An investigation into the structural changes in the arteries in General Paralysis of the Insane.

This investigation carried out in the laboratory of the Scottish Asylums has occupied me for the past seven months. My object was to inquire if any structural changes existed in the general arterial system, or in cases of paralysis of the insane, excluding the arteriolic and capillary changes in the central cortex.

Although from lack of material it was impossible to examine in each case all the main arteries or their branches in the non-nervous organs, the investigation over the whole series of cases includes most of the important vessels or their branches in the non-nervous organs. By such a study I hope to arrive at some conclusion with regard to the pathogenesis of General Paralysis. If structural changes in the arteries do generally occur, it would go far to prove that underlying General Paralysis there is a toxic condition in the blood—an auto-intoxication.
Methods employed:

1. The first set of cases were in Bichromate Solution. The hardened tissues were cut in destrie, stained by Shibli's Haemotoxylin + Eosine + mounted in Benzole Balsam.

2. The second set of cases were Formalin-hardened tissues. The method employed at first was to oxidize the sections in water in which about 20 drops of a 1/49o solution of Pot. Permananate, then placed the sections were stained in Haemotoxylin (1/2%), fixed in 17% Alum sulphate, decrummy in 1-50o acid spirit, washed in water, 

3. For the detection of fatty changes, etc., the method was used.
4. Other methods employed forever to be unsatisfactory, e.g. methyl violet; Nigrosin carmine with a light green counterstain.

Literature on the Subject:

The systematic investigation of the arterial changes in General Paralysis has been carried out so far as I can judge from the literature on the subject. Häckle has studied the macroscopic changes in 100 cases of General Paralysis noting among other tissues, the condition of the arteries. His conclusion is that atheroma of the cerebral vessels, coronary and temporal arteries is so inconstant in General Paralysis that no direct connexion between the two can be assumed. But I find that in many cases of General Paralysis the arteries, which to the naked eye appear quite normal, show distinct intimal and proliferative changes on microscopic examination.

Möllt (in Archives Neurology) has noticed that atheroma of the aorta
and endarteritis cerebri are specially frequently met with in general Paralysis. Indeed, in no other form of insanity, if we except syphilitic insanity, is this vascular lesion so common and so pronounced. In juvenile general Paralysis, on the other hand, he has never found endarteritis cerebri, although in most cases there was more or less evidence of a fatty, atheromatous change in the subendocardial tissues of the aorta. He has found that more or less atrophy of the central arteries of the nodular circumventrical form very frequently occurs in general paralytics who die after 45 and "if many of the arteries of the brain are so affected the mechanism of the circulation is interfered with." He attributes this early occurrence of degenerative changes in the vessel to the action of the syphilitic virus. As a result of this syphilitic nodular endarteritis this way, in some cases, he found paralyses preceding the onset of the symptoms of general Paralysis, while in
other cases the nodular encephalitis may not have advanced to such an extent as to lead to such paralyses. In his classification of the lesions in brain syphilis, he includes cases of General Paralysis where the characteristic primary decay of neurons depends on a specific encephalitis.

In his book on General Paralysis and in the article in Brain, he records the observations of others on the vessel changes of in General Paralysis, but most of these observations are on the changes in the cortical vessels. Raymond observed that in syphilitic cases, the syphilitic sheath of the capillaries of the cortex show an acute inflammatory proliferation of cells and in the large basal vessels there may be a nodular or diffuse periarteritis or an obliteratoris endarteritis.

Collelba concludes that in syphilitic cases the primary change is in the blood vessels of the brain whilst in cases apart from syphilis the blood vessels are healthy. Binswanger, too, discusses the vessel changes
in the cortex without any reference to the larger vessels inside or outside the cranium. The changes, however, in the cerebral vessels are of the nature of hyaline fibroid degeneration with proliferative thickening of the intima and consequent narrowing of the lumen. This thickened intima may later on show degenerative changes.

Strasburg considers that the lesion in the cerebral vessels is of the nature not of an atheroma proper but of an endarteritis syphilitica. He says, on the other hand, that it has been found that the aorta is very frequently the seat of atheromatous change. Whether these special changes in the blood vessels occur in all cases of general Paralysis is not yet proved. At any rate it but proves that the paralytic process is intimately connected with the vessel changes.

