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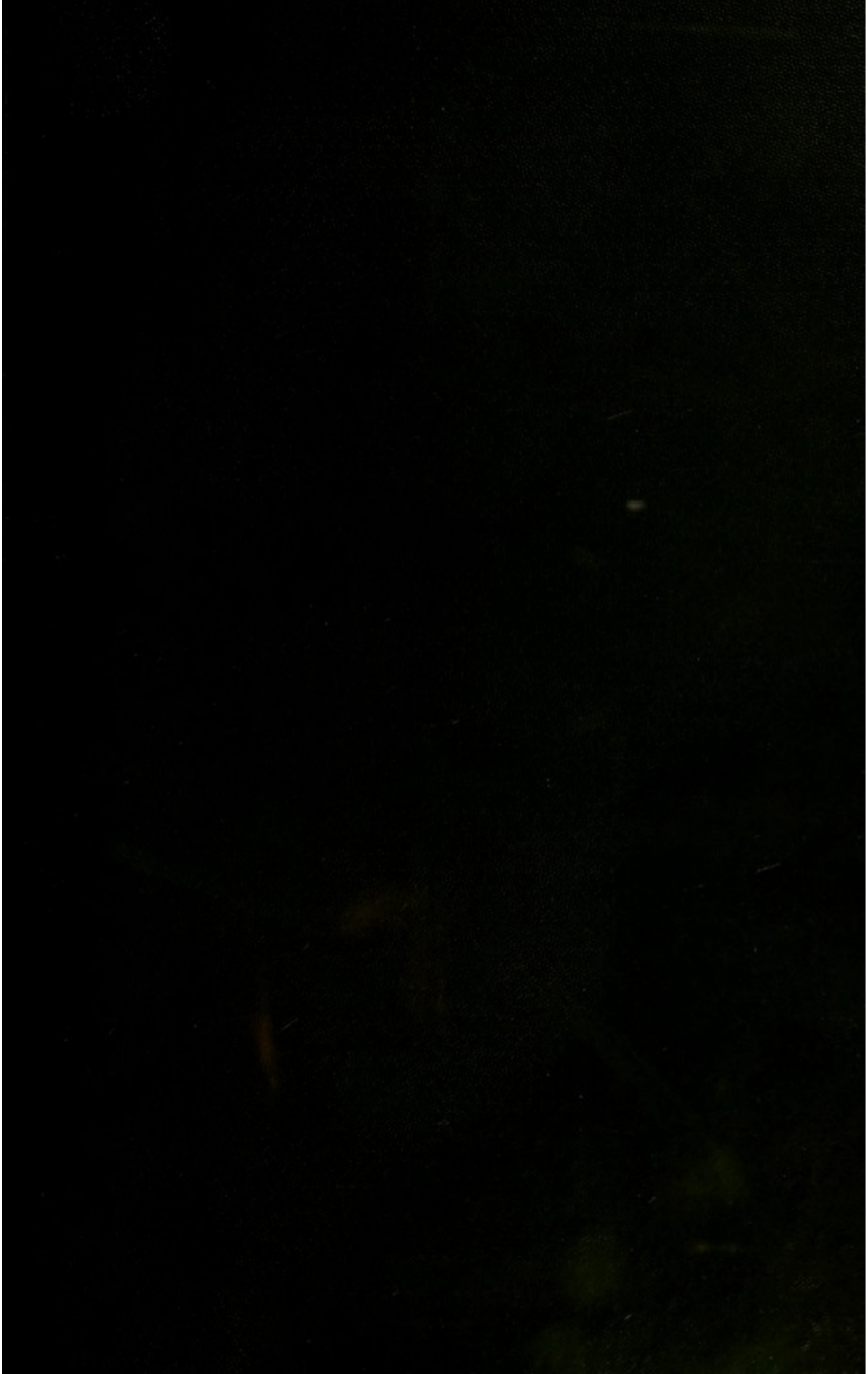

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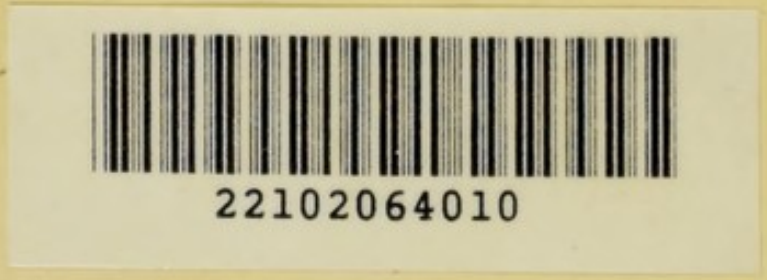

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With the Kind regards of

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SELECTED RESEARCHES

IN

PATHOLOGY

BY

ALEX. GUNN AULD, M.D., M.R.C.P.

AUTHOR OF
"THE PATHOLOGICAL HISTOLOGY OF BRONCHIAL AFFECTIONS,
PNEUMONIA AND FIBROID PNEUMONIA"

WITH ILLUSTRATIONS

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PREFACE.

This volume contains a selection from my investigations in the various branches of pathology, apart from those already published in book form. Most of the results have, from time to time, been submitted to pathologists at scientific meetings, and thereafter published in convenient fashion in *Transactions* and Journals (referred to at the end). All the work has been thoroughly revised, and renewed examinations have been made of the specimens on which the observations relating to Morbid Anatomy are based. The investigations relating to Experimental Pathology and to Bacteriology were carried out in the Laboratories of the Royal Colleges of Physicians and Surgeons, and I desire to express my indebtedness to the Laboratories' Committee for the privileges extended to me in connection therewith.

There has been little occasion to make any material alteration in the work on Emphysema or in that on Hæmatogenous Jaundice. The work on Pneumonia, on the other hand, has but recently been finished. The chapters on Bright's Disease and Addison's Disease are re-written, and new observations are incorporated. The final chapters on

Atheroma and Aneurysm are the joint production of the late Professor Coats and myself, being indeed the last investigation in which that distinguished pathologist was engaged. The matter of these remains, of course, as in the original, except for a few verbal abridgments.

It has been my aim throughout to present the researches in as concise a form as possible.

A. G. AULD.

London, *April*, 1901.

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CHAPTER I.

EMPHYSEMA.

The different forms of vesicular emphysema may first be briefly considered, then the character and course of the minute textural changes; to this follows an account of certain fibroid lesions which seem to form an integral part of the disease, and lastly I shall offer a few considerations respecting the pathology of the disease, based upon certain changes which are to be found in the pulmonary nerves.

Varieties of Emphysema.

Several varieties of emphysema are described, although the classifications adopted by different writers are by no means alike. In Wilson Fox's work are given—(1) Acute vesicular emphysema, a recoverable condition, and of either a general or partial character; (2) chronic local emphysema; (3) generalised "large-lunged" emphysema (Jenner); and (4) generalised atrophous emphysema ("small-lunged" emphysema of Jenner). Hertz classifies emphysema as "substantive" or "substantial" and "vicarious". The former he describes as an idiopathic affection developed in all diseases which are accompanied by severe paroxysms of coughing, or in any other forced movement of the breath; vicarious emphysema, on the other hand, is found in connexion with conditions of the pulmonary parenchyma, in which, owing to the impermeability to air of certain parts of the lung, the remaining alveoli become over-distended. Waters in his monograph—a

work characterised by the most admirable fidelity to detail and impartial analysis—describes three varieties. The first of these he names "partial lobular emphysema". It is found either involving a few air sacs or a single lobulette, when it has much the appearance of vesicles of pemphigus. These vesicles push out the pleura, thus raising it above the level of the surrounding lung tissue. In other cases it exists along the margins of the lobes of the lung, resembling a row of beads. This "partial lobular" emphysema is, however, only rarely found as an independent affection; it is most commonly found in lungs in which the second form exists, or "lobular" emphysema. This is the form of the disease most commonly met with at *post-mortem* examinations; it involves one or more lobules in different parts of the lungs, especially the anterior margin, the margin of the base, and the apex; in the latter situation it is not infrequently associated with healed phthisis. The third, and by far the most important variety, Waters terms "lobar". It most frequently attacks both lungs and the lower as well as the upper lobes. Lungs so affected possess a peculiar doughy feel, pit on pressure, are wanting in healthy crepitation, and have a colour like that of a calf's lung. No collapse occurs on removal of the chest-wall, but, on the contrary, the organ often bulges forward.

