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SPERM BANKING IN EDINBURGH*

*Timothy B. Hargreave MS, FRCS***

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Now that effective chemotherapy is available for Hodgkin's disease and testicular malignancy, attention is being focused on criteria other than survival rates. Most modern regimes of combination chemotherapy are damaging to spermatogenesis, and sperm banking has been offered to help to solve this problem. The following questions need to be considered.

1. Is spermatogenesis normal prior to chemotherapy?

There is evidence that a significant percentage of men may have impaired spermatogenesis before treatment is begun, and therefore care must be taken before ascribing damage to a particular drug. It is also possible that men with depressed spermatogenesis prior to therapy may suffer less damage following therapy than men with normal spermatogenesis prior to therapy.

2. Is the proposed regime known to be damaging?

The current evidence is that most of the alkylating agents including chlorambucil, melphalan, cyclophosphamide, nitrogen mustard and disulphide have been shown to damage human fertility. Many other chemotherapeutic agents are suspect; for example the effects of cis platinum are as yet not well documented. Methotrexate given for psoriasis produces oligozoospermia which improves when the drug is stopped.

3. Is there likely to be any recovery?

Reports in the literature suggest sterility may be permanent. In our experience the time needed for recovery following chemotherapy can be as long as three years, and it is wise to wait this length of time before giving definitive advice about fertility or contraception following cancer chemotherapy.

* From the Department of Surgery/Urology, Western General Hospital, Edinburgh, United Kingdom.
** Honorary Consultant Urological Surgeon, Western General Hospital, Edinburgh.

4. Is sperm banking appropriate?

The value of sperm banking in terms of subsequent fertility has not yet been fully established (Table I). New techniques such as *in vitro* fertilization may enable stored samples to be used when the pre-storage sperm measurements were poor (low density, poor motility). There can be considerable psychological benefit from the knowledge that samples have been stored. If sperm banking is undertaken samples should not be used until the maximum at risk time for tumor recurrence has passed, in most cases 2 years.

TABLE I

Sperm Analysis Prior to Storage

Diagnosis	Numbers of patients	
	Sperm density<10^6	Sperm density>10^6
Testis tumor	9	17
Hodgkin's	—	12
Histocytoma of tibia	—	1
Hypogonadotrophic hypogonadism after Pergonal® treatment	2	—

5. Is there any treatment that will prevent damage?

The use of gonadotrophin releasing hormone analogues given before the chemotherapy may have a protective effect on spermatogenesis. So far this has only been evaluated in an animal model.

REFERENCE

1. Hargreave TB. History and examination. In Hargreave TB (ed). *Male Infertility.* Berlin: Springer Verlag, 1983, pp 9 - 45.

DISCUSSION

Şimşek: How many samples do you collect from one patient?

Hargreave: Well, it's a terrible problem because you see, the patient is not very well, and the sperm samples have to be produced next to the liquid nitrogen bank, they can't be produced at home and then brought to us later because then they're no good; so we have, in our department, what has been termed in Australia, a "masturbatorium". We have a private room, that is comfortably furnished, with a door that locks. When a patient is coming I tell him to bring a Playboy magazine or

something like it, because in hospitals it's really very difficult to produce samples. Before I started to do this, before I had a little chat with them, many of the men could not produce a sample; remember, they're not well, they don't feel like it, they don't feel sexy. Chemotherapy is usually pressing and we want to get on with it, so the simple answer is we try to collect as many samples as we can before chemotherapy has to start. We usually wait for two days between each sample and we hope to get maybe one, maybe two, maybe three, depending on whether it's metastatic and how urgent chemotherapy is. We have never yet had more than three samples from any one patient. Each sample is stored down in 1 ml aliguots and so we may have something like 20 ampuls from one patient to give us a chance of 20 separate cycles of insemination. And when we get to the insemination we try to time the insemination using ultrasound control of ovulation etc, but that's another story.

Smith: How long can you use the samples?

Hargreave: I don't know. I mean in the vet banks they've had samples in 20 years. We really have no idea how long you can store human samples. This is routine practice for animals and they store samples 5, 10, 15 years.

Smith: And they can still use them for insemination?

