PATHOLOGICAL REPORT ON A CASE OF DERMATITIS VESICULO-BULLOSA ET GANGRÆNOSA MUTILANS MANUUM (DUHRING), WITH A CONSIDERATION OF THE RELATIONS OF VASCULAR AND NERVOUS CHANGES TO SPONTANEOUS GANGRENE AND RAYNAUD'S DISEASE.[1]

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Plates IV and V.

This case was reported clinically by Dr. L. A. Duhring[2] in 1892 under the title of a "Case of Dermatitis Vesiculosa Neurotraumatica of Forearm." Dr. Duhring thought that the case was obscure and difficult to classify, and notwithstanding the presence of hysteria he believed that the symptoms could possibly be explained by regarding the process as a traumatic ascending multiple neuritis, although he was guarded in expressing this view.

A later clinical history was published by Dr. Sinkler[3] in 1897, in which much of the earlier history given by Dr. Duhring is included. A brief abstract of Dr. Sinkler's paper is as follows:

The woman, A. A., was 35 years of age in 1897. For years she had had many symptoms of general nervous disorder which included frequent and protracted attacks of gagging and vomiting, palpitation of the heart, crying spells and globus hystericus. In Sept., 1890, she was burnt with a flat-iron on the flexor surface of the left forearm just above the wrist, the area being about the size of a silver dollar. The burn was superficial but did not heal readily or completely, and from some unknown cause began to break out anew. Within a month of the acci-

[1] Read before the Section on Neurology and Medical Jurisprudence of the American Medical Association, June 5, 1900.

[2] *International Medical Magazine*, 1892, i, p. 140.

[3] *Journal of Nervous and Mental Disease*, 1897, xxiv, p. 687.

dent it began to show a superficial gangrenous patch which remained about six weeks. The whole forearm became reddened and the seat of throbbing and darting pain. About six weeks after the accident the burn seemed to be nearly healed, and then a single pimple, a papulo-vesicle, formed on the extensor surface of the forearm near the burn. In a week or two this lesion ulcerated and crusted, and then other similar pimples formed near the original one; some of them vesicles and some blebs, covering by degrees the greater portion of the wrist. The morbid process continued on the left wrist and upper part of the hand for three years, migrating from place to place and breaking out anew as soon as any point became healed. By the early part of 1894 the left arm was entirely healed.

Just at the time of the healing of the left arm a papulo-vesicle similar to those which had invaded the *left* arm appeared at the end of the *right* index finger. This followed the same course of breaking out into an ulcer and then healing; new papulo-vesicles formed on this finger and then attacked the adjoining fingers. The affection subsequently spread to the dorsal and palmar surfaces of the hand and finally implicated all of the fingers. At times gangrenous patches appeared on the fingers, followed by sloughing and more or less loss of tissue. In this way the fingers and thumb were lost. The patient suffered from pain in the right hand. Objective sensation was unimpaired. The sloughing began with discoloration of the skin and the skin rapidly became black and dry and the slough was thrown off leaving a granulating surface. The urine was free from sugar.

Dr. Sinkler concluded after a careful study of the case that the disease was a trophoneurosis dependent upon an hysterical diathesis.

I made a brief examination of the patient in June, 1899, and observed certain symptoms that caused me to believe that the woman had Graves' disease. I made no notes of her condition, knowing that the case had been studied clinically by Dr. Duhring and Dr. Sinkler. Dr. Sinkler later informed me that the patient had marked evidences of Graves' disease; at least she had distinct exophthalmos and rapid heart's action without much, if any, thyroid enlargement.

In June, 1899, the right hand was amputated by Dr. W. J. Taylor just above the wrist and was given to me for examination (see Plate IV, Fig. 1). The part had become useless and pus had formed in the stump of the fingers. Dr. Sinkler tells me that the patient had

been for years an opium eater. After the amputation she did very well and was improving steadily when one day she received a large quantity of opium pills from some friends. She probably took several of these, as in the evening after the visit of her friends she vomited and was found in a condition of stupor. The next morning she had a convulsion. The urine was examined but no evidence of nephritis was obtained. The convulsions became more frequent, the stupor continued, and she died on the third or fourth day after taking the opium.

Previous to her death Dr. Duhring[4] published another clinical report of this patient and a beautiful colored drawing of the right hand.

Dr. C. W. Burr made the necropsy and kindly placed at my disposal the brain, cord and some of the peripheral nerves.

Dr. Joseph Walsh made a bacteriological examination of the amputated hand. Important results were not expected from this examination as the parts were exposed to various kinds of infection. His report is: "Aërobic and anaërobic cultures were made from suppurative foci on the fingers and hands and from non-suppurative portions. The results were positive and pure cultures of staphylococci were obtained, the great majority being white staphylococci. Inoculation into guinea-pigs of pus from the suppurating foci and of the pure cultures in agar produced no effect."

The microscopical examination of the tissue was made by me.

Right upper extremity: Ulnar nerve and artery.—The ulnar artery taken from the amputated limb is much thickened, both in the media and intima, especially in the latter. The lumen at one part is almost entirely filled by an organized thrombus (see Plate IV, Fig. 2). An elastic membrane is seen along one side of this thrombus. This thrombus is separated from the intima by a clear space throughout most of its extent.

The nerve fibres of the ulnar nerve in the same section in which the thrombosed ulnar artery is found, appear to be normal by ammonia carmine and the Weigert hæmatoxylin stains. The ulnar artery towards its peripheral terminations is still much thickened, and yet the nerve fibres of the accompanying nerve are normal by ammonia carmine or

[4] *International Atlas of Rare Skin Diseases*, xiv, March 22, 1899.