Although, no doubt, certain discrepancies exist regarding what may be classified as "local," or "vicarious," or "substantive" forms of the disease, it is clear that, generally speaking, chronic emphysema is either definitely partial or localised, or else pretty uniformly lobar or generalised. Of more importance is the question of the exciting causes and pathology of these different kinds. While admitting the great influence of the mechanical forces of respiration in the production of emphysema, more especially that of expiration, as the work of Jenner has so clearly shown, it nevertheless has been forced on the attention of all observers that in many cases, and especially in the "large-lunged" or substantive form of

the disease, a primary dystrophic lesion of the pulmonary tissue has to be reckoned with. So impressed was Waters with this circumstance that he regarded all cases of "lobar" emphysema as of this nature. "This form of the disease," he remarks, "differs very materially in its pathology from the partial emphysema I have spoken of in a former paragraph. . . . I do not entertain the slightest doubt that the disease in its severer forms is of a constitutional nature; that one of its most important features, and perhaps the primary step in it, is a malnutrition of the pulmonary tissue, causing its degeneration and giving rise to all the structural changes which I have previously described." In many cases this pulmonary defect is congenital and originates in childhood,* but experience also teaches that it may be induced without hereditary predisposition.

The Minute Changes in Emphysema.

It is only in recent patches of the limited or compensatory variety of emphysema that the minute textural alterations can be traced from their very beginnings. It is the prevailing view with respect to these alterations that they are of a degenerative and atrophic character throughout. Such changes, according to the researches of Rainy, Waters, Rindfleisch and others, may be summed up as loss of elasticity and degeneration of the elastic fibres, stretching and progressive wasting of the capillaries, and granulo-fatty degeneration of the epithelial and connective tissue elements of the air cells. Perforations of the alveolar walls ensue, which lead to fusion of the air cavities. A

* A case which made a marked impression on my mind was that of a boy, aged fourteen, who was an out-patient of mine at the Glasgow Royal Infirmary. Since his second dentition he had been gradually developing generalised emphysema until his chest was enormously distended. The emphysema was quite unattributed to any bronchial affection; indeed, cough had been but slight, and when I saw him he complained but little of it. He was, however, as may be expected, very cyanotic, and was generally emaciated and in a debilitated condition.

hypertrophy of the muscular fibres around the infundibular openings has likewise been noted along with this degeneration. It is usual to regard the wasting of the capillaries as the proximate cause of the nutritive changes. Some, however, amongst whom may be mentioned Hertz and Ziegler, consider the degenerative change in the walls to be antecedent to, and so far determining, the destruction of the vessels.

The observations which I have been enabled to make are such as to negative the supposition that in emphysema there is wholly a degenerative and atrophic process. On the other hand, there appear to be two stages in the morbid anatomy of the disease: one reactive and productive, the other degenerative or atrophic. Further, the course of the changes is not such as to warrant the view that the lesions of nutrition are entirely dependent on the vascular conditions.

In a portion of lung about to become the seat of a compensatory emphysema, the first effects of the mechanical strain are a general dilatation of the part and a reduction in the velocity and volume of its blood circulation. The dilatation involves the smallest bronchioles, alveolar ducts, infundibula and air cells. Seeing that the air cells are mutually arranged like the cells of a honeycomb, their expansion must in the first instance be mainly uniform in all diameters, and not, as some have supposed, a mere flattening out, in order to effect which an extensive destruction of the septa would be necessary. The slowing and diminution of the circulation are caused by (1) impairment of the normal recoil, (2) the expelling influence of the air at a high pressure, and (3) stretching of the vessels, more especially those disposed round the mouths of the alveoli. A great deal depends, however, on the extent and site of the involved part and the surrounding conditions, as the size of the capillaries is chiefly regulated by the amount of blood, and a heightened pressure (as from congestion) would overcome a certain degree of

stretching, so that in the early stage of emphysema it is sometimes difficult to detect much alteration in the size of the capillaries. Now, as to the air cells, the first effect of the increased tension is to produce a compensatory reaction in the respiratory elements. It is a mistake to suppose that they immediately submit to the injurious influence. Both the epithelial and connective tissue cells enlarge, and many of them divide. They behave, in fact, like any other tissue on which an inordinate demand is made, and this hypertrophy is indeed the analogue of what occurs in the muscle nuclei in the infundibula. I have carefully guarded against the possibility of confounding this change with a merely inflammatory phenomenon. It is true that Villemin, Klob and Wunderlich have noted an increase in the intercapillary nuclei in emphysema; this, however, they regard as a secondary inflammatory process, and unconnected with the heightened air pressure. But the phenomenon now described is compensatory, occurs at the very beginning, and is not to be confused with the later inflammation. It may not inaptly be compared to what occurs in certain cases of atheroma, in which the increased tension in the vessel leads to swelling and division of the nuclei in the intima. As in atheroma also, this nuclear change is accompanied by a swelling of the areolar ground tissue. The result is a widening of the capillary meshes, with consequent narrowing of the capillaries. Many of the endothelial nuclei of the capillaries likewise enlarge and ultimately cause a permanent constriction of the vessel opposite the point. (Fig. 1.)

The reaction of the respiratory cells is not of long duration; they shortly enter on the degenerative stage. Their protoplasm becomes granular and fatty and the nuclei vacuolate and fall to pieces. The part has, however, become permanently enlarged through atony of the elastic fibres, and many of these show a granular change—a finely beaded state of the fibrils. Small holes

appear in the granular protoplasm, which speedily enlarge, and in this way many of the septa become completely destroyed. The capillaries undergo the following further changes: their walls become increasingly attenuated and the pressure of the endothelial nuclei blocks the circulation at many points; the red corpuscles become elongated and some of them undergo a granular degeneration (*g* in Fig. 1) until many of the capillaries soon come to appear as whitish

