HYALURONIDASE AND CANCER

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In 1968 a paper by the undersigned appeared in this Gazette entitled "Cancer: an Immune Response Through Cell Evolution". Immediately afterwards, the eminent onchologist Sir Peter Medawar, found time to comment on it in a personal letter. He remarked it was very similar in many ways to the theory of the late Professor H.N. Green, with which he did not agree anyway.

I have recently gone through Prof. Green's last and comprehensive book "An Immunological Approach To Cancer", which I recall having read before 1968 but to which I had made no reference because with respect. I considered my approach differed fundamentally from his. Whilst Green's masterly work deals with the tumour-cell RE-cell relationship, my own armchair theory stipulates that cancer cells are ordinary tissue-cells turned immunocyte against carcinogen, the latter being the antigen.

There is now ever-mounting evidence that RE-cell immunity towards cancer-cells does exist, but paradoxically, tumours become established even if highly antigenic because "tumour-associated antigens are shielded from immunocytes" (Leroy, 1975) This is an argument parallel to my own, in which I suggested that new tumour-cells, acting as immunocytes" are shielded from the carcinogen, acting as antigen. According to Burnet's phenomenon of "Immune Surveillance", the immune system constantly detects and destroys any abnormal clones of cells that arise in the body. Presumably here the immune system responds at least as rapidly as the clones develop. A tumour is "established" following continued carcinogen action, which, by accelerating the speed of growth, relatively slows down the immune response. (Bowry, 1975) Whether my original contention was correct or not, i.e. that the tumour-cell itself is a form of immunocyte, the fact remains that tumour-cells, being independent of any growth-controlling influence, undergo rapid mitoses in all directions and at all sites of the tumour, peripherally and centrally, there producing that compactness of cells which is felt clinicaly in an advanced neoplasm as deep induration. The cells become so thickly packed that intercellular spaces are virtually obliterated. This impenetrability of spaces is possibly what physically constitutes that "shielding" which prevents effective completion of the immune response, even after carcinogen is discontinued.

If this be so, is there any means whereby these spaces could be widened sufficiently to facilitate the deep penetration of immunocytes and humoral antibodies, the neutralisation of tumour cells and their eventual elimination? In my first publication on the subject, mentioned at the beginning of this paper, I had suggested the use of a carcinogen-hyaluronidase combination to induce immunological paralysis of the tumour-cell's action against the carcinogen. The enzyme hyaluronidase would act by dissolving the "shield" formed by the intercellular connective tissue. Not surprisingly, the suggestion has remained, as far as I know, a voice in the wilderness — after all, let's face it, the idea of injecting more carcinogen into a cancer patient can hardly be expected to be taken seriously!

Over and over again, hyaluronidase has been shown to be clinically effective and harmless when used for the dispersal of bruises and the extravasation of anaesthetics; and also for aid in the absorption of opaque X-ray material which then concentreated in the kidneys within a few minutes from the time of injection. This latter example shows the rapidity of its absorption and universality of its distribution through the body. An other instance is the rapid dispersal of a facial haematoma after injection of hyaluronidase into a site as far removed as the buttock.

This, then, more than any other, would seem to be the most likely means for removal of the intercellular barrier or "immunological shield".

The examples given above show the way hyaluron dase acts in certain given conditions in an otherwise healthy individual. How would it behave in a debilitated patient with poor circulation? Would it reach the tumour site or sites and, once there, would it be effective in pervading and widening the obliterated intercellular spaces to the desired degree? The likelihoods seems poor, especially with regard to the deepest cells. The optimist is left with the hope that it would be a matter of time, the peripheral cells being dealt with first, before the enzyme and the following immunocytes and antibodies find their way to the deepest recesses.

The use of carcinogen-hyaluronidase combination, as originally suggested, would obviously imply previous animal experimentation, for which this writer has no facilities. With our long clinical experience of hyaluronidase on its own, and its harmlessness and effectiveness in other fields, would one not be justified, scientifically and ethically, to enlist its aid in all cases of malignancy? There would appear to be no reason why the orthodox measures should not be continued at the same time. In the more debilitated patients an eye would also have to be kept on electrolyte balance (Bailey & Love, 1971).

If, in the process, my first contention should prove to have some foundation, i.e. that hyaluronidase aids cancer cells to dispose of the carcinogen macromolecules, there could certainly be no objection to this double action.

Just in case the "practical hypothesis" summarised in this short paper should actually find a following, a note of warning would not be out of place. Should it turn out that hyaluronidase does widen intercellular tumour spaces to the point of allowing entry of RE-cells, might it not, at the same time, have the effect of detaching clumps of malignant cells and actually predisposing to metastasis formation? — even though, one hopes, these cells would be again attacked at their new site(s) of adoption. For this reason, initial use of this method would have to be confined to experimental animals with "primary", i.e. non-transplanted, tumours or, clinically, to patients who have been declared inoperable and are not responding satisfactorily to conventional treatment. Naturally, they would have to be made fully aware of the implications before being asked for their consent.

On the other hand, it would not be fair to expect hyaluronidase to work miracles on terminal cases who would die anyway even if, so to speak, the entire tumour disappeared spontaneously overnight.

Over several decades thousands of dedicated researchers have been employed and millions spent in the all-out war against this cruel scourge we call cancer. The expenditure involved in the trial of just one other possible adjuvant and its rejection (or acceptance) would surely be negligible.

References

SAMMUT, J.J. (1968) St. Luke's Hospital Gazette, Vol. III, No. 2, pp. 102-111.

GREEN, H.N., ANTHONY, H.M., BALDWIN, R.W., and WETROP, H.W., London 1967.

LEROY, G.J. (1975) "Immunological Surveillance against Cancer: Critique of an established hypothesis", published in "Medical Hypothesis", Newcastle-upon-Tyne, No. 1, pp. 43 *et seq.*

BOWRY. T. (1975) "Medicine Digest", England, October p. 24.

BAILEY and LOVE's "Short Practice of Surgery", XV Ed., London 1971, p. 88.