Weigert's hæmatoxylin stain, or at most are very slightly altered. A section of the ulnar nerve taken from the amputated limb and stained by Marchi's method shows only a moderate amount of black masses within the nerve fibres, and it is questionable whether the nerve could be regarded as degenerated from the evidence furnished by this method.

Nerve fibres from the right hand—I cannot say which nerve—taken just above the finger and stained in the fresh state by osmic acid and teased appear to be normal. The same is true of nerve fibres taken from the lower third of the right forearm.

Median nerve.—A piece of the median nerve, taken about 8 cm. above its termination in the stump, shows some proliferation of the endoneurium with possibly an atrophy of some of the nerve fibres. The extreme end of the branch to the middle finger is considerably degenerated and the endoneurium is much proliferated. Many nerve fibres have disappeared and the small accompanying arteries are much thickened. The extreme end of the branch to the index finger shows some degeneration of the nerve bundles. The extreme end of the branch to the thumb shows distinct degeneration of nerve fibres and proliferation of the endoneurium, but many nerve fibres are still present.

A section from the median nerve of the amputated hand and forearm stained by the Marchi method shows degeneration in some of the nerve fibres, but the degeneration is not excessive and is not so great as that seen in the left brachial plexus. Masses stained black by the osmic acid are seen in many of the fibres.

Radial nerve.—The radial nerve from the amputated part, taken 6 cm. above the styloid process of the radius, shows distinct diminution in the number of nerve fibres and overgrowth of the endoneurium (see Plate V, Fig. 3), but the degeneration is slight in comparison with that of the distal portion of the branch to the thumb. With the Marchi stain the degeneration 6 cm. above the styloid process is considerable. At the distal portion of the branch of the radial nerve to the thumb (Plate V, Fig. 4) the alteration of the nerve fibres is greater than in any other nerve. The fibres here have mostly disappeared and the connective tissue is greatly proliferated.

A branch of the radial artery taken just above the thumb and 4 cm. below the styloid process of the radius may be regarded as normal, although the radial artery examined 8 cm. above the styloid process shows distinct, but not excessive overgrowth of the intima, this being considerably less than that seen in the ulnar artery.

Right brachial plexus.—The brachial artery and the nerve fibres ap-

pear to be normal by Weigert's hæmatoxylin stain and the ammonia carmine, and the degeneration is unimportant by the Marchi method.

A vein taken from the back of the right hand shows some proliferation of the intima.

Left upper limb.—A small portion of the radial nerve and a portion of the brachial plexus were the only tissues of this extremity placed at my disposal for study.

The left radial nerve at a point unknown to me shows as distinct a diminution of nerve fibres and proliferation of the endoneurium as does the right radial 6 cm. above the styloid process.

The intima of the left brachial artery is slightly thickened. The nerve bundles of the plexus by the ammonia carmine stain are normal and yet the Marchi method shows a very intense degeneration of the myeline, which must have been recent—a greater degeneration indeed than is seen in any other nerve except perhaps the right radial. In the left brachial plexus in certain nerve bundles are a few areas in which no nerve fibres exist and only loose fibrous connective tissue is found. These areas are sharply defined from the surrounding nerve fibres of the bundle. In one bundle two such areas are seen. It is impossible to say whether these are imperfections in the original development of the tissue or the result of degeneration of nerve fibres.

Muscle.—The first interosseous muscle of the right hand is not much altered. The muscular fibres are nearly normal in size. The larger intramuscular nerve bundles are wonderfully well preserved, although the smaller bundles show some proliferation of the endoneurium. The intima and media of some of the small vessels within this muscle are thickened.

The skin from the back of the hand just above the fingers has lost the epidermis and the papillæ of the cutis vera are flattened.

Spinal cord.—Sections were taken for microscopical study from the lower cervical and upper thoracic regions and were found to be normal. Nissl's method could not be employed as the spinal cord had been put in Müller's fluid. Some of the motor cells of the anterior horns are vacuolated, but the cells have normal processes and do not appear to be atrophied. Cells found in the area corresponding to Clarke's columns are not atrophied, and so far as can be determined by the carmine stain they are normal. The nuclei in some are eccentric.

The medulla oblongata is normal. The brain by macroscopical examination is normal.

The lesions in this case in brief are as follows: The central nervous system is normal. The nerves in the distal portion of the right hand near the metacarpo-phalangeal articulations are much altered, especially the radial; the ulnar less distinctly so. The right median nerve is slightly altered at about 8 cm. above its terminal portion in the stump of the hand, and the right radial 6 cm. above the styloid process is somewhat degenerated. The nerves could not be studied at higher levels, as the tissue necessary for this was not in my possession. The right brachial plexus is normal. The ulnar nerve is normal except in its most distal portion where the alteration is slight.

The arteries of the right upper limb are diseased in some parts. The ulnar artery near the wrist shows the greatest amount of thickening of the intima and at one portion an organized thrombus is found. The right radial artery shows some proliferation of the intima.

The brachial plexus of the left side gives evidence by Marchi's method of intense recent degeneration, but this is not seen by the ammonia carmine stain. The intima of the left brachial artery is slightly thickened. The left radial nerve is not entirely normal.