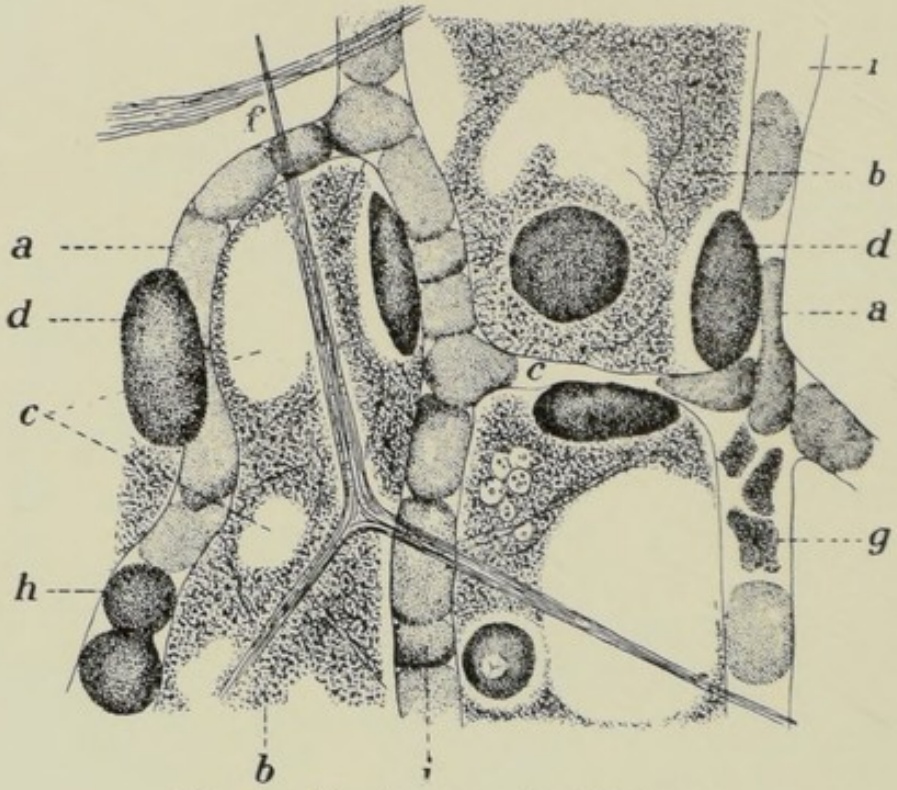

FIG. 1.—Emphysema, atrophic stage.

a, capillaries, containing shrivelled red corpuscles, and compressed by endothelial nuclei, *d*; *b*, granular and fatty condition of air cells; *c*, perforations; *e*, collapsed capillary; *f*, elastic fibres; *g*, remains of red corpuscles; *h*, leucocytes.

lines stretching across the granular substance. It was asserted by Isaakssohn * that the vessels were blocked by what he terms "white thrombi"—*i.e.*, colourless blood-corpuscles. He affirmed that the alteration began by a granular change in the endothelial walls of the capillaries, so that the characteristic white lines did not appear on treatment with nitrate of silver. On these granular places white

* *Virchow's Archiv*, Bd. liii., p. 466.

blood-corpuscles were deposited and became so firmly fixed that even a strong injection would not drive them away. New homogeneous deposits were gradually formed over these cells, the whole obstructing mass soon undergoing a fatty degeneration. Now I am not disputing these conclusions in the main, for it is evident that a granular state of the capillaries ensues, and it is likewise true that leucocytes are frequently found in the vessels at points where they are breaking down; but it is certain that this is not the only mode of obstruction of the capillaries, for they are often seen interrupted at points where only red corpuscles are to be found, and in particular by the encroachment of endothelial nuclei on their yielding walls.

Now, while these phenomena are to be observed in recent cases of partial emphysema, it is not possible to demonstrate such a sequence in cases of old-standing lobar emphysema. In these, no doubt, the very earliest changes are often impossible of detection; but, apart from this, it is extremely doubtful if an hypertrophy of the corpuscles ever occurs. It is more likely that degenerative changes alone take place. My reason for inclining to this view is that in examining air cells which had undergone no dilatation whatever—cells in the centra portions of such lungs—many of the corpuscles had already undergone a highly granular change. This seemed to show that a nutritive alteration had taken place apart altogether from dilatation of the vesicles. Herein the protoplasm becomes granular and often all but disappears, and the delicate connective tissue membrane likewise becomes granular and riddled with holes, which enlarge and coalesce. Not, however, until these destructive alterations are fairly established do the capillaries begin to disappear, and it is clear that deprivation of blood is not the determining cause of the textural alterations; in fact, it is often surprising what a discrepancy sometimes seems to exist between the blood supply and the lesion of nutrition.

As regards the elastic fibres, no structural alterations can be made out with the microscope until a comparatively advanced stage of the disease, and even then only the finest of these seem affected. This also consists in a finely granular degeneration. No doubt an atonic state of these fibres is early engendered, as evidenced by their rigid appearance and absence of any disposition to curl up, together with frequent ruptures.

Fibroid Lesions in Emphysema.

It is familiarly known that emphysema may occur side by side with fibroid induration, and that such fibroid changes may own diverse causes, but it is perhaps not so generally recognised that there are certain fibroid lesions which are the direct outcome of emphysema, and which, in many cases, have characters peculiarly their own. Jenner, indeed, regarded the fibroid variety of degeneration to be that most frequently met with in the emphysematous lung, and held that it was "the consequence of the exudation of that variety of lymph which escapes from the capillaries when they are the seat of slight but long-continued congestion". This opinion has been questioned, but the observations go to support Jenner's statement. In cases of partial or localised emphysema the inter-lobular septa and the adventitious tissues of the pulmonary vessels and bronchi are notably thickened and infiltrated and present an unusual deposit of pigment. The branches of the pulmonary veins are irregularly puckered and frequently quite collapsed in the midst of this tissue. The peculiarly irregular character of this contorsion quite negatives the possibility of contraction occurring *in articulo mortis*. Many of the arteries are partially occluded or else appear as solid cords, from obliterative endarteritis (see Fig. 2). Notwithstanding the serious nature of this change, numbers of dilated capillaries are often found in the thickened tissue, and,

judging from the nuclear character of certain areas, it is not improbable that some of these vessels are new-formed. As the main vascular branches, and especially those of the pulmonary veins, become gradually narrowed, congestion and dilatation of the capillaries ensue, and this in turn tends continually to augment the indurative change. This induration, then, which has its chief seat around the blood vessels, traverses the emphysematous area in the form of an irregular network. Many of the con-

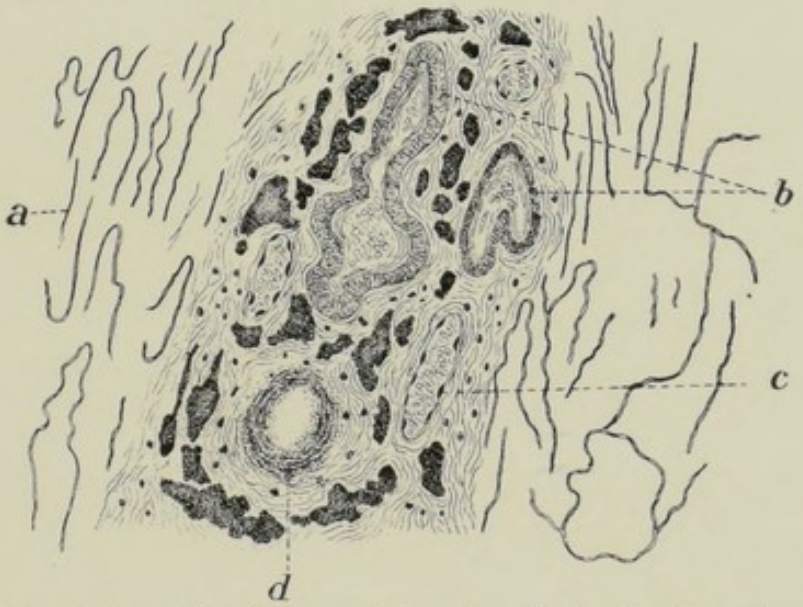

FIG. 2.—Indurated and pigmented septum in localised emphysema.

a, remains of flattened and wasted alveoli; *b*, compressed and contorted veins; *c*, dilated capillary, possibly new-formed, which has also undergone some compression; *d*, artery, becoming occluded by endarteritis obliterans. [The black masses are deposits of pigment.]

tiguous air cells also partake of thickening, although it is likewise common to find them wasted and flattened out from the impact of the column of air which acts from the centre of the lobule towards its periphery.

