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PERSONAL VIEW

SOME CYTOLOGICAL ANSWERS TO ATHEROSCLEROSIS

Iftikhar Qayum

Abstract: A concise review of the atherosclerotic process is presented and a new concept is proposed as to the fundamental nature of atheromas and the process of atheromatosis. Evidence and arguments are provided to consider the atheroma as a newly developing and evolving vasculo-endocrine unit of the vessel wall, secreting steroidal chemicals and hormones into the blood stream. These hormones are of probable importance as trophic factors for the vascular tunica interna and are also of circulatory value for enhancing trans-capillary transport of nutrients and metabolites and catalysing the tissue reactions of metabolism in the tissue spaces (thus being tissue circulation promoters and enhancers). They may be of use in preventing or treating various tissue metabolic storage disorders as well as in creating better general and special tissues for the body.

Introduction and present state of knowledge

Atheromas are yellow and white coloured, soft to firm, maculo-papulo-nodular streaky or plaque-like structures, from 2mm to 5cm in size, located in the subendothelium of essentially arterial blood vessels.[1–4] They are focal, multifocal or patchy in distribution, occur in all human beings from childhood onwards, and are commonly found in the Aorta and its major branches, and importantly also in the regional blood vessels of vital body organs like the Brain, Heart, Kidneys, and Pancreas.[1–4] The intimal and subintimal location of the atheroma gave rise to various theories of the origin of atheromas secondary to haemodynamic and metabolic abnormalities affecting the vessel wall, that by injuring the endothelium and causing abnormal leaks in the Intima, produced the atheroma in the subendothelium.[1–4] The main lesion was believed to be the intimal and subintimal accumulation of various abnormal fatty materials, believed to have been sequestered from the plasma, the tissue reactions in the subendothelium being in response to these abnormal chemicals, cholesterol and its crystals and cholestryl esters being the main tissue atheromatous chemicals.[1–4] This accounted for the yellow colour of the atheroma, as well as for the histological patterns seen in the subendothelium. These theories could not explain the focal and multifocal distribution of the atheroma since a general blood or metabolic abnormality would affect all the cells of the intima and subintima and not just a few areas of the vessel wall. Electron microscopic studies of the pre-atheromatous intima failed to show any endothelial cell injury and no abnormal or leaky permea-

From Ayub Medical College, Abbottabad
IFTIKHAR QAYUM, MBBS, MD, Dept of Anatomy

tion by the endothelium could be demonstrated. These changes actually happened some time after the atheroma had established itself, thus being secondary to the atheroma and not primary.[4] The generalised theories had to be abandoned in favour of focal theories that stressed the occurrence and nature of the atheroma as a basically focal proliferation of subendothelial tissues in the vessel wall.[4,5] It was categorically shown that the first atheromatous change is the proliferation of subendothelial connective tissue cells, which undergo differentiation to a number of other cell types, that make up the cells of the atheroma.[4,5] More importantly, it was shown that the subendothelium reverted to embryonal mesenchymal tissue before differentiation to increase its pluripotency and then became differentiated—this explained the varied and primitive appearance of the atheroma cells. These cells are of several types including fibrous and mucoid mesenchymal cells, fibroblasts and fibrocytes, lipoblasts and lipocytes, epithelioid cells, myoid cells and histiocytes. The special atheroma cells were named Foam cells, as they contained fatty material inside their foamy, vacuolated cytoplasm, and were arranged in small groups and clusters in the atheroma. The other cell types were helper and worker cells helping in the proliferation and establishment of the atheroma.[4,5] We know that the blood vessels are derived from angioblastic mesenchyme and this tissue is maintained in the formed vessel as reserve subendothelial connective tissue—thus it is easy for this tissue to become embryonal and proliferate to different cell types. This gives us the concept that reserve angioblastic mesenchyme is being reactivated in the subendothelium and this tissue then becomes the progenitor tissue of the atheroma. This concept fits in much better with the observed and recorded data.[4,5] Of course the next question to be answered is, if this mesenchyme is being reactivated to form a new structure in the vessel wall, of what importance is this, and why should it happen—apparently the vessel is adding on new parts to its Tunica Interna. It seems to be an addition of some importance, since it is originating in the mainstream vessel, the Aorta and its major branches, and in regional arteries of vital body organs, and must be fulfilling vital circulatory and nutritional and metabolic needs of the body, as the prime role of the circulation is to cater to the general and specific nutrition and metabolism of the tissues of the body. The location in the Aorta indicates that this structure is probably secreting some material in the general body circulation, and the regional atheromas would be secreting regional chemicals for the organs of supply. The secretory role of the atheroma has not yet been fully established, even though the fatty materials contained in the Foam cells and the endothelial cells of the atheroma have been biochemically analysed and do tend to fit in the class of lipid and steroidal secretions like the steroidal hormones.[4] This would mean that the vessel wall is creating a new endocrine unit in its tunica interna. The intimal and subintimal location favours ease of secretion into the general or regional blood stream.

