucleus and this

can be described as the blueprint that codifies our personhood, in other words the way we look, our height, the color of our eyes, and to a large extent our attitudes and intelligence. Hidden in the cytoplasm between the nucleus and the cell membrane and only clearly seen on electron microscopy are the mitochondria. These tiny structures are vitally important in providing the energy for cellular activity. In other words, they operate as batteries at the molecular level and one can only gaze with awe at the exquisite organization of this microcosm. The mitochondria are peculiar in that they contain their own DNA, which codes for the organization of these miniature powerhouses. This mitochondrial DNA is now known to be entirely maternal in origin, handed down through the generations via the maternal line. The mitochondrial DNA also differs in subtle detail, between individuals, and it is possible to trace the origins and migration of peoples of different ethnicity from the first hominids who evolved from the apes in Central Africa in the dark distant past. Once again genetic anthropology confirms that the majority of people who consider themselves Jewish are indeed Jewish, as judged by their mitochondrial DNA. Subtle differences in this coding also allows us to trace the migration of the Jewish people over time and even suggests that our origins might indeed have arisen from four different matriarchal tribes.

Sadly, along the way the Jewish people have collected a number of deleterious mutations within their cellular DNA of the germline that has also been passed on through the generations. These include the mutations that are associated with Tay-Sachs disease, and the *BRCA* mutations that increase the risk of developing breast cancer. The origin of these mutations in time can be traced by considering the migration and dispersion of the Jewish people in ancient history. The story starts about 3000 years ago.

In 586 BCE, following the Babylonian conquest and the fall of the first Temple, the major Jewish dispersion was to Mesopotamia; “by the rivers of Babylon, there we set down yea we wept when we remembered Zion” (Psalm 137). Some Jews migrated to Egypt and others north into Syria. After the passage of years many Jews drifted back to the land of Israel, but after the revolt against Persia in 359–338 BCE many Jews migrated north towards the Caspian Sea with gradual migrations through

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trading further north into Europe. The Jews who migrated to Mesopotamia enjoyed a long history, emerging ultimately as Iraqi Jews, all of whom were expelled after the Second World War.

The next cataclysmic event in Jewish history was the sacking of the second Temple by the Romans in 70 CE. This event was celebrated by the Roman legions in the bas relief seen on the Arch of Titus in Rome, where the Temple menorah is seen carried on the shoulders of the triumphal Roman legionnaires. This is also celebrated by the coin that was struck, embossed with the words *Judea Capta*. At this point 80,000 Jewish slaves were shipped across to the Roman province of Hispania and settled in the region just south of Cordova. This colony ultimately gave rise to the Sephardic population. Some Jews remained behind in cities such as Jerusalem, Hebron and Safed with descendants to this very day, whereas others continued their migration through Asia Minor into Eastern Europe. Until the expulsion of the Jews from Portugal and Spain at the end of the 15th century, there was very little intermarriage between the Sephardim and the Jews in Mesopotamia, Asia Minor and Europe. With these historical facts in mind it is then all the more interesting to look at the distribution of the *BRCA1* and *BRCA2* mutations among women from the different Jewish communities.

The first speaker at our conference was Prof. Ephrat Levy-Lahad, professor of epidemiology at Shaare Zedek Medical Center in Jerusalem. She and her team have done a phenomenal job of tracing these genetic mutations among affected and unaffected Jewish women in Israel. To put it into perspective, mutation within these genes in the majority of populations occurs with a frequency of between 1 in 300 and 1 in 800. The second highest frequency occurs in Iceland with about 1 in 170 (0.6%) women affected. However, among Jewish women in Israel, 1 in 40 women (2.5%) are affected; and when you look at the individual genes you see how the history of the Jewish people has been reflected, once again at the molecular level. First of all Sephardic women do not carry any of these mutations. Therefore, the mutations that have been identified must have occurred after the fall of the Second Temple or among those families that remained in Mesopotamia or migrated north after the fall of the first Temple.