In the "large lunged" form of emphysema, and especially in those cases which seem to originate as an independent affection not due to chronic bronchitis, fibroid development is a characteristic feature. Sometimes the fibrosis partakes of the character of that already described, but I have observed several cases in which hyperplastic

changes of a highly organised character were uniformly proceeding throughout the organ. In such, the bronchial tubes were thin and wasted and somewhat dilated, but the outer coat of the pulmonary vessels, the inter-lobular septa, and regularly recurring groups of the pulmonary

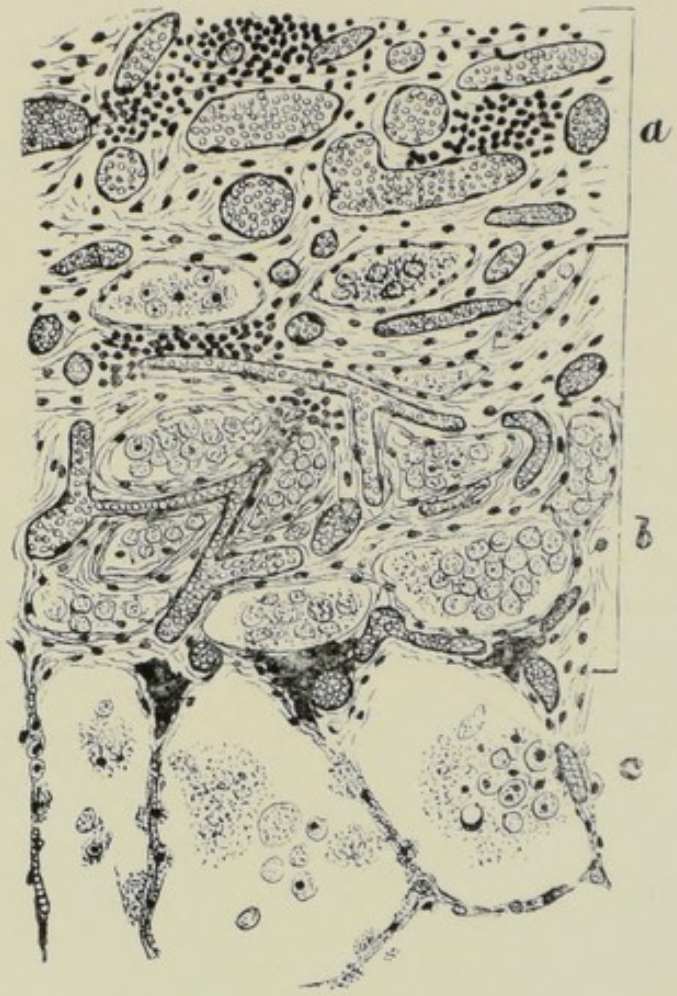

FIG. 3.—Vascularisation and fibrosis in Emphysema.

a, outer edge of adventitia of a pulmonary blood vessel, consisting of a highly vascular and nucleated tissue; *b*, part of pulmonary parenchyma involved in the new vascular connective tissue growth, the alveoli thickened and containing desquamated epithelium; *c*, dilated and ruptured alveoli, with granular walls and contents, and showing deposition of pigment at their junction with the fibroid patch.

alveoli were invaded by a growth of delicate new tissue of a most vascular character. There was no shrinking or obliteration of the main vessels in the septa; on the contrary, they were as patent as in the normal condition, for the lungs were uniformly expanded. But the majority of the air cells were granular and anæmic, and, as if to com-

pensate for this, the remarkable development of vascular tissue had occurred. No doubt a great number of highly dilated capillaries existed along with the newly formed vessels, but the evidence as to the latter was quite unmistakable. The change appeared to begin by the deposition here and there of small clusters of nuclei, thickly set together, and in some of these clusters the delicate new vessels were easily seen just in course of formation and extending in interbranching lines to others outside the clusters. The vessels so formed assumed fairly large dimensions and formed a fairly extensive anastomosis. Considerable areas of alveoli became the seats of this vascular growth; their walls were much thickened and in their interior there were a number of granular corpuscles (Fig. 3, *b*). Sometimes the new vessels dilated until some of them became confluent at points, when the resultant vessel had an irregular appearance in the tissue. In other cases they ruptured into the alveoli, and it was not infrequently difficult to determine whether the alveolus with its nuclear lining was not in reality a large-sized blood vessel. In regard to these appearances it may be mentioned that Rindfleisch * has described the existence of an anastomosis between the pulmonary artery on the one hand, and the pulmonary and bronchial veins on the other, in cases of emphysema.

Condition of the Pulmonary Nerves: The Pathology of Emphysema.

Allusion may first be made to the structure and distribution of the nerves of the lung. Working in Professor Chrzonszczewsky's laboratory on the pulmonary nerves in amphibians and mammals, Egorow states † that the main trunks are found to be of a mixed character—that is to say, they contain medullated and non-medullated fibres.

* *Pathologische Anatomie:* Article, "Emphysema".

† *Centralblatt für die Medicinische Wissenschaft*, 1879, No. 18.

The chief bulk of the fibres is derived from the pneumogastric, the others pertain to the sympathetic nerve. In the course of the nerves, and especially at their bifurcations, there are many small ganglia. These ganglia are often surrounded with an endothelial-lined sheath. The medullated fibres after leaving the main stems pass through the walls of some alveoli in a diagonal manner and, losing their sheath, terminate in a network in the sub-epithelial layer of the alveolar septa. Many of the non-medullated fibres likewise distribute themselves to the alveoli, and, in addition, to the pleura and the walls of the blood vessels.

These nerves are to be found in abundance in the fibrous septa of the human lung, and especially in connexion with the smaller branches of the pulmonary artery which run in this situation. In cross sections small ganglia are often observed in them, and I have counted as many as six or seven. They are usually surrounded by a clear space which shuts them off from the nerve fibres; at one pole, however, a nerve fibre may be traced entering the ganglion.

When examining microscopically the lungs from a case of emphysema, my attention was directed quite by chance to a most abnormal condition of certain nerve fibres, and in all cases of extensive emphysema which were thereafter examined marked interstitial changes have been present in the nerves, with usually granular degeneration of many of the fibres. This change was found in nerves not directly involved in the emphysema, in those near the root of the lung, and in cases where bronchial atrophy existed, as well as in those presenting chronic bronchial inflammation. In the earliest stage it is found, on making longitudinal sections, that the nerve trunk is inflamed, as evidenced by distention of its blood vessels and occasional hæmorrhages. Along with this, the corpuscles in the endoneurium are increased and often mitotic, being engaged apparently in the formation of young tissue. Latterly, as the interstitial tissue increases and becomes more fibrous, the number of

nuclei becomes much diminished and the nerve fibres, in isolated and irregularly distributed patches, tend to assume a granular character (Fig. 4). In some fibres, however, the sheaths of Schwann are quite well defined in the midst of the fibrous tissue, while in others they cannot be demarcated.