Hargreave: There appears to be no great drop off in fertility. I think the great drop off in activity is when you freeze and when you thaw, and that the deterioration with time actually in the bank is pretty small providing you keep your bank filled up. And don't underestimate the difficulty of this. A bank has to be filled up again every two weeks with nitrogen. So it's not something you can do just in a day. There's got to be a lot of planning; you have to know that you can get liquid nitrogen.

Khalifa: Is liquid nitrogen expensive?

Hargreave: It's not terribly expensive in the U.K. If you want to know something about the running costs for such a bank, we spend about £700 per year on liquid nitrogen and then we have to buy a container which costs about £500 and then there are the little ampuls, which are plastic, but they have to be good plastic or they explode.

Özen: I'm interested in those twelve patients of yours who, on analysis, had adequate sperm counts. How many of them have an undescended testis related to a testicular tumor? Could it be that there was an intrinsic defect that caused undescended testis, that caused infertility and that caused testicular tumor? It's all rather hypothetical.

Hargreave: Thanks very much for the question because I don't know the answer and I should find out. I think the point you make is very interesting; one should ask

why there is so much wrong. I wonder what I'd find if I biopsied the other testicle in those cases.

Şimşek: Mr. Hargreave, do you believe that some cancers are familial?

Hargreave: Well that's what my end remarks were saying. I know of no evidence with which to answer this sort of question. To a certain extent I can only trust that I'm doing the right thing. If you want to say I am doing the wrong thing, please do so. I don't really know.

Şimşek: It's off the subject of testicular cancer, but you mentioned you were storing AID specimens, and I just wondered how many donors you had and how often they came.

Hargreave: Well that's another matter altogether. The only reason I've stored AID samples is because in my hospital, even though I've got a most superb secretary, who is dedicated to this type of work, it's terribly difficult to organize the lady to ovulate at the time the sample is there and in fact it's beyond my organization. This simply allows me to have the sample at the right time. So those AID samples in the bank are merely a matter of administrative convenience and at any one time we have about 60 couples attending my clinic for AID and I think that's something really totally different.

Blandy: Still let's pursue it. We're inevitably using rather poor sperm. Not for AID; But in the case of these chaps with testicular tumors, as you pointed out, quite a lot of them have rather indifferent sperm. AIH with rather poor numbers of sperms in our clinic is really rotten and most disappointing.

Hargreave: Yes. The only reason I've accepted these cases is that I think we might be able to use them for IDF. The numbers, of course don't matter too much, it's the quality. All I can say is we've got one pregnancy progressing. Now I don't know how that will result; that's an IDF pregnancy from rather a poor sample, and who knows what will happen.

Blandy: Yes it is interesting. I was talking to someone in Dallas who'd set up a multi-million dollar sperm bank, and his lawyers told him to drop it. I don't know if you've had any sort of legal troubles about it. What happens of you have a baby born with a harelip or worse?

Hargreave: I talk to the people and tell them we are venturing into the unknown. I'm just trusting to a certain extent that I'm doing the right thing and we'll have to monitor carefully what I do. I think I am at a risk, and it may be that I'm going to be sued or our defence organization is. I think this is a very risky area of medical practice. I tell people that I can't guarantee the Bank's existence, and that if we have a strike and no liquid nitrogen, the whole lot may thaw out. We are, of course,

in the privileged position that we are not charging patients for this service. It is offered as part of the Health Care Services and so it's perhaps less likely that patients would sue us. Especially when we make it very clear that we can't guarantee the sample. And I've told patients that I can't guarantee pregnancies. And I say to patients that there is absolutely no evidence about malformations. I feel that nature is a great corrector and that there are in these mechanisms of conception and pregnancy safety mechanisms of conception and pregnancy safety mechanisms to abort fetuses that are abnormal and I hope that will rescue me. I emphasize, when I give any treatment for infertility, that the risks of fetal malformation are, as far as I am aware the same as everybody else's risks, and one harelip wouldn't alter this.

Blandy: No I just mentioned this because I do think that this is a real worry. It certainly deterred me; not actually the problem of regular supplies of liquid nitrogen, but the possibility of getting sperm samples muddled up. In my part of London the population mix is extraordinarily diverse. A mistake could be very upsetting.

