Conclusions

No instance has been discovered in the literature of a history such as is recorded here, of a woman surviving a large choroidal sarcoma for 10 years, then developing a metastasis in the opposite orbit, which being encapsulated could be completely removed leaving normal vision.

I am grateful to Dr. Norman Ashton for all the trouble he has taken over this tumour, and also to Dr. Hansell of the Medical Illustration Department of the Institute of Ophthalmology for his fine photographs.

REFERENCE

GINSBERG, S. (1912).—*Graefe's Arch. f. Ophthalm.*, **82**, 1-57.

HISTO-PATHOLOGICAL STUDIES OF THE BLOOD-VESSELS OF THE EYE*

BY

R. SYSI

HELSINKI

THERE are numerous publications in the literature dealing with arteriosclerotic vascular changes in the eye. Most of them are based on a comparatively small material, which explains the diverging opinions on many points. Thus Koyanagi, Friedenwald and lastly Bergstrand consistently noted more conspicuous changes in choroidal vessels than in those of the retina, while Rintelen observed marked vascular changes in the retina only in few cases. He rarely found any considerable changes in the a. ciliares posteriores, while the others found pronounced sclerosis therein. Rintelen denies the existence of any severe sclerosis in the blood-vessels of the iris and the corpus ciliare, in contrast to Gasteiger and, more recently, Rones, who found great changes in these vessels. There are also differences of opinion as to whether the sclerotic changes spread as far as the anterior parts of the choroid and the retina, or whether they occur only nearer to the posterior pole of the eye. These examples will suffice to show that further studies on vascular changes in the eye are not out of place.

* Received for publication, June 1, 1949.

From the Patho-Anatomical Institute, University of Helsinki.
Chief: Professor Arno Saxen, M.D.

Research workers have as a rule discussed the condition of the eye vessels and their changes in cases of general arteriosclerosis, renal diseases such as nephritis, nephrosclerosis, etc., or when vascular sclerosis of the brain has been present at the same time, but no comparative study has been made of the age-changes occurring in the ocular blood-vessels, when there is no general sclerosis nor any marked local sclerosis in other organs. Thus it is these so-called normal cases that show general wear-and-tear in the vascular system with advancing years.

It was the effect of renal disease in impairing vision that first drew the attention of physicians to the close connection between ocular blood-vessels and those of the rest of the organism (Bright). Clinical experience proved later that many other diseases may give rise to vascular lesions in the eye. Only a few of these ocular changes caused by various general diseases or affections in some other organ come within the scope of the present investigation. Some of these changes we consider physiological, others are on the borderline of the pathological. Some of them occur irregularly, occasionally even in comparatively young individuals, sometimes no traces of them are found even in advanced age, such are gerontoxon, atrophy of the iris and miosis, retinal and choroidal changes, concentric or partial contraction of the visual fields, etc. In other changes, however, such as failing accommodation, we note strict regularity, for this diminution begins in early childhood and nearly always follows the same time-table, to such an extent that a person's age may be determined with considerable accuracy from his accommodative capacity.

Some of these changes must obviously be ascribed to arteriosclerosis. Others again, occurring where there is no arteriosclerosis present, can be explained by changes and wear caused in the tissues by age. A corresponding phenomenon may be noted in many other organs, notably in the blood-vessels. The occurrence of this phenomenon in the blood-vessels does not, however, mean that the wearing-out of the tissue results from vascular changes, but rather that both phenomena arise from the same fundamental cause at the same time, but independently of each other.

When beginning to study the blood-vessels of the eye it is advisable first to note the changes which occur normally in otherwise healthy individuals, before we tackle the question of strictly pathological, arteriosclerotic phenomena. I have therefore collected an extensive control material of cases where no general arteriosclerosis or renal diseases have been diagnosed. Both series have been collected, treated, studied and evaluated in similar circumstances and according to the same principles.

The material studied was taken from 204 corpses, and consists of 408 eyes. The preparations were obtained by dividing the eyes in front of the equator and taking the whole posterior part of the eye with the orbital part of the optic nerve and the surrounding tissue. From the anterior part of the eye the parts within the cornea and sclera were removed for study by detaching them with a spatula, as in the operation of cyclodialysis. The preparations thus include all parts of the eye except the cornea and the 4-5 mm. wide anterior part of the sclera. The preparations were fixed in formalin and stained by van Gieson's method and with elastin. Part of the preparations were also cut with a freezing microtome and stained for fat. We have full clinical records of all the cases, and all the corpses had also been fully dissected.