The point which came up for consideration was whether or not the nerve degeneration was merely an expression of that occurring more or less generally in the organ. Inflammatory and degenerative changes are usually found surrounding the nerves, but in certain cases the amount of change observed in the nerve was scarcely compatible

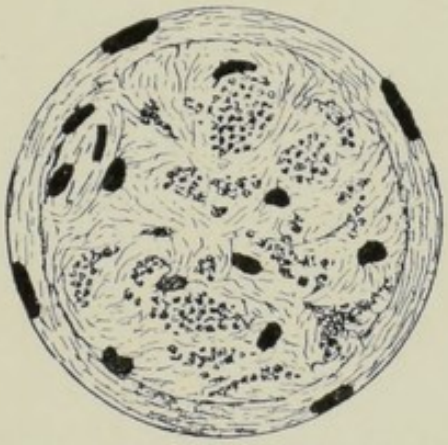

FIG. 4.—Section of a pulmonary nerve in emphysema. The greatly thickened perineurium and endoneurium are seen, the latter containing a few scattered nuclei. In the thickened tissue irregular groups of nerve fibres are seen, being mostly in a state of granular degeneration.

with that in the surrounding tissue, and also great degeneration of the nerves was found in the midst of tissue which had not been much affected by inflammation.

The experiments of Brown-Séquard have proved that irritation of the pneumogastric quickly develops emphysema. He states that emphysema will appear on irritation of the brain by cutting or crushing when not a single respiratory movement takes place, and in a communication to the French Academy he showed that excitation of the vagi immediately after death would produce emphysema, and the nearer the lung the excitation is made the more apparent is this emphysema. Hence he concluded that

nervous disturbances in the pneumogastric play a part in the production of emphysema along with the mechanical forces of forced inspiration and expiration. The rapid accession of emphysema in cases of nervous asthma he also held to be confirmatory of this opinion.

In cases of idiopathic or substantive emphysema (already referred to) the idea of a primary lesion of nutrition may, possibly enough, find its solution in the condition of the pulmonary nerves. It is quite possible that a trophoneurosis may be engendered, due to the action of a poison affecting the nerve endings in the lung (as, for instance, in whooping-cough). The frequent association of this form of emphysema with gout likewise suggests such an etiology, as the latter disease is thought by many to be a species of peripheral neuritis. In like manner joint diseases of nervous origin are to be considered in this connexion. On the other hand, in those cases of emphysema which seem dependent on chronic bronchitis it may be surmised that the chronic irritation which undoubtedly extends to the nerves in the fibrous tissues of the adventitia is such as to provoke the development of the disease and to render the action of the respiratory forces more speedy and certain. The rarity of emphysema in cases of hysterical cough, even when severe and long continued, seems to lend confirmation to this view.

CHAPTER II.

PNEUMONIA.

THIS investigation relates entirely to the pneumococcus, or *diplococcus lanceolatus* of Fraenkel, its chemical pathology and the action of its toxines in rabbits.

This organism has never been absent from the sputum of any case of acute pneumonia which I have examined, and it is extremely doubtful if, after careful examination, it should ever be found absent in any genuine case of this affection. The more the organism is studied, the stronger becomes the ground for its adoption as the cause of croupous pneumonia.

Its morphological and cultural characters are generally well known, and it is unnecessary to recount these here, further than noting a few points which, among others, the investigation brought out.

It may first be stated that in all the cases examined the sputa contained the pneumococcus in association with numerous other bacteria. Attempts were made to isolate these organisms by means of plate cultivations. The pyogenic cocci were often found, especially the *staphylococcus aureus*. Various bacilli and streptococci also were cultivated: Friedländer's *pneumobacillus* being occasionally found, and indeed sometimes not very easy to distinguish from Fraenkel's pneumococcus by the microscope alone. But on further cultivation outside the body it becomes more elongated, forming considerable rods. It also shows this disposition well in the blood of guinea-pigs. Apart from this, its staining reactions and cultural appearances are of course sufficiently distinctive. Some of the

bacilli isolated gave negative results after inoculation in rabbits and guinea-pigs, but one of them induced an illness in the former which was characterised by wasting and chronic diarrhœa. Further cultivation of this organism proved it to be the *bacillus coli communis*.

Special mention must be made of the circumstance that the *micrococcus septicæmiæ* of rabbits seems to be not infrequently present in the human mouth. Its effects have often been mistaken for those of the pneumococcus. On several occasions this organism made its appearance amongst the animals, but its source remained uncertain. It spoils everything, but is soon recognised by its intensely poisonous effects and by its microscopical and cultural characters. It shows polar staining. Its virulence remains unchanged in all subcultures in bouillon, and its toxine produces intense collapse, from which, however, recovery often ensues, even if the animal should lie on its side in a seemingly moribund state.

The pneumococcus is a very troublesome organism to work with, owing chiefly to the fact that its virulence quickly dies out. Preserved in blood, however, the organism will retain its virulence, at least for some months. The method I employ is to take up the blood from the heart directly with a small specially-made pipette. The ends of the pipette have each a constriction near the bulb (in its centre). The bulb being filled, or nearly so, with the blood, the constrictions are sealed by the Bunsen jet. Preserved in this fashion, the organism will retain its virulence for months. It is unnecessary to keep these bulbs in the incubator; the temperature of an ordinarily warmed room is sufficient.

If the rusty sputum of pneumonia be inoculated underneath the skin of a rabbit, death by septicæmia usually occurs from the second to the fourth day thereafter. Sputum taken at the crisis of the disease is sometimes less virulent, and sputum taken after the crisis may produce merely a localised inflammation, from which the animals

recover. In one case the sputum, several days after the crisis, remained as virulent as ever. In other instances complications ensue from the presence of associated micro-organisms. After subcutaneous inoculation of rusty sputum, the blood of the animal contains as a rule a pure growth of the pneumococcus. The animal should not however be allowed to die and the cultures taken from the blood thereafter, as in this case secondary infections may occur from the abdomen, etc. It is best to kill the animal within thirty-six hours, and to make cultivations immediately from the blood of the heart.

The best test for the purity of a pneumococcus culture taken from an animal in the manner described is the appearance of the growth on ordinary agar (which should be made slightly alkaline). On the surface of this medium it forms a close aggregation of minute, transparent droplets, like drops of dew. These are perfectly transparent to reflected light, showing no opacity whatever. This growth might even be mistaken for droplets of water on the surface of the agar. After a few days, or longer, the culture begins to die, and then it assumes a certain degree of opacity.

Although this agar test applies to first cultivations of the pneumococcus from rabbit's blood, it does not apply so strictly in the case of subsequent cultures carried over from rabbit to rabbit. This seems to depend partly on the fact that such cultures assume a greater and greater virulence, which entails modifying conditions on the organism's growth. Still, even in these cases, agar streak cultures present a degree of transparency rarely found in other organisms. The same applies also to its growth in bouillon and other media. A first cultivation in bouillon at 37° C. produces a cloudiness without any film in about six or eight hours. This lasts for about thirty-six hours, when the cocci subside, forming a granular sediment, and the bouillon again becomes transparent. But when the organism is carried over for several generations, and its virulence highly exalted, the growth in bouillon lasts much longer

and may form thick flakes and masses suspended in the medium. In this case, however, the bouillon must be rendered much more alkaline to begin with, as shall subsequently be alluded to. The majority of the cocci forming the sediment die in a few days, but a number of them retain their vitality at least for months, and new cultivations can be made from them. Some of these are unusually large, stain very deeply, and are probably of the nature of arthrospores. After the organism has ceased growing, the supernatant fluid is found to be distinctly acid, and when tested it gives the reaction for lactic acid. It is probable that the production of this acid has an inhibitory effect on the further growth of the organism.