This is the concept that classifies the atheroma as a vasculo-endocrine structure; it may be called an athero-endocrine unit. There is no mention of this in the literature and I must say that it is as yet my own concept of the

fundamental nature of the atheroma. This is not to say that I am deviating from the data in the vast literature on the atheroma, which has labelled the atheroma as a dangerous and even fatal, obstructive lesion of the vessel wall. Certainly the list of abnormalities and diseases associated with the atheroma is impressive enough.[1–4] I simply feel that the matter is not yet finally settled and there is still another aspect to the atheroma that should be considered, and this is the view that the atheroma is an evolving vasculo-endocrine unit, at present facing great odds, and finding it difficult to stabilize itself as a bona-fide new addition of use to the body. It is possible that with progressive evolution, it will overcome its diseases and emerge as a true vasculo-endocrine unit. There are many processes in nature that start out as deviant, but later become normal and useful. It may become possible to control the deviations of the atheroma and make it useful.

The Concept of the useful Atheroma

This is the new concept being proposed, and we must see the arguments in favour of this. These are:—

1. The occurrence pattern of atheromatosis is widely different from the occurrence pattern of even common diseases. Atheromas occur in all human beings, and remain persistently in the body vessels till the life-span of the person. Other than congenital, non-fatal diseases, there are probably very few diseases that show this pattern, and even the congenital diseases are not found in all humans. Furthermore, a congenital tissue anomally may persist for long in the body, since the embryonic tissue is non-immunogenic, but new structures arising later on in body tissues are not easily accepted by other body tissues for long unless they are proved useful. The atheroma however actually starts after embryonal life, in childhood, and keeps recurring at various times and ages in the body, without being rejected to any significant degree. This may be because the progenitor tissue is embryonically reversed, or it may be that the atheroma is of use to the body.
2. It is claimed by statisticians that the incidence of atheromatosis seen at autopsy or in medical practice is actually much less than its real incidence in the body. This means that a large number of atheromas are not inciting disease or death, and a relatively smaller number are pathogenic. Even at autopsy, the appearance of most atheromas, excluding those of older people is of either the Fibrofatty and Fibrous Plaque, or even the Fatty streak, and only a few areas of pathological atheromas are evident. There is minimal inflammatory or immune reactionary response in the atheromatic tissue, as seen by the cellular infiltrate. This also indicates that most atheromas are innocuous, and the few that are pathological are only mildly so in the majority of cases. It is also possible that a significant number of lesions may be spontaneously regressing in the body.