There are three "Jewish" mutations. These can be roughly dated by analysis of mitochondrial DNA. The oldest mutation (185del AG) on the *BRCA1* gene occurs in 1% of both Ashkenazi and Iraqi Jews and is estimated to be between 2500 and 3000 years old. This, therefore, must have occurred by a founder germline mutation in Mesopotamia shortly after the fall of the first Temple and also must have been carried north among those Jews who ultimately contributed to the foundation of the Ashkenazi tribes. The second mutation (617del IT) is on the *BRCA2* gene and is found in 1.4% of Ashkenazi Jews only and is estimated to be about 700 years old. Clearly, long after the fall of the Second Temple the founder germline mutation almost certainly must have arisen from the Jews who had settled in Eastern Europe. The third mutation (5382ins C) is on the *BRCA1* gene and occurs in 0.1% of the Jewish population and is said to reflect another tragic event in Jewish history. This mutation is

also seen among high risk non-Jewish women of East European origin and is sometimes described as "a pogrom" mutation. In other words, the consequence of pregnancies following rape, yet another component in the repertoire of humiliations experienced in the Jewish ghettos of the Pale of Settlement between the 13th and 19th centuries.

These three *BRCA* mutations are distributed among Jewish people in an identical way in New York and Manchester. The incidence and type of mutations among the Manchester Ashkenazi population were documented and described by Prof. Gareth Evans of the British contingent. Both the Israeli and the British experience confirm that women carrying one of the *BRCA1* mutations have a close to 80% chance of developing breast cancer by the time they are 80, whereas those carrying the *BRCA2* mutations have about a 35% chance of developing breast cancer by the age of 80. These mutations are also associated with an increased risk of ovarian cancer, but also, curiously enough, prostate cancer among the male members of the family. Rarely can these mutations be carried and express themselves as breast cancer in the male relatives of such at-risk groups.

The experience of all researchers in this field has confirmed that what marks these cancers as uniquely difficult is the early age of onset, which is on average 10 to 15 years younger than what you might expect with sporadic breast cancer. For that reason they occur more often in premenopausal women where mammography is singularly unhelpful. However, there was a glimmer of hope in this direction when Prof. Ruth Warren from Cambridge University presented her encouraging results for the detection of early breast cancer in *BRCA* carriers using magnetic resonance imaging scans.

The other curiosity about these cancers is their morphology (how they look under a microscope) and the increasing understanding of why these specific mutations contribute to early presentation with the disease. Prof. Alan Ashworth, Head of Breakthrough Breast Cancer at the Institute of Cancer Research in London, gave a spectacular talk that explained the biology of these cancers. It appears that the normal *BRCA* genes play a central role in the repair of DNA. The DNA in our body is constantly being damaged either spontaneously at the time of cell division (transcription error), or by exogenous factors such as ambient radiation or cosmic rays. For those with a deep understanding of the subject, the miracle is not why people get cancer but how the species survives at all, *free of cancer*. Clearly, a long way back in the evolution of mankind, a necessary condition for life was the development of extremely rapid DNA repair systems. Thousands of mutations occur in our body daily and these are closely monitored and repaired with mechanisms of awe-inspiring ingenuity that makes one speculate about "intelligent design." The *BRCA* mutations mean that these repair mechanisms are disturbed, and if a number of these DNA fractures or faults of transcription are allowed to accumulate, then the cell takes on the malignant potential of unchecked cellular division and dissemination. Prof. Ashworth and his colleague Prof. Andrew Tutt from Guy's Hospital described a therapeutic breakthrough that they call the Achilles heel of the *BRCA* cancers. They have

developed a specific type of chemotherapy that further disrupts the DNA only in the cancer cells exploiting the inadequacy of the repair process. This is indeed a biologically directed smart bomb. The British group is now ready to launch a clinical trial for patients with these cancers but of course the incidence of such cancers in the UK is very low, whereas in Israel – because 1 in 40 of the Ashkenazi women carry the mutation – it ends up that about 1 in 10 cancers developing in Israel would make an excellent target for the trial. Following the formal meeting, informal corridor conversations, often fuelled by local beer, led to an agreement for Anglo-Israeli collaboration. The Israelis can identify the cases and administer the treatments. The British have designed the drug regimens and can coordinate the study; all that is required is about £100,000 to kick-start the process.