The distribution of the cases into a control series, arteriosclerotic cases without hypertension, nephritic cases and cases with nephrosclerosis, and into different age groups appears from the following table :—

TABLE 1

Age	0-15	16-30	31-40	41-50	51-60	61-70	71-80	81-90	Total
Control cases	7	9	11	17	22	10	—	—	76
Arteriosclerosis	—	—	—	5	6	6	5	3	25
Nephrosclerosis	—	—	—	7	17	31	17	5	77
Nephritis	1	3	6	4	6	3	3	—	26
Total	8	12	17	33	51	50	25	8	204

Several investigators have noted what was found by us in studying the present material—namely, that the blood-vessels of the eye are subject to the same pathological changes as occur elsewhere in the organism. In different parts of the eye these changes take place with varying intensity and in different relations to each other. Opinions vary in the literature as to what, and how great, changes occur in different parts of the eye. It is therefore not out of place to give a short account of these changes as they appear in the present material.

The optic nerve has two kinds of blood vessels, first, the central retinal artery and vein which pass through the nerve, and secondly, the small pia and septum arteries providing for the nutrition of the nerve itself.

Great changes of the intima are observable in the *arterioles* of the optic nerve, also homogenization and thickening of the wall, and, more often than anywhere else in the eye, complete hyalinization and obstruction of the blood vessel.

In the arteries of the retina, extensive proliferation of the intima and fatty change, also homogenization of the vascular wall occur. In the elastica there are no marked changes. Considerable thickening and increase of the number of nuclei is often noted in the adventitia. In the smallest vessels the changes are especially frequent in the intima. One generally finds that the changes are most

obvious in the retinal parts nearer the papilla, and that they grow less farther away from it. Yet one sometimes notices such changes even in the outermost retinal arteries.

A. ciliares posteriores, which are relatively large blood-vessels, show all these changes in the vascular walls. Besides changes in the intima, severe proliferation of the elastica, delamination and muscular hypertrophy are found. The only actual instance of atheroma occurred in these vessels, and completely obstructed blood vessels are not infrequent.

In the large blood-vessels of the choroid, besides intimal proliferation and fatty change, severe proliferation and delamination and thickening of the muscularis and the adventitia sometimes occur. Changes in the intima and fibrosis are noted in the small vessels, sometimes homogenization. As in the retina, the greatest changes take place in the posterior parts of the eye, but there is less difference in the choroid between the anterior and posterior parts.

In the *corpus ciliare* and in the *iris* the changes are usually slight. Some intimal changes occur, and also fibrosis and homogenization. Here it is more difficult to estimate the changes than elsewhere, since the general hyalinization of the tissues, which sometimes takes place, makes it difficult to distinguish the actual vascular wall from the surrounding tissue. In the iris vascular changes are generally still smaller than in the *corpus ciliare*. Yet even in the blood-vessels of these organs there is sometimes quite obvious sclerosis.

As well as in cases with arteriosclerosis, changes of this kind occur in the control series, where they must be regarded as normal for every age-group. We know that such changes occur in various parts of the vascular system from childhood, according to recently published statistics on general sclerosis, 8 per cent. in 0-9 year-olds and 23 per cent. in 10-19 year-olds (Eskola).

In the various groups the changes do not differ from each other qualitatively, but they certainly do quantitatively. All parts of the eye have this in common that, when changes occur, their intensity varies greatly even in the same region, so that one finds, side by side, healthy and diseased blood-vessels.

On first comparing the different groups and age-groups one finds that the quality of the changes is easy to estimate exactly, but there are no clearly defined standards by which we can measure the quantity of the changes nor any formula by which they can be expressed exactly, but one has to be satisfied with one's personal observations as regards the intensity of the phenomena and its relation to a change observed in some other vessel.

The number of control cases in the material which show no hypertension, no noticeable arteriosclerosis and no renal lesion is 76 (Table 1). Their ages vary from new-born to 70 years.