It does not seem probable that the vascular changes alone could have produced the peculiar trophic lesions of the right upper limb. Even the organized thrombus of the right ulnar artery had not caused degeneration of the accompanying nerve, and the changes in the right radial artery were not very important. The slight alteration of the ulnar nerve in its most distal portion was probably the result—as was the alteration in the other nerves of the hand—of spontaneous amputation and gangrene, and not of thrombosis of the ulnar artery. The veins had not escaped. The nerves of the right upper limb were seriously diseased only at their terminations near the gangrenous area, except perhaps the radial which was diseased at least 6 cm. above the styloid process of the radius. It is questionable whether so extensive lesions can be explained by so slight degeneration of nerves.

Where peripheral gangrene occurs and the vessels and nerves of the gangrenous limb are found diseased several questions are at once suggested:

1. Was the gangrene caused by the endarteritis obliterans?

2. Was the gangrene caused by the degenerative changes in the nerves?

3. Was the degeneration of nerves and vessels the result of the gangrene?

4. Were the nerve lesions the result of vascular disease?

5. Was the degeneration of the vessels produced by the changes in the nerves?

These questions can be best answered by a study of the cases reported in literature, and they will be considered seriatim.

Raynaud[5] began one of his papers on symmetrical gangrene with a quotation from a work of Victor François written in 1832: "Everything concerning spontaneous gangrene is in a state of distressing uncertainty." These words are not quite so true as they were at the time they were first written, but much of this "distressing uncertainty" still remains. Cases of gangrene in which the cause cannot be determined are still reported as shown by an interesting paper by McFarland.[6]

1. *Can gangrene be caused by endarteritis obliterans?*

Many cases have been reported in which obliterating endarteritis was believed to be the cause of gangrene. The description of the "gangræna ex endarteriitide hyperplastica" as given by Billroth represents the disease as beginning with prodromal symptoms lasting many years, viz., disturbance of circulation, cyanosis of the limbs, a sensation of cold and weight, paræsthesia, and inability to stand long or walk far. The gangrene is produced by a slight cause and is usually moist.

Von Winiwarter[7] concluded from his examination of several cases of so-called primary, spontaneous gangrene that the underlying cause is an endarteritis terminating in complete closure of the affected vessels. Zoege von Manteuffel[8] finds that this form of endarteritis is the result of successive deposition and subsequent organization of layers of thrombi,

[5] "On Local Asphyxia and Symmetrical Gangrene of the Extremities," by Maurice Raynaud. Translated by Thomas Barlow. London, 1888. The New Sydenham Society, vol. cxxi.

[6] *Transactions of the College of Physicians of Philadelphia*, 1898, 3. s., xx, p. 160.

[7] *Arch. f. klin. Chirurg.*, 1878, xxiii.

[8] *Deutsche Zeitschr. f. Chir.*, 1898, xlvii, p. 461.

so that finally the lumen of the vessel becomes filled with vascularized connective tissue, and Hoegerstedt and Nemser[9] believe that in general thrombosis participates in a similar way in the production of obliterative endarteritis. Haga[10] in his interesting paper on spontaneous gangrene describes and pictures obliterative endarteritis, which he believes to be of syphilitic origin, as a cause of this disease. The association of gangrene with the group of symptoms called "intermittent claudication," studied by Charcot, Goldflam, Erb, and others, and shown to be dependent on arterial disease, is well recognized. It is not to be doubted, therefore, that gangrene may be caused by endarteritis obliterans, nor is it difficult to understand why this should be so.

Arterial thrombosis, with or without pre-existing arterial disease, is a demonstrated cause of senile gangrene, and may be the cause of the gangrene occurring occasionally as a complication or sequel of infectious diseases, particularly in influenza, typhoid and typhus fevers.[11]

2. *Can gangrene be caused by degenerative changes in nerves when the blood vessels are healthy?*

The idea that gangrene may be due to diseases of the nervous system alone without any vascular disease is not new. Raynaud[12] refers to the thesis by Zambaco[13] in which this view was expressed. The paper of Pitres and Vaillard[14] is often quoted in support of the possibility of gangrene resulting from degeneration of nerves. These writers reported two cases in which symmetrical gangrene of the feet occurred, and the arteries and veins were normal. The nerves of the lower limbs were much diseased below the knees, but not above. Those of the upper limbs were normal. Dehio[15] in criticising this paper states that the writers have not proven that gangrene may result from neuritis without vascular disease. Dehio, I think, is quite right in this criticism. The case does seem to show that endarteritis may be absent in gangrene, but the finding of nerve lesions and gangrene in the same limb does not prove that the latter is the result of the former. Both conditions may

[9] *Ztschr. f. klin. Med.*, 1896, xxxi, p. 130.

[10] Virchow's *Archiv*, 1898, clii, p. 26. Since the completion of this article C. Sternberg's paper (*Virchow's Archiv*, 1900, clxi, p. 199) has appeared with a full consideration of the relation of obliterating endarteritis to spontaneous gangrene.

[11] See Welch, Article "Thrombosis and Embolism" in Allbutt's System of Medicine, vol. vi, p. 178. London and New York, 1899.

[12] Loc. cit.

[13] Paris, 1857.

[14] *Arch. de phys. norm. et path.*, 1885, 3. s., v, p. 106.

[15] *Deutsche Zeitschr. f. Nervenheilk.*, 1893–4, iv, p. 1.

result from a common cause, or the gangrene may produce the degeneration of the nerves, as will be mentioned presently. In the report of a necropsy in a case of symmetrical gangrene Raynaud[16] says that the results obtained by himself were absolutely nil in so far as the circulatory system was concerned, so that without Pitres and Vaillard's case we have known for many years that gangrene may occur when the vessels are normal.