Dr. Robertson has found atheroma of the large cerebral arteries in only 3 out of 100 cases of General Paralysis. But he has noticed that, in the majority of general paralytics, the intima of the large cerebral arteries
shows some fibro-cellular thickening. He is doubtful if such a change is similar to endarteritis deformans. In this latter point he concurs with Strand's opinion. Bevan Lewis lays special stress on the vessel changes in the pia and brain, but leaves out of account the general arterial change.
Description of the structural changes:

I have examined altogether 24 cases of General paralysis.

The arteries examined were the following:

1. Middle Cerebral or branches: 14 cases
2. Basilar or branches: 12 cases
3. Vessels of the Pia-arachnoid: 5 cases
4. Aorta: 2 cases
5. Coronary or the branches of heart: 7 cases
6. Ulnar or radial: 6 "
7. Posterior Tibial: 2 "
8. Common Iliac: 1 "
9. Iliac arterial Artery: 1 "
10. Branches of hepatic artery: Liver: 4 "
11. Branch of artery or branches: Kidney: 4
12. Adrenal gland: 1 case
13. Arteries to Stomach wall: 1 case
14. Splenic Artery or branches: 3 cases
15. Pancreatic vessels: 2 cases

For detailed description, see along with microscopic sections.
lesion in these cases cannot be distinguished from atheroma, for in the deeper part of the thickening degenerative changes are usually pronounced as revealed by the marchi method.

In the cases where the lumen is unaltered in size, there is frequently a swelling or hypertrophy of internal elastic lamina. This swelling of the elastic membrane is also present in most of the cases which at the same time showed the fibrocellular overgrowth. In these latter cases the elastic lamina is often seen to split into secondary bundles with the cellular fibrous elements of the thickest intima between them. These secondary bundles may further on the circumference of the section meet and fuse the original lamina.

Fusilay in his research into the pathology of the choroid plexus discusses this point. This formation of secondary laminae is not altogether due to the mechanical separation of new formed tissue of the bundles of the original lamina, for in some cases the
Endothelium takes on the function of forming new elastic fibres just as it formed the base to grow the embryos over the muscular layer. But in the cases where there is no proliferation of endothelial cells or subendothelial connective tissue, the hypertrophy of the laminae may, according to Findlay, be due to "some inherent vitality in the elastic lamina itself."

Again associated with the thickened elastic laminae, the subendothelial connective tissue, in cases where there is no proliferation, appears to be swollen and hyaline-looking. Probably, this is one of the earliest phenomena of irritation, viz., hyaline swelling of the subendothelial layer and later on this hyaline tissue may become invaded by cells and be converted into fibrous tissue and so leads to narrowing of the lumen. Later on afterwards changes may occur in the newly formed tissue in the parts furthest distant from the endothelium.

The vessels which shows the changes most markedly were the middle cerebral
the Basilar arteries, the Coronary artery and the Aorta.

In the 2 cases where the aorta was examined, both showed distinct 
oroma

In the first case (\textsuperscript{12}) there was also cellular infiltration in lines parallel with the fibers. The patient in this case was 24 years of age.

In the other case, which was 48 years of age, a similar change was found.

Out of the 4 coronary arteries examined, 3 revealed the atheromatous change.

One of them was in an adolescent male (20\textsuperscript{th}).

The second was in a female of 40 years (14\textsuperscript{th}).

The third was in a male of 65 years (21\textsuperscript{st}).

Out of the 11 middle cerebral arteries examined 11 revealed atheroma by Marchisio's solution. Their ages were respectively:

(male), 35 (female), 47 (male), 65 (male).

Out of the 12 Basilar arteries, 6 revealed atheroma. Their ages were respectively:

41 (male), 51 (female), 40 (male), 47 (male), 35 (female), 65 (male).

Changes in the Muscular Coat: This coat
frequently shows changes of a degenerative or atrophic character. In other cases, the coat appears normal or even hypertrophied. This apparent hypertrophy of the media seems to me to disprove Thomas's theory with regard to atheroma of the intima viz., that it is compensatory to weakness or atrophy of the muscular wall. In the elastic muscular coat of the aorta, the presence of lines of cells between the fibres is characteristic. It is associated with atheroma. The atrophic change in media is usually best seen over the site of greatest thickening of the intima.