Under 30 years no vascular changes have been observed in the eyes of the cases in this control series (Chart 1). The changes begin to appear between 31 and 40, and then first in the *a. ciliares posteriores* and the arterioles of the optic nerve, and even in these in somewhat over a quarter of all the cases. In the next age group, 41 to 50, changes appear in all vascular areas. They are still most frequent in *a. cil. posteriores* and after that in the blood-vessels of the choroid and in the arterioles of the optic nerve. There are fewer changes in the other regions, least of all in *a. centr. retinae* and in the blood-vessels of the *corpus ciliare*. In the following age groups the frequency of the changes in the *a. ciliares posteriores*, in the vessels of the choroid, and in the arterioles of

the optic nerve increases regularly, reaching about 90 per cent. in the age group 61-71, but being much less in the other groups.

Thus, in the control cases the changes occur most frequently in *a. ciliares posteriores*, in the choroid, and the arterioles of the optic nerve. It is in these vessels, too, that among the cases examined the changes are clearest and greatest. In other regions, *i.e.*, in the retinal vessels and the corpus ciliare and in the *a. centr. retinae* the changes are slight. This relation between the intensity of the changes in the different areas is typical of these control cases, where there is no general sclerosis or renal lesion.

Also qualitatively the changes in the control series show special features. The changes mostly occur in the outermost parts of the vessels. In *a. ciliares posteriores* especially the muscularis and the adventitia thicken, but also the *elastica interna* may show some thickening though no delamination. The vascular

changes in the choroid are likewise unmistakable, but here also mainly in the outer parts. Fibrosis and homogenization occur to some extent in the smallest vessels. In *a. centr. retinae* one meets only very slight thickening of the muscles and of the adventitia, and in the small vessels of the optic nerve one may find some homogenization. The changes in the blood-vessels of the retina and the corpus ciliare are extremely slight.

In the material there were 25 cases of arteriosclerosis without hypertension in the 40-90 years age groups (Table 1). General arteriosclerosis occurred in 11 cases, in 19 cases the sclerosis was most advanced in the valves, vessels, and aorta of the heart. It should be noted that the material includes 9 cases with obvious sclerosis of the cerebral blood vessels. The sclerosis in the different organs varied from mild but clearly obvious to the most severe forms.

As regards the vascular changes in the eye, we note that their frequency, when compared with that of the former group, is slightly larger (Chart 2). Only in the highest age group, 81-90 years, do we here reach the 100 per cent. limit. This does not mean that patients of this age with arteriosclerosis always had changes in all the vascular regions of the eye, since the number of cases in this group is only 3, which is too small a number for conclusions. This is quite apparent from the following Chart (No. 3), showing a group of cases with

nephrosclerosis, where even in the highest age group there were some without any changes in the blood-vessels of the corpus ciliare and the a. centr. retinae.

In this chart as in the former, the curves divide into two groups. The curves representing the a. ciliares posteriores, the arterioles of the optic nerve and the choroid together rise high above the others, while the three other curves, forming a group of their own, are much lower. The interrelation between the frequency of changes in the different vascular areas within the group of arteriosclerotic cases is roughly the same as in the control material. The frequency of the changes in the cases with arteriosclerosis is slightly higher in the younger age-groups than in the control cases, but then the rise is less steep. Thus there is no great difference ascertainable in the frequency of the changes between these groups.

The difference in the quality of the changes, on the other hand, is remarkable. Besides the changes noted in the control cases, which were most marked in the outer-most parts of the vessels, intimal changes now become clearly discernible. All the changes are more pronounced and greater than in the preceding group. In the a. ciliares posteriores one can see relatively marked proliferation of the elastica and evident delamination. The changes are most intense in the arterioles of the optic nerve and the choroid, but there is not yet any delamination to speak of in the latter. In a. centr. retinae, in the retina and in the corpus ciliare the changes are still mostly rather small, but with a few exceptions, where rather severe sclerosis occurs.

Although general arteriosclerosis was the rule in the other blood-vessels of the organism in this group of cases, there were several in whom the changes differed neither in quality nor in quantity from those in the same age-groups of the control series.

In this group there were 9 cases of vascular sclerosis of the brain. The relation of this disease to retinal vascular sclerosis must be investigated on the basis of these cases, since in the following group with nephro-sclerosis there is the complication of another disease which may affect the retinal blood-vessels. 6 out of 9 cases in our series had vascular changes in the retina and 7 in the choroid. In two cases, of which one was as old as 72, both the retinal and choroidal vessels were normal.