Dejerine and Leloir[17] in reporting two observations of gangrenous eschars of the skin, in which they found the nerves diseased, have collected most of the evidence existing at the date of their publication in favor of the occurrence of gangrene as the result of disease of the nervous system. The possibility that neuritis may produce gangrene must, I think, be admitted, although there is not agreement of opinion among authorities as to the interpretation of the experimental and clinical data adduced in support of this view.

3. *Does gangrene cause alterations of vessels and nerves?*

Lapinsky[18] has recently discussed this question quite fully and I cannot do better than to refer to his papers. The investigations of Hodson, Friedländer, Cornil and Ranvier, Ivanowski, Ziegler and others have shown that chronic inflammation has an injurious effect upon the vessels in the neighborhood and causes peri- and end-arteritis. Lapinsky noticed these changes of the vessels in some cases of his own in and near the gangrenous areas.

In reference to the nerves he says that the importance of local gangrene and suppuration in the production of changes in the nerves of the diseased limb has often been discussed without great weight being attributed to those conditions as etiological factors. He quotes a number of cases in which gangrene was found and was not believed to have caused degeneration of nerves, and he attributes no importance to the local gangrene in the production of the degeneration of the nerve stems in cases of his own. It is well known that ascending neuritis from a suppurating wound is of very rare occurrence.

Pitres and Vaillard allude to the fact that nerves passing to a gangrenous area do not necessarily show degeneration, and they say that this was recognized by Vulpian in 1866 and later by Dejerine and Leloir. However, it is probable that in some cases gangrene does cause alteration of nerves, possibly through alteration of the blood-vessels.

[16] Loc. cit.

[17] *Arch. de phys. norm. et path.*, 1881, 2. s., viii, pp. 989 and 391.

[18] *Deutsche Zeitschr. f. Nervenheilk.*, xv, p. 364.

4. *Does degeneration of blood-vessels produce changes in the nerves of the same territory?*

In studying nerves for degenerative changes it is not sufficient to examine sections taken at a distance from the peripheral ends of the nerves. The increase in the degree of degeneration of nerve fibres towards the periphery was observed by Mannkopf in 1878 in a case of embolism of the popliteal and crural arteries.[19] The greater alteration of peripheral ends of nerves has also been seen by Hans Gudden[20] and other investigators. The importance of the recognition of this fact is seen, for example, in a case of spontaneous gangrene reported by C. Sternberg.[21] The sciatic nerve of the diseased limb did not contain degenerated nerve fibres but the vessels were much altered. I am unable to determine from the report of this case whether or not the peripheral ends of the nerves in the amputated limb were studied.

Schlesinger[22] says that the primary nature of the vascular disease and the secondary nature of the neuritis are not recognized by all, but he thinks that the vascular alteration occurs first. He reports a case in which pain in the feet and livid discoloration of the feet and hands were followed after some months by gangrene of the left foot. The left foot was amputated and the arteries and veins of the nerves within it were much thickened. The nerve fibres were normal in many bundles but in most they were more or less altered and the connective tissue of the nerves was proliferated. He thinks that without doubt the vascular degeneration occurred before the degeneration of the nerve fibres in this case, and he seems to have based this opinion chiefly on the clinical signs, and yet the disease began with pain in the feet as well as with livid discoloration.

When closure of an artery occurs the degeneration of the nerves may be only in the part below the thrombus, as seen in cases studied by Lapinsky. It is not necessary to quote many examples of this. We can accept without dispute the statement that a nerve speedily degenerates when its blood supply is abruptly cut off. Lapinsky says that in cases of acute ischæmia he found the changes of the nerve fibres more marked towards the distal ends where the effects of closure of the arteries were most felt.

The nerve changes are not so perceptible in chronic vascular disease,

[19] Cited from Lapinsky.

[20] *Arch. f. Psychiatrie*, 1896, xxviii, p. 643.

[21] *Wiener klin. Wochenschr.*, 1895, viii, pp. 650, 687.

[22] *Neurologisches Centralblatt*, 1895, xiv, pp. 578, 634.

and according to Lapinsky they have been seen in only comparatively few cases. In some cases the changes of the nerve fibres were very slight and occurred only in certain areas; in other cases the nerve fibres were well preserved and the connective tissue about them was proliferated; in still other cases the nerves were perfectly normal. Lapinsky has collected the reports of a number of cases from the records bearing on this subject. He observed 8 cases of vascular disease; in 7 of these the arteries of one lower extremity were affected, and in one the arteries of both extremities were diseased, and gangrene developed in the part imperfectly nourished. The connective tissue of the nerves was increased in all the cases and this was especially true of the endoneurium.

In the case reported in the present paper the ulnar nerve showed no degeneration as a result of the thrombosis of the ulnar artery.

Joffroy and Achard[23] seem to have been the first to describe neuritis of vascular origin. In a case of neuritis they found that the most pronounced lesions of the vessels were associated with the most pronounced lesions of the nerves, and from this they concluded that the degeneration of the nerves was due to the thickening and obliteration of their nourishing arteries. Neither this case nor the one published by Dutil and Lamy[24] establishes beyond question the vascular origin of neuritis although such an origin seems very probable. Dutil and Lamy say that in their case the parallelism existing between the vascular and nervous lesions justifies attributing the degeneration of the nerves to the thickening and obliteration of their nourishing arteries.