Hargreave: That is another matter altogether, and quite simply a matter of administration. We have some rules. There is one person only who is allowed to withdraw samples from that bank. And she is in total command and she tells me what to do. You have to have an absolutely rigid and well-worked out identification system. We use those little ampuls because they are honestly easier to identify than the straws which are commonly used. We do not run a racial sperm bank. I will not accept patients privately for AID and we are only offering this service to our indigenous population of Scotland. The possibilities for error of a white woman carrying a black baby or a black woman carrying a white baby would be too much.

DISCUSSION

Özen: Have you run into much in the way of legal and other difficulties?

Hargreave: When patients come for counseling I talk to them and I also give them a written explanation about these things. I always hope that if you are careful about your counseling that there will be no problems later on with legal difficulties; and actually I think that this applies to much of medical practice. I think that if you are careful to tell patients what you're doing and why, then you'll have very few such difficulties.

Blandy: I'm sure that in general that's absolutely right.

Djani: Does the wife really appreciate the seriousness of the condition in the partner before she embarks upon such a problem.

Hargreave: Usually yes. I think in our country most of the people who are coming to us have a very good idea that these tumors will kill.

Djani: In such a situation, I imagine, the wife would not want to have a child.

Hargreave: Your point is a very good one. Similar, is the question of whether I use the sample for the wife whose husband has died? These are difficult problems.

Blandy: We've had both reactions from our patients. Some have begged us to put sperm down in storage because they want to leave something behind to father a child before they go on. Others have taken quite the opposite view. It is very interesting. I think it's up to us, if we can, to provide the service but it's jolly difficult. I congratulate you on how far you've got.

Djani: This is changing the subject rather, but what is the stand of the Church on this matter?

Hargreave: Well, that is almost a subject for another symposium. The ethical, moral and religious problems about fertility practices are very great, but let me just say something. In the United Kingdom recently, Mrs. Thatcher commissioned a review to look into these sorts of questions, and if I understand the emphasis of these things correctly, most of the procedures that will enable a man and woman to have their own biological child are allowed, but there is much more caution about procedures that would involve a third party in any way, particularly if the third party is a woman; and there is some doubt as to whether laboratory procedures where there are interactions between humans and animals should be allowed; and also there are doubts about how long you can ethically allow, in a test tube, products of conception to grow for experimentation. But in general I don't think the Churches we are dealing with would censure us in any way if we're doing something between the husband and the wife.

A DISCUSSION ON CYTO-REDUCTIVE SURGERY

Blancy: Can we hear about your experience with cyto-reductive surgery?

Akdaş: We have had, as I said, only one patient with teratocarcinoma and after the chemotherapy with PVB, debulking surgery was performed. The pathology was mature teratoma. Treatment was apparently successful.

Smith: I really have almost nothing to add. There is a distinction between cyto-reduction before chemotherapy and cyto-reduction after chemotherapy, and the evidence so far as I am aware, suggests that cyto-reduction before chemotherapy offers no real benefit over chemotherapy alone. Probably we should limit the discussion to the removal of the tissue hardened at chemotherapy.

Blandy: I think you've made a very important point. Some quite good evidence has been produced to suggest that attempts to debulk, so as to make it easier for the chemicals to kill what was left, were a waste of time. Isn't that right?

Smith: Yes.

Akdaş: ... After the chemotherapy, if the markers are still positive, and there is a lump in the abdomen, is surgery recommended?

Blandy: Well, I think that's a very important point. A lot of people would say don't start the surgery until the markers are right down. What do you think?

Akdaş: As far as I know, it is inadvisable to do that sort of surgery if the markers are still raised. But in the case of a patient with normal levels of markers and a lump in the abdomen, I think surgery is suggested.

Blandy: Yes, I think that's right. Have you any views about the morbidity of this operation? I once made a hole in the colon.

Akdaş: I must confess, we have had one experience only and we also made a hole in the gut. But it was alright in the end.

Blandy: So far, this sort of surgery does seem to be worthwhile. There's a paper from an Australasian source, which I was asked to look at for some journal. In this, they had followed up a series of cases where they had not done debulking surgery, and they had some evidence which suggested that the results were no worse if you didn't remove the lump. In such cases one has to work very closely with one's oncologist. I'd rather do what I'm told under these circumstances.

Kırkalı: Would you touch a lump in the abdomen when the markers are high?