As far as I was concerned that was a sufficiently good outcome to justify the whole investment for the meeting. However, other things were to follow, which were in some ways of equal importance. The third day of the conference involved a tour of the north of Israel, including Nazareth, the Golan Heights and Safed. Two events in Nazareth gave me pause for thought. We happened to be there on *Yom HaShoah* (Holocaust Memorial Day) when at 11.00 a.m., the sirens are sounded and everybody in Israel stands for two minutes to remember the Holocaust. The commemorative pause was recognized by the Christian Arabs in the grounds of the Church of the Annunciation, but the Muslim Arabs made a point of continuing to drive and hooting loudly to drown the silence. In contrast, the other event, which warmed my heart, was a tour of the Church of the Annunciation that included a visit to St. Joseph's Church in its backyard. Joseph, the father of Jesus of Nazareth, lived at this spot and the Church was built over the ruins of his house. Our guide, Benny, took us down into the basement, the site of the excavations of the home of a prosperous artisan dating back to the 1st century CE. The guide pointed out the system for collecting water and the steps leading down to the well. As far as I was concerned there was no doubt whatsoever that the arrangement of the water system, the dimensions of the "well," its mosaic floor and the steps leading down, that this was an ancient ritual bath (*Mikveh*). I am happy to believe that this was indeed Joseph's house and I am happy that this confirms that Jesus was an observant Jew from a prosperous family (didn't the lad do well!)

However, the main reason for visiting the north of Israel was to see the oncology clinic at the hospital in Safed and in particular to meet the Director of the Unit, Dr. Jamal Zaidan. The Oncology Unit is spick and span and state of the art, thanks to the funding by the Israel Cancer Association. As the name might suggest, Dr. Zaidan is not Jewish but a member of that exotic and handsome ethnic minority – the Druze. The Druze are a mysterious sect that keeps their religious practices secret, but one thing we know for sure – you cannot convert to become a Druze. You can only become a Druze if both your parents are Druze. Dr. Zaidan described to us some fascinating work concerning breast cancer among the Druze. The incidence is high

and the pattern of disease is like that of Jewish women with *BRCA1/2* mutations. Yet the Druze are genetically quite distinct and do not carry these mutations. However, what is special about their people is that the size of the global population is so small, approximately 1 million, with only about 20,000 in the whole of Israel, that intermarriage among close relatives is quite common. It is likely, therefore, that with consanguineous marriages, both husband and wife might carry genes that predispose to breast cancer. These might be recessive genes or ones with low penetrance that could express themselves if the cells have two copies, one from each parent. Dr. Zaidan's team thinks this might be the case; if so, this would be a world first and might lead the race to find the common mutations that are linked to so-called, sporadic breast cancer. This is the "holy grail" of cancer genetic research.

After Safed our tour took us sightseeing on the Golan Heights, with a view of Damascus on the horizon, and then along the eastern shores of the Sea of Galilee, across the Jezre'el valley and on to the Mediterranean sea for a late supper in Caesarea. The last day of the event was spent touring Jerusalem. The weather was balmy and the spring flowers that decorated the sidewalks and squares sparkled like kaleidoscopes in the bright sun. Seen from the Mount of Olives, the Old City truly looked golden and seen through the eyes of my friends on their first visit to Israel, I rediscovered the enchantment of my first visit to this point shortly after the Six Day War in 1967. One of our group, Dr. John Warren, a tall, rather austere English gentleman of the old school, was particularly excited as this was a journey of discovery of special import. His great-grandfather was the Captain Warren who sank the first shaft (known as Warren's shaft) that led to the discovery of the ancient city of David. He asked our guide Benny whether this event was recorded. Benny, with a wry smile, said, "let's see." We boarded the bus, entered the old city and were led to the Davidson museum in the archaeological park outside the southern walls. Halfway down into the underground vaults was a film show describing the history of these excavations. The story that was told started with photographs of a bewhiskered Victorian gentleman, Captain Warren. For a moment or two John Warren's stiff upper lip trembled and a mote of dust must have entered his eyes as they moistened into what might be mistaken for a tear. That night he and a few others of our party were taken along Hezekiah's tunnel discovered by that great Victorian adventurer, John's great-grandfather. The story might end here at a neat point where 21st century clinical scientists returned to the city of David, which marked the start of the journey that led to the Jewish Diaspora and three germline mutations that incidentally described our migrations.

Of course I hope it does not end there and that we can raise sufficient funds to find the cure for the Ashkenazi *BRCA* breast cancers.

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