5. *Does degeneration of nerves cause alteration of the vessels in the same territory?*

Bervoets[25] claims to have demonstrated that cutting nerves causes thickening of arteries in the same territory, and he believes that he has demonstrated that neuritis is a cause of endarteritis. A. Fraenkel[25a] obtained similar experimental results, whereas C. Sternberg[25b] had only negative results. Czyhlarz and Helbing[25c] find an explanation of this discrepancy in their observation that changes in the vessels following experimental lesions of nerves occur only when ulcers result from the operation. Lapinsky[26] has collected from the records a large amount

[23] *Arch. de méd. expér.*, 1889, i, p. 229.
[24] *Arch. de méd. expér.*, 1893, v, p. 102.
[25] Over spontaan gangreen, etc., Nykerk, 1894.
[25a] *Wiener klin. Woch.*, 1896, ix, pp. 147, 170.
[25b] Loc. cit.
[25c] *Centralbl. f. allg. Path. u. path. Anat.*, 1897, viii, p. 849.
[26] *Zeitschr. f. klin. Med.*, 1899, xxxviii, p. 223.

of evidence in support of the neuritic origin of endarteritis, and he concludes that these vascular disturbances may be of several varieties. In some cases the lumen is enlarged in the vessels of the territory in which the diseased nerves lie, and this part of the body becomes hyperæmic and its temperature is raised. The vessels may become broadened and lengthened and tortuous. In some cases the nutrition of the vascular walls is affected, as shown by local œdema and occasionally small hæmorrhages in the distribution of the diseased nerves. In some cases anatomical changes in the vessels have been found.

Lapinsky refers to a number of clinical cases in which œdema or redness and increase of temperature followed injury or disease of nerves. This causes us to think of erythromelalgia, inasmuch as this redness and increase of temperature were found in later stages of neuritis as well as in the early. Alteration of nerves and vessels was very marked in a case of erythromelalgia reported by Dr. S. Weir Mitchell and myself.[27] Lapinsky refers to a number of cases in which changes in the walls of the vessels were believed to result from neuritis. He reports two cases in which disease of the walls of the vessels developed in the distribution of diseased nerves. He believes that the disease of the nerves causes a loss of tonicity and elasticity in the walls of the vessels and a disturbance in the nutrition of the vessels; the enlargement of the lumen, the increased intravascular pressure and the slowing of the blood current lead to further changes.

I have referred elsewhere[28] to the views of Thoma. Thoma has shown that when the lumen becomes too great in proportion to the amount of blood flowing through it, as for example after amputation, a compensatory connective tissue thickening of the intima occurs and the proper relations are restored. He has shown that neuritis produces a similar change in the vessels.[29] He studied the soft tissues taken from both temples in a case of left supraorbital neuralgia. More or less hyperæmia occurred in the painful area at the time of the attack. He found that the arteriosclerosis in the area of the supraorbital neuralgia was considerably greater than in the corresponding area on the other side. Thoma had acquired so extensive a knowledge of the vascular system that he was able to name most of the large arteries when transverse microscopical sections of them were shown to him. It seems that the vasomotor change caused by the pain in Thoma's case led to this thickening of the intima.

[27] *Amer. Jour. Med. Sciences*, Jan., 1899, cxvii, p. 1.

[28] Ibid.

[29] *Deutsches Arch. f. klin. Med.*, 1888, xliii, p. 409.

More recently this subject has been again studied by Lapinsky.[30]

Although the evidence, especially on the experimental side, is conflicting, there is support for the view that degeneration of nerves may cause degeneration of vessels.

From the preceding statements and review of the evidence relating to the association and correlation of arteritis, neuritis and gangrene it may, I think, be stated:

1. Gangrene may be caused by endarteritis obliterans.

2. Alteration of nerves alone without alteration of the vessels is believed by some to be a cause of gangrene. We need probably more evidence before this conclusion can be definitely accepted.

3. Gangrene may cause degeneration of the vessels, especially of the portions near the gangrenous area.

4. Gangrene is less liable to cause degeneration of nerves except of the portions within or near the gangrenous areas.

5. Sudden closure of blood-vessels causes degeneration of the nerves nourished by these vessels, unless an adequate collateral circulation is promptly established. If the vascular disease is of a chronic type the nerves may escape, at least for a time, but do not always do so, the result doubtless depending upon circulatory conditions which vary in different cases.

6. Degeneration of nerves is a possible, but not thoroughly demonstrated, cause of degeneration of the blood-vessels.

I have noticed in this and other cases of arterio-sclerosis a multiplication of the elastic membrane. This is probably a new formation. It has been regarded by some as merely a separation of the layers of the previously existing elastic membrane, but this explanation is not satisfactory for all cases. In order to furnish so much new elastic tissue the old must have become very much thickened. I have found an elastic membrane in the organized thrombus of the case A. A., and the thrombus was here separated by a clear space from the proliferated intima. It probably represents here newly-formed tissue. Similar views are held by Dmitrijeff[31] and others.

[30] Lapinsky, *Arch. de méd. expér.*, 1899, xi, p. 109.

[31] *Ziegler's Beiträge*, 1897, xxii, p. 207.