Blandy: In our practice it depends on how much chemotherapy they've had. I've done two of these, when the markers hadn't come right down, in the hopes that I could remove the remaining bit of cancer: I don't know whether that did good or not. Most people would say that it was the wrong thing to do, but the chemotherapy is so horrible for these people. If you can spare them an additional course by removing the lump it seems it ought to be right.

Khalifa: In this connection what do you feel about radiotherapy?

Blandy: Do you know, I honestly think that radiotherapy has been overtaken by chemotherapy, in the treatment of this disease. Some people have been in favour of a sort of sandwich treatment with radiotherapy and a comparative study was carried out and they found there was no benefit from sandwich radiotherapy if they were going to do a surgical removal. I've no experience of it myself. I don't know whether anyone else has.

Şimşek: It seems we're advised not to perform bulk reduction if the markers are raised; but isn't there a chance of getting them down, if we take some of the tumor tissue out, or perform a radical surgery?

Akdaş: As I have said, I don't have much experience with bulking. But generally surgicial intervention is not recommended if the markers are raised.

Şimşek: Well, what are the reasons for this?

Blandy: I think it's not a question of reason, it's a question of experience. We have to follow the lead of the big North American centers because they're talking about 40's and 50's of these cases, whereas most of us, I think, have only done about 16 or 17 of these operations.

Şimşek: Logically though, if the markers are up, and chemotherapy doesn't help the patient, then why not try and get the tumor out?

Akdaş: They used to do that and they didn't get good results.

Smith: Two of my slides this morning referred to this; one was a general statement. Much of it was in favor of alternative chemotherapy if the first four cycles of inductive therapy did not drop the markers, If the traditional concept is four cycles of therapy, patient marker negative, residual tumor, were limited. If it's four cycles of chemotherapy, markers not negative, the assumption is, this tumor is not under control. Therefore, change therapy; give either two or four more cycles, check the markers, and then do the surgery. That's the logic behind it. It obviously doesn't work in every case; you will perhaps remember, I showed a slide where there had been interference to do debulking surgery in a patient whose markers were very wrong. So, I can't take it any further than that, but it seems to me that we're currently at the frontiers of such knowledge as is available.

Akdaş: May we go back to subject of chemotherapy? We are using PVB for four cycles or sometimes six cycles. What do we do for the non-responders? The second or third choice for chemotherapy has usually been Methotrexate or Adriamycin® and other drugs; but these are not useful. Which treatment would you suggest for the nonresponder group of patients?

Blandy: The fallback of chemotherapy? I'm afraid I can't answer that. I don't know enough about the chemicals.

Akdaş: Do you have the JM8? They may be getting some good results with this drug.

Blandy: Well, I'm not sure that they'd use JM8, if they'd already tried cis platinum. But this is not my subject.

Akdaş: Back to debulking for seminomas. Is there any place for debulking in seminoma stage III patients?

Blandy: Well, I've got the experience of one patient only. Most people's experience with the salvage surgery of seminoma, as opposed to teratoma, has been most discouraging, moreover what actually is removed is differentiated teratoma.

There is another question I'd like to raise which I think is fairly important. Not uncommonly now, we can cure people, of disseminated disease, with chemicals, and then if we can see nothing wrong with either testicle, what do we do then?

Akdaş: We have had one patient like this. He came from the Eastern part of Turkey. One of the testicles was suspicious and we performed an orchidectomy and it was normal. But because of the histopathology of the lump we gave chemotherapy. Soon he was all right again. It cured him.

Blandy: Well, lastly, let me put it to Mr Smith, that all the advances in chemotherapy in testicular cancer have been made, not because of but in spite of the use of controlled chemical trials. Would you accept that?

Smith: Anytime.

Blandy: It's very curious, isn't it? It's gone at such a pace, that there's never been time to do a control trial of anything. Except possibly in your case when you showed that you didn't need to give an unnecessary high dose of the toxic.

Smith: By controlled clinical trial, do you mean a randomized one?

Blandy: I don't know, you're the trial expert.

Smith: Well, for me "controlled" implies there's either some control or some other thing, or it maybe that it's just well followed up; because this annual study was a study which was done with some care. And if you like, represented some form of sequential development. So I would say "without any form of randomized trial", because you only do a randomized trial for two things. Either to prove the negative which is common or to prove that something is, some relatively minor degree better than another; and here there was just a great leap.