Referring again to first cultivations on solid or liquid media, we find that the organism has lost its capsule and presents the forms of single cocci, diplococci and streptococci. The chains consist of from three to fifteen elements, but probably the majority consist of seven or eight. I have had some interesting results in the case of carrying over the organism for many generations in rabbits. The capsules are sometimes present both in bouillon and agar cultivations. In the former it is often surprising to find nothing but capsulated diplococci under the microscope—no chains being formed. On the other hand, the capsules are sometimes absent from cocci obtained direct from the animal's blood.

If a pure moderately virulent culture of the pneumococcus be inoculated, either subcutaneously or into the internal cavities of a susceptible animal, it produces around the site of inoculation intense congestion, exudation of sanguineous serum, and fibrin. That is its characteristic and invariable lesion, and it produces directly no other. Should resolution not occur soon, we have of course, after a variable time, an exudation of leucocytes, the gradual collection of which may give rise ultimately to what has the appearance of a mass of pus. I have generally found such pus to be very

viscid. This secondary invasion of leucocytes, when it does occur, is merely a result of the continued irritation of the part. It is a healing process and not a part of the characteristic lesion of the pneumococcus. There is more than this to be said about it. While it is possible that the "pus" so formed may yield a pure growth of the pneumococcus, most of the cases which I have examined have shown streptococcal and other infection as well. The conclusion cannot be avoided that most of these purulent collections ultimately forming are instances of mixed infection. In acute pneumonia, grey hepatisation is not pus in the lung. If, as some allege, the pneumococcus is a frequent pus-producer, how is it that pus is hardly ever found after acute pneumonia, even when the lung has broken down?

Chemical Products of the Pneumococcus.

These were first extracted from the blood and tissues of rabbits suffering from pneumococcal infection. The organism was inoculated into the pleural and peritoneal cavities, so as to obtain the local lesions, and the animals were killed as their symptoms indicated. There was always severe pleurisy in the cases of chest inoculation, the false membrane being grey or blackish-grey. Consolidation more or less of the lungs was frequent, or else a severe congestion; in two cases pneumonic consolidation of an entire lobe was found, the air cells under the microscope being filled with granular fibrin. Pericarditis was usually present also. In the cases of peritoneal inoculation, in addition to the local lesions, there were often congestion and exudation in the thorax.

The extraction of the tissues is a long and tedious process, occupying many weeks. A summary of the method will suffice here.

Mode of Preparation.—The local lesions, lungs and spleer, were minced and pounded, and, together with the

blood, placed in a large quantity of rectified spirit. After standing for from four to six weeks the spirit was filtered off, and the residue extracted with water. This was accomplished in twenty-four hours, and was assisted by an electrically-driven "shaker". The watery extract was filtered from the coagulated proteid, refiltered, and then, as also the alcoholic filtrate, evaporated *in vacuo* at 37° to 40° C. The concentrated liquids were then mixed and thrown into a large excess (8 to 10 times their bulk) of absolute alcohol. A large precipitate fell, which was again extracted with absolute alcohol, filtered, and washed with alcohol. This precipitate was then dried at 37° C., and the resulting product was a very fine cream-coloured powder, which gave all the characteristic reactions of an albumose. It was soluble in water, completely precipitated by saturation with neutral ammonium sulphate, and gave a distinct biuret reaction. The entire quantity obtained from the lungs, spleen, and blood of six rabbits was less than three-quarters of a gramme.

The alcoholic filtrates were then added together and evaporated *in vacuo* to a very small bulk at 37° C. This was again thrown into absolute alcohol and allowed to stand for ten days. It was again filtered, evaporated, and the residue washed with alcohol. This residue was then a reddish-yellow amorphous substance having a somewhat viscous consistence. It was agitated and re-agitated with ether, when a considerable quantity of fatty matter and free acid was dissolved out. The precipitate in ether was finally thrown into chloroform, and the final product was a yellow amorphous substance, nearly altogether freed from its previously viscous character. The quantity obtained of this substance amounted to 0·5 gramme. When tested it was found to be strongly acid, very soluble in water, and gave no colour reactions with Millon's re-agent or potassio-mercuric iodide, nor was any biuret reaction given. Whatever else this substance contained, it was evident that it contained a large quantity of an organic

acid. Both the ether and residue gave Uffelmann's reaction for lactic acid.

It may be mentioned that the tissues were extracted in the manner described twice over. There was no difference in the results, a relatively small quantity of albumose and a still less quantity of an organic acid being yielded.

Effects of the Albumose and Organic Acid.

Both the albumose and organic acid were then tested on rabbits. The former was injected in doses of 0·02 gramme (1) intravenously (in salt solution); (2) into the pleural cavity; (3) underneath the skin of the ear. The result of the intravenous injection in a rabbit weighing 2,480 grammes was initial shock and fall of the temperature over 1°. In an hour or two the temperature began to rise, and in three hours had risen to 104·8° F. (the normal temperature of a rabbit is about 102·6° F.). Next day it had fallen to 103·4° F., and then gradually sank to the normal. No other pathological effect was produced, but the animal lost slightly in weight.

The result of the intrathoracic injection was very interesting. There was no initial depression, but marked dyspnœa soon set in. This continued and was accompanied by a rise of temperature to 103·8° in three hours. Next day the dyspnœa was still present, and the temperature 103·4°. On the third day the animal was killed. There was right-sided pleurisy, and the entire lower lobe of the right lung was completely consolidated. No other lesions were found. Inoculations were made from the blood, and also from the serum in the pleural cavities in solid and liquid media, with a negative result. Double the quantity of albumose was also intrapleurally injected in another rabbit. Next day the temperature was 104·6°. On the following day the animal was killed and severe right lateral and also diaphragmatic pleurisy was found, with pericarditis and hard consolidation of the upper part of the lower lobe of the right lung. The injection beneath

the skin of the ear in a rabbit weighing 2,550 grammes gave the following results: The temperature slowly rose to 104° on the following day, and the ear was inflamed. Next day the ear was greatly inflamed and swollen, and a bloody serum issued from one or two cracks in the skin. The temperature rose to 106·2° on the third day. It then gradually fell, and the inflammation subsided, until on the sixth day it was nearly all gone. The animal lost 60 grammes in this time.

The consolidation in the lower lobe of the right lung was very typical of ordinary lobar hepatisation. It was one of the best examples I have seen of lobar consolidation in this animal.

The effects of injecting the organic acid or at least the acid residue were very slight. The intrapleural injection of 0·1 gramme produced no result. The intravenous injection of a similar quantity was followed by slight rise of temperature (about 1° F.) in the course of a few hours. Next day it had returned to the normal and the animal remained well.

Chemical Products of the Pneumococcus in Artificial Media.

The organism used was one of moderate virulence and it was grown in veal peptone bouillon previously rendered alkaline. As the commercial peptone used for the broth contains much albumose, it was resolved also to try cultivations in broth made without peptone, and the organism grew freely in this medium. In addition, an artificial serum was made containing pure alkali albumin, and the various salts which exist in normal blood, in their respective proportions. The serum was prepared according to the formula given by Dr. Sidney Martin in his anthrax investigations.* The reaction of the broth must be alkaline to ensure a successful growth.

As soon as the organism has grown, the previously alkaline medium becomes distinctly acid, and this acidity is

* *Local Government Board Reports*, 1889-90.

permanent. After two days' growth the cultures were filtered through a Chamberland candle, and the clear toxine evaporated at 38° C. to a sixth of its bulk, thrown into absolute alcohol, and the copious precipitate obtained treated exactly in the same way as already described in the case of the tissues extraction. In like manner the alcoholic filtrate was evaporated and the residue purified. Both products in appearance and chemical reactions were exactly similar to those obtained from the tissues, one being an albumose and the other an organic acid, a lactic acid reaction being obtained by Uffelmann's test. Injected into animals also they produced similar effects to the tissue products, but the dose of albumose required was very considerably larger. This is to be explained by the production of much weaker toxines in ordinary media than in the living body. A large dose of the albumose (½—1 gramme) was also injected into the peritoneum. The temperature rose to 105·4°, and continued high (nearly 104°) for about three days, and the animal lost 56 grammes in weight.