The number of nephrosclerotic cases in the material is 77 (Table 1), and their age varies from 41 to 90 years. All these cases showed according to the case record a considerable rise in blood pressure, varying between 170 and 280 mm. Hg. In this group the frequency of the changes (Chart 3) was from the first greater in the retinal and choroidal vessels than in the earlier groups. In the other vascular regions, on the other hand, the frequency was approximately the same as in the earlier groups. In the higher age groups the frequency of changes in the choroidal and retinal vessels rose rapidly to 100 per cent. In the others the course of the curves was approximately the same as in the previous ones, and as far as the vessels of the corpus ciliare and the a. centr. retinae are concerned it was lower than for cases with arteriosclerosis.

The grouping of the curves has thus changed. The curves of choroidal and retinal vessels form a group in themselves, with the greatest frequency of changes. Since this fact may give a misleading picture, it is especially important to point out how variable in quantity the changes are. This group contains 4 cases in which the changes are no greater, in any part of the eye, than the changes in quality or quantity occurring in other cases of the same age group. There are, in addition, 3 cases in which the vascular changes in the retina may be placed in the same group as the arteriosclerotic cases of the same age.

Although there is wide divergence in the severity of the changes, they have on the whole increased considerably, especially in the retinal vessels. Pronounced changes are also observed in other vascular regions, but the difference compared with earlier age-groups is smaller in them than in the retina. In other regions,

too, the variations in the severity of the changes in the same vascular region are considerable. Both great changes and almost intact blood-vessels may be found everywhere.

The most important difference compared with earlier groups is the remarkable increase in the severity of the vascular changes in the choroid and in the retina while the increase is smaller in other vascular regions. Other authors, and quite recently Bergstrand, have pointed out that in these cases the changes in the choroidal vessels are more severe and occur earlier than vascular changes in the retina. This phenomenon was also obvious in the present material, but with exceptions to the rule in so far as there were certain cases of choroidal changes which fell far below those in the retina in intensity. Yet since there has been no series of excisions on the eyes for investigating this particular point, the apparent exceptions may be due to the fact that the intensity of the changes also varies at different points of the same vascular region.

In the vessels of the corpus ciliare and in the iris the changes are still usually slighter than in other parts of the eye, but this group contains cases where they are conspicuous. As regards the quality of the changes, it is the same as before in this group, but the various types of changes now appear more strongly and clearly. Usually all the layers of the vascular walls are involved in the process. Intimal proliferation, fatty changes, proliferation of the elastica and delamination, thickening of the muscularis and the adventitia are not very pronounced. We even find in the a. ciliaris posterior of a 49-year-old case the only instance of actual atheroma.

In the a. centr. retinae we find changes in all layers of the wall, but they are usually slight. Only rarely was the intima markedly thickened and the elastica delaminated. The arterioles of the optic nerve show relatively great intimal proliferation and one often meets hyalinization and even complete obstruction of the vessel. In the choroid all layers are affected by the process, and the present material contains cases where the elastica also is strongly delaminated, although this phenomenon is otherwise rarer in these vessels than elsewhere. The smallest vessels show advanced homogenization and hyalinization, and obliterated vessels are not uncommon. In the retinal vessels we find marked fatty changes and changes in the adventitia. There are other less obvious changes. The difference between these changes and those observed in earlier groups is so great that it is only in this group that one can speak of unmistakable changes. This does not rule out the existence of obvious changes earlier, but they are not common until we reach this group.

There were 26 nephritic cases (Table 1), and their ages varied from 18 to 80. This group is very heterogeneous and difficult to estimate. Indeed, the group contains cases whose ages vary greatly, cases without diagnosable sclerosis, and cases of severe general sclerosis. All these factors in themselves affect both the picture of the single cases and the frequency chart (Chart 4). The number of the cases is, however, so restricted that to separate the arteriosclerotic cases would mean breaking up the group entirely. Thus all the cases have been treated together, which fact should be kept in mind when estimating the general picture. From a critical point of view we may, however, point out that in this group the changes mostly occur in the vessels of the retina and the choroid and in the a. ciliares posteriores, and they are also frequent in the arterioles of the optic nerve. In this respect the curves have roughly the same course as in nephrosclerosis. However, the greatest frequency occurs in a younger age group than in nephrosclerosis.