The case of A. A. was not a typical one of Raynaud's disease but it bore certain resemblances to it as Dr. Sinkler pointed out. Local syncope or local asphyxia is not mentioned in the history. The affection was of the distal parts of both upper extremities, in which papulovesicles were important features. Dr. Sinkler describes the sloughing process as first a discoloration of the skin, involving perhaps one-half the surface of the finger; this portion of the finger rapidly became black, then dry, and the slough was thrown off leaving a granulating surface. This account is not unlike that of a case of Raynaud's disease. Monro,[32] in his excellent monograph on Raynaud's disease, says that in less than two per cent of the cases of this disease gangrene alone is mentioned, and a careful perusal of these cases makes it almost certain that there was a stage of asphyxia. In the same proportion of cases, syncope and gangrene alone are mentioned, but in the majority of these asphyxia also was probable. This case A. A. could be considered at most only as an atypical one of Raynaud's disease, but it may have a similar etiology.

There is a class of trophic diseases having certain resemblances to one another but still with distinctive features. Erb[33] compares Raynaud's disease with intermittent claudication. The two disorders resemble one another in the paræsthesia and pain, in the vasomotor disturbances, in the cutaneous gangrene of the fingers and toes, and in the occasional mutilation. In Raynaud's disease neurasthenia, even psychopathies, may occur; the fingers are chiefly implicated; the gangrene is usually limited to the superficial layers of the skin; the symptoms are paroxysmal but not so intermittent as in intermittent claudication and do not depend directly on the use of the limbs. In Raynaud's disease marked changes in the vessels (arteriosclerosis, absence of pulse) and severe gangrene have not been observed. After making these distinctions, Erb refers to Dehio's findings of endarteritis and phlebitis in a case of Raynaud's disease, and says that after all there may be a closer resemblance between Raynaud's disease and intermittent claudication than has been supposed.

[32] T. K. Monro, Raynaud's Disease. 1899.

[33] *Deutsche Zeitschr. f. Nervenheilk.*, 1898, xiii, p. 1.

Angiosclerosis, according to Erb, is manifested clinically in a variety of forms. Simple or obliterating arteriosclerosis without nervous symptoms causes senile gangrene or simple spontaneous gangrene; the combination of obliterating arteritis with symptoms of vasomotor irritation and of sensory and motor disturbance causes the intermittent lameness; the combination of symptoms of vasomotor paralysis (possibly of irritation of the vasodilators) with sensory irritation and obliterating arteritis is possibly the cause of erythromelalgia; the combination of obliterating arteritis with vasomotor and trophic and nervous symptoms may be the cause of Raynaud's disease; the combination of arteritis with intense degeneration and inflammation of the nerves causes the angiosclerotic neuritis of Joffroy and Achard, Dutil and Lamy, and Schlesinger; the vasomotor and sensory irritation without the endarteritis causes acroparæsthesia. It is to be noted that in these diseases a functional disturbance in addition to an organic one is common, and in reading the clinical report of the case A. A. as given by Dr. Duhring and Dr. Sinkler I am impressed by the fact that the disturbance was certainly in large part functional.

The interpretation of the lesions found in the case A. A. is difficult. The woman had stigmata of hysteria and probably had Graves' disease. Destruction of nerves near the seat of spontaneous amputation is nothing more than one might expect as a result of the amputation and suppuration. This degeneration decreased upward quite rapidly, and 6 cm. above the styloid process of the radius was slight in the radial nerve except by the Marchi method and was not very evident in the ulnar or median nerve at parts only a short distance from the seat of spontaneous amputation. The vascular disease seems hardly sufficient to explain the loss of the fingers. The ulnar artery from the amputated limb was nearly closed at one part by an organized thrombus, but this had not caused degeneration of the accompanying ulnar nerve, and it is hardly reasonable to suppose that it had caused such serious changes as the loss of the fingers. The alteration of the radial artery was certainly insufficient to explain the symptoms. The right brachial plexus was normal and there was no evidence here of ascending neu-

ritis. The alteration of the left brachial plexus as seen by the Marchi method is difficult to explain. The appearances were those of recent degeneration. Shall we believe that trophic lesions would have reappeared in the left upper limb if the patient had lived longer, or shall we believe that the findings were artefacts? The left radial nerve was as much altered as the right radial 6 cm. above the styloid process of the radius. This alteration may have been due to the serious lesions that had formerly existed in the left upper limb. Dr. Sinkler regarded the case as a trophoneurosis dependent upon an hysterical diathesis. There is much to be said in favor of this opinion, but there was nevertheless neuritis of high degree in the periphery of the right upper limb, moderate degeneration of nerves several centimetres above the wrist of the same limb, and some vascular change in the amputated part; and the radial of the left upper limb was diseased. The question as to whether these lesions were primary or secondary I do not think can be positively determined. I have attempted to show that they might have been either. At all events the condition in A. A. was not the result of any distinct lesion in the central nervous system. Functional disturbances in the circulation of the peripheral ends of the limbs, in connection with the organic changes, probably increased the peculiar lesions in the case A. A. Her relapses seemed to depend to some extent on functional disorder.

Dehio [34] examined fingers that had been amputated on account of Raynaud's disease and found in these endarteritis, endophlebitis and degenerated nerves, but he only had about 1 cm. of normal tissue above the gangrenous area for his investigation. He, too, was uncertain whether the vascular sclerosis preceded the gangrene or vice versa.

The microscopical examination in the case I report is valuable on account of the extreme rarity of a case of this character with necropsy. It would be most unscientific, however, to be too positive in the interpretation of the lesions, although these were of a definite character, as I have already shown that there is at present considerable difference of opinion concerning the explanation of similar or identical lesions in cases of gangrene.

[34] *Deutsche Zeitschr. f. Nervenheilk.*, 1893–4, iv, p. 1.