3. A study of the blood circulatory system, even a basic one, will convince anyone that the circulatory system is stringent and meticulous in maintaining its composite parts in a healthy state.[4, 6, 7] We must remember that the primary role of the circulation is to provide the proper nutritive and metabolic milieu interior for the tissues, and the circulatory system developed secondary to this need of the body. Thus in addition to maintaining its circulatory apparatus in proper order, it is also geared to the nutritional and metabolic changes in the body, and can develop new structures in its apparatus for this. The atheroma with its periluminal location and possible secretory role may have developed in response to such body needs, alongwith growth of the body during the growing years; it probably stabilizes in the middle ages of life, and ages along with the body tissues—again showing the pattern of an integral body tissue or organ.
4. Histogenetically the atheroma originates in reactivated mesenchyme of angioblastic type. Thus the atheroma is arising in and from the progenitor tissue of the circulatory system. Obviously this parent tissue will give rise to structures that are of use and value to the circulatory system. Again we know from biological studies that it is not an easy job to reactivate a resting or reserve mesenchyme, particularly of a system like the blood circulatory system, that is vital to the body and remains in a dynamic running state all the time—this is like a continuously running motor or machinery that will seldom allow changes in it during its working cycle, unless they are really required or offer new benefits to it. The subendothelial connective tissue normally supports, nourishes and maintains trophic effects on the Tunica Interna, and to expect it to give rise to markedly deviant structures is not good biological sense.
5. There is some evidence at least that the atheroma has lipid mobilizing and steroidal synthetic and secretory activity, although this is still in a rudimentary and underdeveloped form.[2, 4] The nature of these chemicals is still being studied and we may ultimately get the needed secretory material and the nature of steroidal hormone. That mesenchyme can be endocrinally active is known, as the ovary makes oestrogens and progesterone from cells of the zona granulosa and the lutein cells of the corpus luteum, both of which are secretory phases of the same stromally derived cells of the ovarian follicle—the corpus luteum even has a yellow colour, like the adrenal cortex and the atheroma which also makes steroidal hormones. Thus it should be in the realm of possibility for angioblastic mesenchyme to become endocrinally active and the foam cells should be studied for this possibility. The hormones being secreted by the atheroma, ATHEROHORMONES or ATHORMONES are expected to be of circulatory use and may well be of significant value, considering the tortures that the vessel is subjected to during atheromatosis—but if the end justifies the means, who cares?

Discussion and Conclusions

I would venture to state, from all this, that we can certainly make out a case for the atheroma as a newly evolving and useful endocrinally active structure of unestablished value to the circulatory system. It is hoped that as the atheroma evolves out of its disease-riddled shell, it will be gradually established as a vasculo-endocrine unit in the vessel walls of not only important vessels, but all the vessels of the body, and its secretory role will become firmly established. In general, all the steroidal hormones of the body are very potent and very useful to the tissues. I think that with the joining of the circulatory system, the ranks of the steroidal endocrine glands are enriched further. We could postulate the modality of these Atherohormones and predict their role in circulation, i.e., in tissue nutrition and metabolism. Obviously, being useful members of the circulatory system, they would be meant for enhancing the existing working of their system. Thus we expect to find circulatory steroidal hormones that would be expected to enhance capillary permeability and trans-capillary transport of metabolites in both directions, thereby enhancing the circulation of nutritional and metabolic materials in the tissue spaces and preventing the phenomenon of material stagnation in the tissues, a condition that tends to lead to progressive accumulation of materials and wastes in the tissue bed and hampers the health and cleanliness of the tissues, as well as causing earlier tissue fatigue and degeneration reactions due to hypoxia and stagnation of materials that tend to decompose under these conditions. If this is the case, then we can really claim the atheroma as a vital structure, of immense use to the tissue metabolism and the health of tissues. I predict that once the atheroma is usefully evolved, we will find similar atheromatous changes and small athero-endocrine units as extensions from the subendothelium, in the pericapillary connective tissues, both at the arterial and venular ends of the capillary—this will be obviously required since this will make the hormones available close to the actual site of tissue metabolism, and the peri-capillary tissue filter will then become fully effective, for effectively rapid transport out into the tissues at the arterial capillary, and effectively rapid transport into the capillary at the venular capillary. Some of these hormones may also be secreted into the tissue spaces along with the tissue fluids and catalyse the efficiency of fluid and metabolite circulation throughout the tissue area. At present there are no such catalysers available for these reactions, and the tissue area and its circulation is driven by the forces of capillary permeability and tissue metabolic reactionary forces of that area. Although these are really good and proper forces, allowing the tissue circulation to occur at the whims and wishes of the tissues, it is found that there develop hindrances in tissue circulation over a period of time due to deposition of various materials in the tissue circulatory channels, like silt deposition in the river bed, and the problems of waterlogging and salinity. Tissues become oedematous and non-metabolic under such conditions and it is essential that these deposits be cleaned out of these areas and circulated throughout the body tissues rather