The quality of the changes is much the same as earlier, but with this difference that now, besides the changes already mentioned, evident oedema is in some cases observed in the outermost parts of the vessels, which appears as a swelling of the wall, which stains imperfectly. This sign is clear even when no other actual changes are observable.

In the 41-50 years age-group we found retinal vascular changes in the control material as well as in the arteriosclerotic cases. Nephritic cases had changes in the earlier age group, both oedema and fatty changes of the intima. But my material is so small—there are only 4 in the 0-30 age group, and 6 in the 31-40 years group—that we cannot say conclusively that there may not have been changes earlier than in the 31-40 years age group. On the other hand, as even the control series is rather small with 16 in the group 0-30 years and 11 in the age group 31-40, we cannot consider that it sufficiently proves the absence of retinal changes in groups younger than 41-50 years, without actual sclerosis having been diagnosed elsewhere, and with no renal disease present. It therefore still remains open to question whether the changes were actually caused by nephritis. The oedema in the vascular wall may perhaps be considered as an actual nephritic change.

From the facts recorded above, the following points may be emphasised:—

The changes in the control material are slight, occurring mainly in the outermost parts of the blood vessels, and take the form of adventitial and medial thickening, slight fibrosis and sometimes homogenization, rarely slight thickening of the intima, and fatty change.

In connection with arteriosclerosis the changes are usually more obvious, though some cases do not differ from those in the control group. The real difference compared with the control material

is that in arteriosclerosis the changes generally occur in the whole wall and are obvious in the media and also in the intima. Not until arteriosclerosis develops do we find severe proliferation of the elastica, and delamination. Complete hyalinization and obstruction of the vessels occurs sometimes. Atheromatous foci occurred only in one case.

In the quality of the changes nephrosclerotic cases do not differ essentially from cases with arteriosclerosis, but changes are more easily discernible. Nephritic cases have, in addition to the changes mentioned above, oedema in the vascular wall.

The changes both in the control material and in other groups first involve the arterioles of the optic nerve and the a. ciliares posteriores, and afterwards the blood-vessels of the choroid. Changes are rarer in a. centr. retinae and in the retina, and are not demonstrable until severe arteriosclerosis develops. Both retinal and choroidal changes first occur posteriorly, but are occasionally found in the anterior regions of the retina and the choroid. Changes are less frequent in the vessels of the corpus ciliare and the iris than elsewhere in the vascular system of the eye. Thus, though the locality of the changes varies considerably and some vascular areas in the eye are obviously more prone to damage than others, we may say that changes can occur in all the blood-vessels of the eye.

The extent of the changes seems to depend upon where they occur. Generally they seem to be greatest where they appeared earliest, *e.g.*, in the a. ciliares posteriores, in the arterioles of the optic nerve and in the choroidal blood-vessels. The most conspicuous changes were found in the a. ciliares posteriores, which harboured the sole instance of atheroma. In the corpus ciliare and the iris the changes are usually slight.

In all parts of the eye the amount of change varies considerably. Blood-vessels close to each other may differ greatly, one being intact, the next severely damaged, although both belong to the same vascular region of the eye. Likewise the changes vary considerably between different vascular areas. On the other hand there is no marked disparity between the blood-vessels of the left and the right eye.

There is one exception to the rule that the greatest changes occur where they appear earliest, in the mild cases, namely, the changes in the blood-vessels of the retina. In the control cases and in mild cases of arteriosclerosis the retinal changes follow the rule mentioned above, but in more severe sclerosis, nephrosclerosis, and in nephritic cases the changes in the retina are noticeably greater than those elsewhere.

This change in interrelation is especially obvious when the state of the retinal blood-vessels is compared with that of the vessels in the choroid in different groups. In the control cases and in mild sclerosis we find changes in the choroidal blood-vessels without there being anything pathological in the blood-vessels of the retina. Changes in the retinal vessels are always less than those

FIG. 1.

Thickening of the wall of an arteriole of the optic nerve.

FIG. 2.

Thickening of the wall of a retinal vessel.

in the choroid. On the other hand, in more severe cases of sclerosis, nephrosclerosis and nephritis, the vascular changes in the retina may equal those in the choroid.

FIG. 3.

Thickening of the wall of a small retinal vessel.