Rôle of the Albumoses.

From these observations we may infer that the albumoses produced by the pneumococcus are the cause of the temperature and more obvious lesions of that disease. Certain other considerations also seem to point to an albumose as being itself the toxine and not merely the particular proteid to which an hypothetical toxine has attached itself. In particular this view is supported by the results obtained on examination of the filtered bouillon toxine, to which no peptone had originally been added. After two days' growth this filtrate gave a biuret reaction which was entirely absent from the original (control) bouillon. The filtrate also gave a fairly copious precipitate with alcohol and ammonium sulphate. It seems evident from this important reaction that a proteid is formed by the organism from nitrogenous material, the proteid so formed being excreted after digestion as an albumose. It is perhaps hardly

necessary after this to add that the albumose was also formed in the artificial serum.

The views of Sidney Martin may be alluded to in this connection. He has explained the production of toxic albumoses in diphtheria and certain other conditions by the digestive action of the chemical enzyme or toxine produced by the organism on the albumins of the tissues or of artificial serum. The enzyme he supposes to exert this action outside the organisms themselves. Thus in the case of diphtheria the enzyme is absorbed from the lesion, and exerts its digestive action on the albuminous constituents in the spleen and elsewhere.

There is no reason to suppose that albumose may not be formed by either means—by the organisms themselves or by a chemical ferment liberated from them and acting at a distance. The difficulty of deciding as to enzyme action lies in the fact that it is not possible to isolate the enzyme from the albumoses. It is carried down with all precipitants of the latter, but its presence can usually be got rid of by heating to 70° or 80° C. In the case of diseases, therefore, where a toxic albumose is found in various organs and tissues apart from the micro-organisms themselves, it may be due to enzyme action locally, but the reactions described lead us also to believe that it may be derived from the primary lesion by diffusion through the blood and tissues.

Although the temperature reaction and possibly also the consolidation of pneumonia may be ascribed to toxic albumoses, other considerations point to the fact that these relatively simple metabolic products, though having much to do with the superficial phenomena, yet do not form the essence of the disease. On the other hand it seems clear that more complicated bodies, the products of specific reactions between the living bacteria and special cells of the body, whose nature can only be so far guessed at, are the dominating factors of the situation. In the succeeding chapter this matter will receive further consideration.

CHAPTER III.

PNEUMONIA (*continued*).

THE next part of this investigation relates to the methods devised for raising the strength of pneumococcus toxine, and the effects produced by the injection of the toxines into rabbits in connection with the process of immunising. Nearly two hundred animals were experimented upon. A few experiments were first carried out with living cultures, and these may first be referred to.

Cultivations in veal bouillon were carried over a few times. After the third or fourth carry-over a two days' growth was permitted, and doses of one to two cubic centimetres of the living culture inoculated subcutaneously. But little effect was produced. In a day or two, one or two cubic centimetres of a stronger (second carry-over) culture were inoculated, and in a few days more similar quantities of a first bouillon cultivation two days old. Afterwards virulent cultures were inoculated. The results proved that inoculation of the weak cultures had conferred resistance. For instance, three rabbits received 1 c.c. of a weak culture into the flanks on the first day. On the third day they received 2 c.c.; on the sixth day 2 c.c. (of a stronger culture) and on the ninth day 2 c.c. These inoculations raised the temperature about one degree F., but could scarcely be said to have affected the weights. On the twelfth day these animals and a control were inoculated with a virulent culture. The control was dead next day, but the vaccinated animals merely showed very high temperatures (105° to 106° F.) without much sign of

illness otherwise. They also partook of their food. The temperatures remained high for about four days and then quickly fell to about the normal.

Being satisfied that rabbits could be successfully vaccinated against the pneumococcus by means of living cultures, I next turned my attention to the manufacture of a toxine from the organism by means of which an active immunity might possibly be conferred. The first experiments consisted in evaporating the bouillon filtrate (obtained through the Chamberland candle) *in vacuo* at 37° C. to very small bulk. Doses of one and two cubic centimetres of this concentrated toxine administered subcutaneously gave but a very moderate reaction which soon passed off. These injections were repeated until 10 or 12 c.c. had been given. The immunising process was completed by the final administration of living cultures as in the former cases. Tested with virulent pneumococci at short periods afterwards—a week to two weeks—these animals also presented more or less marked degrees of resistance.

The disappointing results hitherto obtained from the toxine, even when concentrated in the manner described, led to the institution of a number of experiments with the nutrient medium. One medium was made with decalcified bouillon * to which five to ten per cent. sterile horse's blood-plasma was added. A second medium was made by adding the red layer of horse's blood to ordinary bouillon; a third, by adding both plasma and red corpuscles to the bouillon; a fourth, by adding ten per cent. Loeffler's serum; and a fifth, by adding a considerable quantity of precipitated chalk to the bouillon. The precipitated chalk was also added to the bouillon which contained the red layer of horse's blood. The addition of the chalk was with a view to counteract permanently the lactic acid

* To decalcify bouillon, add 20 c.c. of a saturated solution of sodium oxalate to a litre of bouillon. Allow to stand for one hour, filter and sterilise. It should give a precipitate with calcium sulphate, but none with ammonium oxalate.

which the organism forms, and which, as already mentioned, appears to inhibit its growth.

These media were first implanted with the blood of rabbits which had previously been inoculated with pneumonic sputum. After two to five days' growth the cultures were filtered, and varying quantities of the toxines (2 to 20 c.c.) injected subcutaneously and also intraperitoneally in rabbits.* The general result of these experiments was merely a slight and transient elevation of the temperature.

The same toxines were again injected into a fresh batch of rabbits, beginning with 2 to 5 c.c. and gradually increasing the dose to 15 c.c. These injections were given twice a week, until, by the fourth week, 40 or 50 c.c. had been administered. To others larger doses, both subcutaneous and intravenous, were given: 10 to 20 c.c. at an injection until 50 or 60 c.c. had been reached. All these experiments were done with strict regard to the weights and the temperatures. For instance in the case of No. 1: 1st day, T. 102·6°, weight 3,540 grammes, 2 c.c. blood and plasma toxine subcutaneous; 3rd day, T. 103°, weight 3,542 grammes, 5 c.c. toxine subcutaneous; 6th day, T. 103°, weight 3,550 grammes, 10 c.c. toxine intravenous; 8th day, T. 103°, weight 3,570 grammes, 10 c.c. toxine subcutaneous; 12th day, T. 103°, weight 3,600 grammes, 15 c.c. intravenous; next day the temperature was 103·2°, and the weight had fallen to 3,530 grammes. The weight kept falling for thirteen days until it reached 3,165 grammes. Then it began to rise and gradually rose above the original weight. In the case of another animal the weight fell from 3,400 grammes at the end of the injection to 3,105 on the eighth day after the last injection, it then gradually rose to 3,150 grammes and remained stationary for twenty days, when complete extensor par-

* As the experiments were nearly all made on rabbits, it is to be understood (to avoid repetitions) that these are the animals referred to, unless otherwise specified.