than causing local accumulations, which give rise to tissue swellings, abnormal storage disorders and diseases, say like focal Amyloidosis or Glycogen storage, Lipid storage and probably also Protein storage disorders and diseases. These are expected not to occur if the Atherohormones are really of circulatory value at the tissue level. Correlation of the presence or absence of atheromatosis and the type of atheromas in patients with these conditions should help to clear this area. Persons with these conditions would be expected to have less atheromas or atheromas that are not secreting the specific Athormone required for the metabolism of the material that is being stored or accumulated abnormally.

The other main role for the atheroma would be related to its derivation from angiotrophic tissue of the vessel wall, i.e., the Subendothelium, which by trophic secretions keeps the Tunica Interna in a healthy state. The atheromas could be endocrine growths of such angiotrophic areas in the subendothelium, and may be secreting chemicals and hormones into the blood stream for maintaining the healthy, trophic state of the Tunica Interna in general, as well as in the specific regional beds of vital organs.

Despite all this, we must take strong note of the pathological atheroma that is diametrically opposed to the health of the Tunica Interna, the vessel wall as well as the tissue circulation. We find that the chemicals of the pathologic atheroma actually destroy the layers of the vessel wall particularly the tunica interna, and also cause sclerotic, desmoplastic, dysplastic and even neoplastic reactions in the general and special tissue spaces, along with the simpler problem of blood flow obstruction to the region of supply. The pathological atheroma thus tells us exactly what should not be in the normal state of the body and tissue circulation. As such it should be rigidly controlled and eliminated.

In conclusion, it should be said that as presently understood, the atheroma is a pathological entity that leads to widespread and serious, often irreversible diseases of the circulatory system. Not only do these lesions have to be controlled, the atheroma itself has to be changed drastically, so that it evolves into a useful body structure, the possible uses of which have been discussed. If this can be achieved, we will have accomplished a medical coup d'grace, otherwise we will remain continual victims of the atheroma. Another good use of the athormones would be to use them for the prevention and treatment of the various tissue metabolic diseases, resulting from poor tissue circulation. If the atherohormones of regional vessels of vital organs are obtained in pure form, they could be used to treat patients suffering from diseases of these vital organs, e.g., the cerebrotrophic athormones could help improve tissue metabolism in the brains of mentally retarded persons and increase their mental levels. The same could be done for muscle tissues in athletes, and so on for each type of tissue in the body. This will be of real benefit to diseased and normal people, who also would like to increase their mental or other faculties. Thus before we finally condemn the atheroma as a pathology, we must look for this athero-endocrine possibility, and if feasible, help to divert the atheroma process towards these useful channels, by

genetic engineering or chemical induction, or other ways, that further research will bring out.

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RAMBLER'S GLOSSARY

Pathological	:	the right road
Interleukin	:	a great place to ski
Invivo	:	full of life
Fibroblasts	:	little holes caused by hot cigarette ash dropping on synthetic fabric.
Thymus	:	the plural of thyme
Liposomes	:	hot lips
Nucleotide	:	quite a wave
Macular degeneration	:	she didn't tie the knots very well

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JAK