Dr. Duhring in his two papers in which he reports clinically the case A. A. refers to several similar cases in the literature. A brief review of some of these may be of interest and of assistance in judging of the etiological value of the findings in the case A. A.

Doutrelepont's[35] case was one of multiple gangrene of the skin over a large portion of the body, associated with vesicles and following the penetration of a needle beneath the left thumb in a hysterical woman. The spinal cord and nerves examined in this case were found to be normal, and the results of the necropsy did not in any way explain the disease.

The case reported by Kopp[36] resembles that reported by Doutrelepont. In Kopp's case the lesions were observed on the left breast, left forearm and left thigh. The neurotic nature of the affection Kopp believed was shown by the unilaterality, the acute development of the lesions in groups, the typical course, and the accompanying neuralgia. An ulcerating keloid on the left hand which developed in the scar of a burn, he thought might have caused ascending neuritis and implication of the spinal cord. Kopp describes the case as one of multiple neurotic cutaneous gangrene.

Galton's[37] patient was a girl of seventeen who had suffered from fits of an epileptic nature, brought on by a fright at school. Patches of redness followed by blebs appeared on the left wrist, hand and arm shortly after she had chopped off the distal phalanges of the index and ring fingers and cut through the middle phalanx of the middle finger. The eruption was peculiar from the rapid way in which it spread. Sometimes within a quarter of an hour the whole hand and arm would be covered with large blebs which would burst and discharge. The circulation seemed very feeble. At one time a crop of vesicles appeared on the left leg. Galton attributed the lesions to a reflex irritation.

Kaposi's[38] patient was a girl of twenty-two years, who had injured her right middle finger by a nail. The part was bound in iodoform. A few days later vesicles appeared on the dorsal surface of this finger and extended and affected the back of the hand and forearm. These vesicles were accompanied by a sensation of burning in the part. Other cutaneous surfaces of the body were attacked. Kaposi did not believe a

[35] *Vierteljahresschrift f. Dermat. u. Syphilis*, 1886, xiii, p. 179, and *Arch. f. Dermat. u. Syphilis*, 1890, xxii, p. 385.

[36] *Münch. med. Wochenschr.*, 1886, p. 665.

[37] *British Med. Journal*, 1891, i, p. 1282.

[38] *Wiener klin. Wochenschr.*, 1890, p. 425.

neuritis existed but thought that an ascending irritation was present and caused redness, exudation and vesicles, and that this irritation extended to the spinal cord. He thinks his case resembled Doutrelepont's, and that it was an expression of hysterical irritability of the vasomotor system, analogous to cases of herpes zoster gangrænosus and of zoster gangrænosus hystericus. No gangrene was observed in Kaposi's case. He calls his case "pemphigus neuroticus hystericus."

Bayet [39] describes a condition known as disseminated cutaneous gangrene. He speaks of it as a very rare affection. Some of the cases have been described, he says, as gangrenous zona, others as pemphigus neuroticus, and others as gangrenous urticaria. The causes of this confusion are the rarity of the affection and the predominance of certain symptoms in different cases; but common to all are the dependence of the lesions on disturbances of innervation and the local evidences of hysteria. Bayet's case is as follows:

A hysterical male, nineteen years of age, burned himself superficially on the anterior surface of the left forearm a little above the wrist. The wound healed at the end of twelve days. Two days after the accident plaques covered with a dry crust appeared on the external surface of the thumb. This crust did not last very long and left a superficial ulcer requiring two months to cicatrize. Within a short time twenty-one ulcers of different sizes, some as large as a franc, appeared on the left forearm. All these ulcers were found on portions of the skin which had not been in contact with the sulphuric acid. These lesions were found later on the hand. Deeply pigmented areas represented the former site of ulcers, and in some of these areas bullæ, containing a sero-sanguineous fluid, appeared. The skin between these lesions seemed to be normal. The case was believed by Bayet to be a multiple gangrene of the skin dependent upon hysteria. He was able to produce a characteristic lesion by suggestion.

Janovsky and Mourek [40] in a study of multiple cutaneous gangrene report two cases in which vesicles were observed but no necropsy was obtained. They give references to several cases of cutaneous gangrene. Whether these cases of cutaneous gangrene should be classed with such a case as that of A. A. in whom the lesions were chiefly of the character of vesicles is questionable. The etiology in all is obscure.

[39] *Annales de dermat. et de syphiligraphie*, 1894, v, p. 501.

[40] *Arch. f. Dermat u. Syphilis*, 1896, xxxv, p. 559.

DESCRIPTION OF PLATES IV AND V.

PLATE IV.

Fig. 1.—Photograph of the amputated part of the right forearm and hand, palmar aspect.

Fig. 2.—An organized thrombus in the right ulnar artery from the amputated part of the limb.

PLATE V.

Fig. 3.—Section of the radial nerve from the right forearm taken 6 ctm. above the styloid process of the radius. The nerve fibres are diminished in number and the endoneurium is proliferated. The degeneration is much less than in the more peripheral portion of the nerve (see Fig. 4).

Fig. 4.—The radial nerve from the right upper limb in its terminal portion. The degeneration of nerve fibres and the overgrowth of connective tissue are extreme.

FIG 1.