FIG. 4

Atheroma in the wall of an arteria ciliaris posterioris.

FIG. 5.
Fibrosis of a vessel of the choroid.

FIG. 6.
Obstruction of a vessel of the choroid.

FIG. 7.

Fibrosis and hyalinisation of the vessels of the ciliary body.

FIG. 8.

Hyalinization of the vessels of the iris.

Concerning the frequency of the occurrence of the changes, we notice that in the present material they begin to appear after the age of 30, and the incidence then increases evenly. In the group of normal changes and in cases with arteriosclerosis the curves (Charts 1 and 2) divide into two fairly distinct groups, of which the curves of the a. ciliares posteriores, the arterioles of the optic nerve and the curves of the choroid form the upper group, while the frequency curves showing vascular changes in the a. centralis retinae, the retina and the corpus ciliare run in a separate group lower down.

When we come to the groups of nephrosclerotic cases and those with nephritis, we have a different grouping of the curves. (Charts 3 and 4). It is the retinal changes that now show the greatest frequency and the corresponding curve has the highest peak. In the a. centralis retinae and in the blood-vessels of the corpus ciliare the frequency of changes remains relatively low in all groups. A renal lesion does not seem to have any appreciable effect on these vessels. As to diabetes, which is known to cause changes in the pigment epithelium of the iris (*Deutschman, Kamochi*), the present material does not warrant any conclusions, for it contains very few cases of diabetes.

From a comparison between the results derived from the present material and those recorded in the literature we would make the following points. In contrast with Rintelen we find frequent and great changes in the a. ciliares posteriores. Nor can we agree with his theory that changes are rare and usually small in the region of the corpus ciliare. My material seems to support the view of many other authors, *e.g.*, Gasteiger, Mylius and Rones, that considerable changes are found here.

My series also supports the findings of Koyanagi, Friedenwald and Bergstrand that severe sclerosis occurs in choroidal blood-vessels. The material contains some severe cases of nephrosclerosis in which the vascular changes in the choroid, though pronounced, are yet slighter than those noted in the retina. We also note, as did Rintelen, Bergstrand and others, that sclerosis of the retinal vessels may extend as far as the ora serrata, though Mylius had earlier declared that sclerosis is limited to the posterior retina.

The oedema in the vascular wall, found in cases with nephritis, supports Wager's statement that it is possible to differentiate between the retinopathy of glomerular nephritis and that of essential hypertension. On the other hand we find that even arteriosclerotic changes are relatively frequent in the blood-vessels of the nephritic group.

My material also supports Volhard's statement that the retina reflects the condition of the kidneys. Advanced changes in the retinal blood-vessels imply the existence of similar changes in those of the kidney, but healthy vessels in the retina are not proof against disease in the renal blood-vessels. Raehelmann's theory that the blood-vessels of the retina reflect the condition of the cerebral blood-vessels has earlier been disproved, and is further contradicted by the present material.

Summary

The material consisted of 408 eyes taken from 204 corpses. It was divided into four parts: the control series, including those cases in which no clinical signs of sclerosis had been recorded, cases with arteriosclerosis, those with nephrosclerosis, and nephritic cases.

The changes noted were always comparatively slight in the a. centralis retinae. In the arterioles of the optic nerve, on the other hand, we found extensive changes, and these blood-vessels were often obstructed. The changes were likewise considerable in the a. ciliares posteriores, wherein atheroma and frequent obstruction occurred. The third region where the changes were often extensive was the choroid. The vascular changes in the retina were as a rule slight in the control material and in cases with arteriosclerosis, while in the nephrosclerotic cases and sometimes in nephritic cases they were more pronounced. Vascular changes occurred even in the anterior parts of the retina. The changes were usually slight in the blood-vessels of the corpus ciliare and the iris.

The changes were of the type usually occurring in sclerosis, with the exception of the oedema in the vascular wall which was noted in nephritic cases.

Among the control cases and those with arteriosclerosis, the frequency of the changes was greatest in the arterioles of the optic nerve, in the a. ciliares posteriores and in the blood-vessels of the choroid. In cases with nephrosclerosis and nephritis the greatest frequency occurred in choroidal and retinal blood-vessels. In the control material the frequency of the changes did not exceed the 90 per cent. limit even in the oldest age-groups.

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