Adventitial Changes: The adventitia is usually normal in appearance but in some cases there is a periatheritis or at least a cellular increase among the fibres. The myelitic fibroid change may be seen among the smaller arteries of the pia arachnoid.

Of the organs examined, the liver revealed a characteristic increase of nuclei around the veins and ducts of the portal spaces.
From the changes just observed in the blood vessels, I cannot but believe that the true interpretation lies in the action of toxins—a general auto-intoxication of the system which induces a involutional & degenerative process in the intima.

The doctrine of auto-intoxication is claiming the attention of neurologists & they see in it much to explain the pathogenesis of the insanities. Indeed, from the studies in bacteriology & pathologic chemistry, disease processes as a rule are found to have their origin in the presence of toxic products in the blood. The alimentary tract is a frequent seat of the production of toxins, and it cannot be doubted that the auto-intoxication from that source plays a part in the production of insanity.

At present there are two hypotheses with regard to the pathogenesis of General Paralysis which go far to explain the
pathological appearances in general paralysis

Inoltre Theory (see Archives of Neurology & Lobotomy Lecture on Degeneration of the Nervous System) is that there is a loss of specific vital energy in the neurons due primarily to the effect of the epidemic process and as a result of our sociological conditions, these neurons permanently degenerate and thus throw into the systemic the products of neuron degeneration (e.g. choline) which act locally and generally leading to a secondary auto-intoxication. As a result of this secondary auto-intoxication, the vessel walls become irritated and so thrombotic changes are brought about. He says "In general paralysis ... there is a primary decay of the nerve cell - a degenerative process which starts in the highest-developed structures. This premature decay is progressive and cumulative, it causes phenomena of irritation manifestly by mental and physical symptoms, such as motor irritation with rise of blood pressure, cerebral anaemia, venous stasis, local
and general auto-intoxication respectively of the products of degeneration and imperfect metabolism. A vicious circle is established which continually is enlarging" (see Archives, p. 42).

Augerella claims that there is a primary auto-intoxication of the system which produces changes in the blood vessels especially the arterioles and capillaries of the cortex. These changes is manner a death sentence results necessarily to this change. The toxic substances in the blood may be either products of syphilitic infection or other infection or else they are produced in the body as a result of the influence of debilitating general poisons. He also says that there may be a direct effect on the nerves by the toxins. The toxic condition of the blood is manifested by the following pathological change in the vessels:

1. Peri-endoarteritis syphilitic origin
2. Peri-endoarteritis of alcoholic
of other origin.

3. Adenitis general hepatitis. arteries constantly show an inflammatory infiltration with cells. For Robertson considers the capillary change of center of primary importance just as it is a seminal insanity. He has seen the central vessels turn or less altered in their whole course. But he does not consider the change of the nature of an asthma. From my observations asthma is an extremely common occurrence.

The proliferative lesion in the intima of vessels tampered supports a close connexion between the vascular from syphilis insanity general paralysis. As General Paralysis usually follows 5 to 15 years after infection of syphilis, it is likely that the alterations in the organism, whether they be of the nature of gross change or of alteration in the individual community, lead to a premonitory auto-infection.
The occurrence of an early atrophy in general paralysis is not against the probable possibility of a syphilitic infection, for caseous change occurs in uninfected syphilis.

Inolt reverts to the irritative change in the intima in syphilitic endarteritis and in criticising Neubner's contention that endarteritis syphilitica never causes, he cites the atrophic change, which he has found in adolescents with focal paralysis syphilitica origin. But this atrophic change, he says, is due to a substantia of the arterial arteriosclerosis constituting an irritative lesion. It is the arteriosclerosis is necessary to the substantia of the arterial arteriosclerosis.

He, then, brings atrophy of the artery companion carotid vessel into the whole primary degeneration of the nerve cells. Both 20 days are due to the deratization influence syphilitic. This, he says, is rather an argument in favour of the antitubercular theory. For if atresia primary is due to
an invincible lesion in the anterior horn neurons, then why not may we not say that degeneration of neurons may be the brought about by capillary artery change in the cortex.
(See Trotto Archeis p. 143).