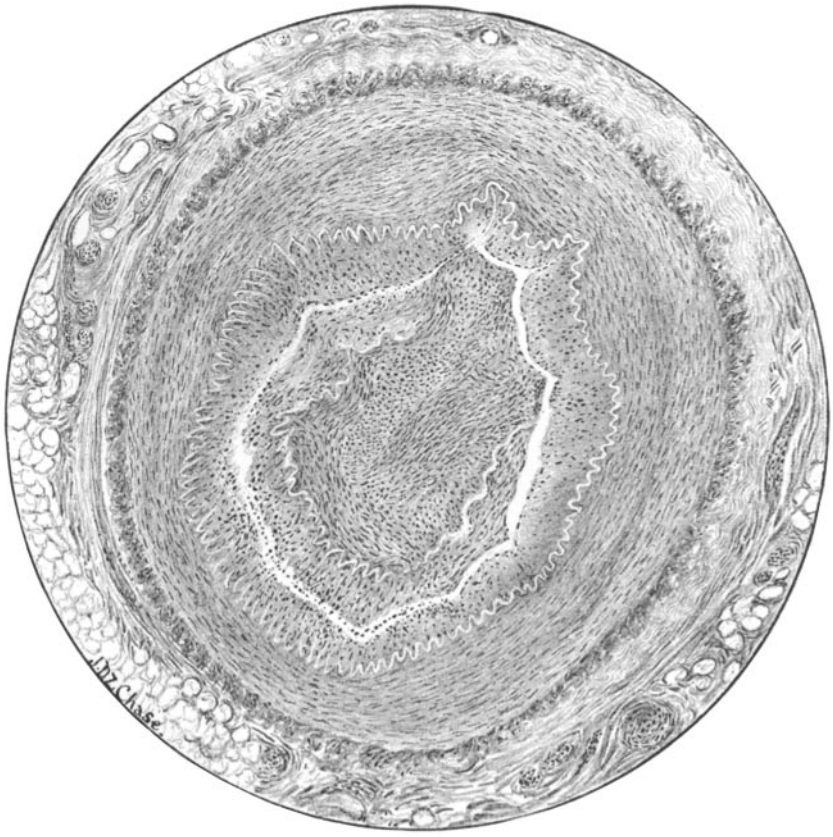

FIG. 2.

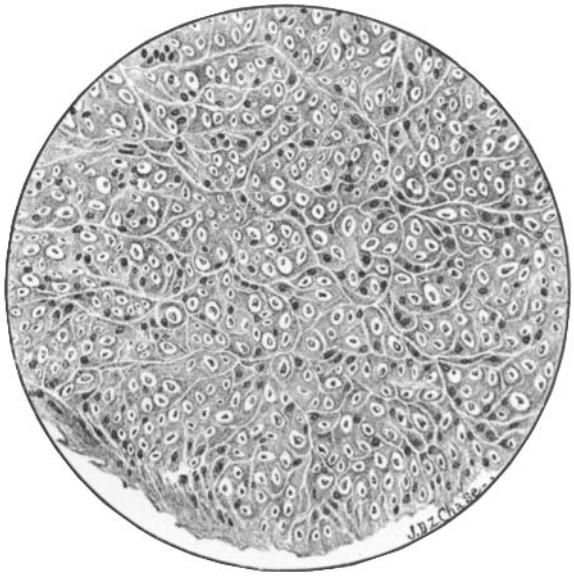

FIG. 3.

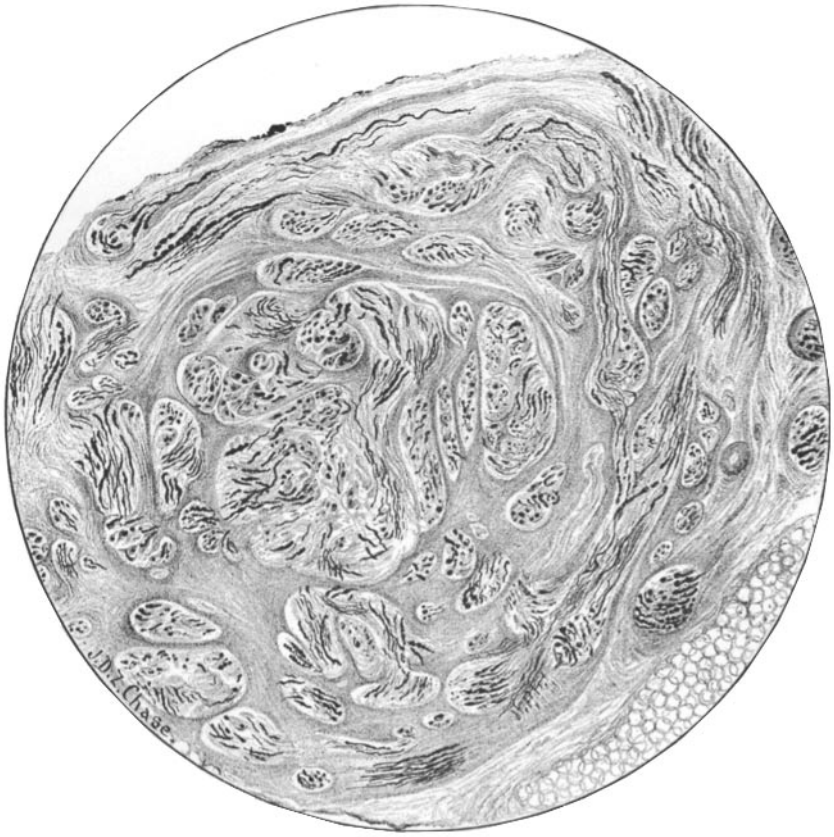

FIG. 4.