This research was carried out in the laboratorv of Scottish Asylums. It was by the kind permission of the Executive Committee that I was able to carry it out.

To

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Description of microscopical sections.

Case 1. Male 43 yr.

1st mid. central or branches: Fibro-cellular thickening of the intima; specially marked round one half the circumference of vessel; this is irregular thickening or hypertrophy of internal elastic lamina. Also slight cellular increase in adventitia.

1st stain: Masson's solution: no evidence of fatty change.


2nd mid. central artery: Shows thickening of intima more uniform and no nodules as last case. Slight periarteritis.

2nd oblique section, stained by Marchi shows arteriosus change.

Case 3. Male 50.

3rd mid. cerebral: Not much change except that internal elastic lamina appears more thickened than in a normal artery; at parts this is a very slight fibro-cellular increase in the subendothelial layer. The subendothelial connective tissue appears swollen.

3rd Heart muscle: Branches of coronary show slight proliferation of endothelium and thickening

...
internal elastic lamina. Light perivascular?

In the case liis pheres cellular increase around vessels & portal tracts.
also, per-arterioid had fibroid change & adventitia & increase of intima.
Ulnar artery pheres thickening.

Case 4. I Male 46.
4. Ulnar artery. fibrocellular thickening
intima  with thickening internal elastic lamina

46. Recent. Coronary branches 6 muscle
stria swelling internal elastic lamina
+ of subendothelial layer. Small cell
infiltration around vessels beneath the fibres.

5 a & 5 B = Ulnar 7 partner Thorial arteries
phere thickened intima & well bordered
muscular coat. No fatty change of branch.

Case 6. Female 40.
6 Low. thin int. thickening of small
hepatic branches. In one section examined
one of branches appears obliterated. Cellular
proliferation portal spaces.

Case 7. I Male 27.
4 A mid. Cerebral slight thickening of intima.

Aorta: atherosclerosis. Cellular infiltration in layers parallel with the fibers of elastic muscular coat. Fatty change also present in this coat.

Case 9. Female 52.

Posterior artery: uniform thickening of intima with diminution of lumen; splitting of elastic lamina; well developed media.

In the case of ulcer there was same change.

Case 10. Male 41

Basilar: moderate atherosclerosis.

Case 11. Female 51

Basilar: general thickening intima.
Case 12. Male 40.
Basilar: pronounced uniform thickening of intima with atrophy of media. Fatty change of media. Slight pericarditis.

Case 13. Female 30.

Case 14. Female 40.
Several arteries examined in this case and all showed more or less change.
14. Basilar: diaphragm thickening of intima; no fatty change.
14. Coronary: pronounced thickening of intima in all vessels with atherosclerotic change in atrophy of media.
Middle cerebral, renal, iliac, and mesenteric all examined revealed same proliferative change.

Case 15. Female 35.
16a middle cerebral 46a basilar plus
nodular thickening of a cellular character
Periarteritis. No fatty change

Case 17. Male 38.
Thick uniform thickening in middle
cerebral & basilar arteries.

Case 18. Male 35 years.
18a middle cerebral: localized thickening.
18b Frontal vessels: thickening
Atypical vessel revealed hemorrhages.
Vessels papilled, thickened pancreas thinned
revels old fat change.

Case 19. Male 47.
19a Basilar: pronounced diminution
of human vessel from fibrocellular
overgrowth of intima. Int. elastic tissue
is present at parts. There is presence of
new elastic fibers, new endothelium.
Atheroma present. Periarteritis
atrophi apiic separation of media.

19b Splanic arteries: thickening 2 intima
(autoptic opales).
19c Coronary: thickening present.
Livers were shown thickening present in the vessels & abundance of cells in portal spaces.

Case 20. Male adolescent.

20A Coronal: otherwise thin skin.

20B: thickening of adventitia & smaller blood vessels.

These are sufficient to show the nature of the change. The other 4 cases reveals much the same change.

A: represents ordinary senile atrophy

B: represents syphilitic endarteritis obliterans.