alysis of the forelegs set in. The animal became very ill, temperature 104°, hair rough, and it seemed about to die. It continued ill for many weeks, but then began to recover slowly from the paralysis, and in about three months it had gained considerably in weight and seemed quite well again. Generally in the others the weights increased, but in some of the cases there were temporary losses during the second week or so. Four weeks after the last in-

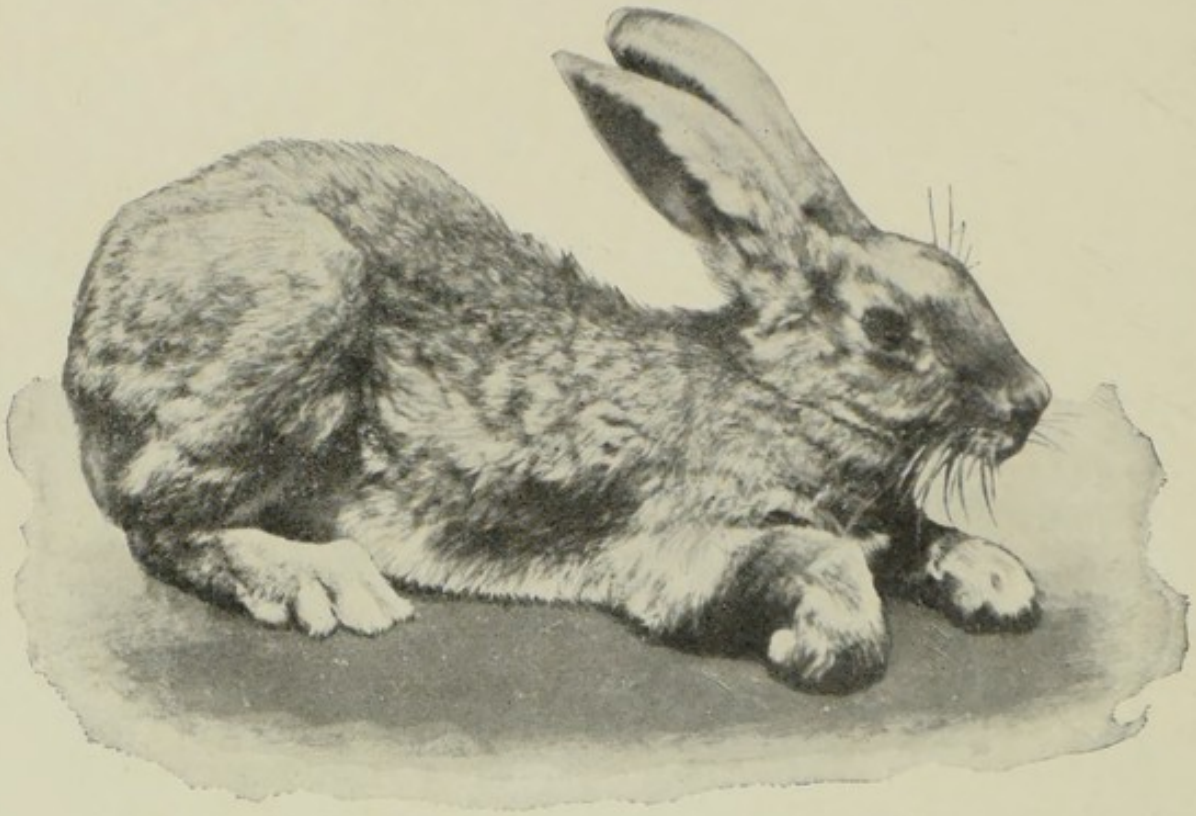

FIG. 5.—Rabbit with extensor paralysis of forelegs, the result of pneumococcus toxine. Shows well the position in which the animal lay.

jections all the animals, with two controls of nearly the same average weights, were tested with virulent pneumococci. The day after inoculation I was surprised to find that all, except three and the controls, were dead. On the third day only one of the controls was alive. On the fourth day this control was dead. After the paralysed rabbit had completely recovered (and not until four months after the last injections) it and a control were tested with virus. Next day the paralysis had returned exactly as

before. Two days afterwards it died, the control surviving it by about eighteen hours.

Believing that the animals had (with possibly one exception) been, to some extent at least, immunised by the toxine, the results were both a surprise and a disappointment. It seemed clear that either any active immunity produced had passed off entirely after a few weeks, or else that the toxine injections only served to render the animals more sensitive.

Fresh Set of Experiments.

A new organism was obtained and carried over in rabbits to the third generation when its virulence was much heightened. After three or four days' growth in the same media, the toxines were filtered off and injections made as before. The results were again disappointing, 20 and 30 c.c. being necessary to give a temperature reaction of over one degree. A curious effect of the toxines now began to come out (subsequently confirmed), *viz.*, that sometimes the animal dies suddenly after two or four weeks or longer, without showing any signs of previous illness, except usually some persistent elevation of the temperature, and without any discoverable *post-mortem* changes. One animal (of this series) died thus on the fifteenth day after inoculation, and another was found dead on the twenty-first day.

A fresh intrapleural inoculation was made from the virulent blood (which had been preserved in a sealed bulb). This was carried over, until at the fifth transmission a single drop of the infected blood was lethal within twelve hours, and at the sixth transmission the organism had acquired such virulence that the smallest loopful of blood killed in eight hours without producing any local lesion—the blood swarming with capsulated diplococci. Finding the former media disappointing, I confined the cultivations to veal bouillon rendered highly

alkaline with precipitated chalk* and to alkaline veal bouillon with 20 per cent. horse's serum. This highly virulent organism grew very richly, especially in the serum bouillon. It continued growing for ten days, forming a thick deposit, and also numerous large flakes and strings suspended in the medium. In the serum broth a fine film formed on the surface, from which the flakes and strings grew down. In this case, as in all the others, the organism was isolated from the medium and subjected to microscopical and other examination. In the case of the serum bouillon the organisms were surrounded with clear capsules, making a striking and beautiful appearance. After a fortnight's growth the media were filtered and injections made which gave the following results: In doses of 10 to 20 c.c. subcutaneous an illness was induced, with rise of temperature, from which the animals recovered, the serum toxine producing the stronger effect. In doses of 30 c.c. there ensued illness with a high temperature (104° to 106°), loss of weight and generally death from the tenth to the fourteenth day. When the toxine was heated to 65° C. the effect seemed to be distinctly more marked in respect of (1) greater rise of temperature, (2) production of diarrhœa, (3) greater intoxication and prostration. The diarrhœa is specially liable to come on when much toxine is administered, and *post-mortem* examination reveals a large quantity of very fluid bile in the small intestine. A dose of 30 c.c. of heated toxine proved fatal to animals weighing 2,700 grammes.

One animal which received 10 c.c of the plain toxine, and in two days thereafter another 10 c.c., gained weight all along, and on the thirty-first day it was inoculated with a virulent culture. Next morning it was found dead.

An attempt was again made to raise the strength of the toxine. The method adopted was to inoculate veal bouillon,

* The flasks were shaken up every two or three days in order to disperse the chalk through the culture medium.

rendered alkaline in the manner described, with the highly virulent organism. After one day's growth sterile horse's serum was added to one set of the culture flasks, which were also at the same time re-inoculated with the organism. To another set of the bouillon flasks the blood obtainable from two rabbits dead of virulent pneumococcal infection was added. Then after two days a fresh quantity of similar blood was added, and after two days again a third quantity. A luxuriant growth was obtained, and after ten days the bouillon thus treated was filtered. It was found, however, that, notwithstanding these measures, the lethal dose of the blood-bouillon toxine was about 30 c.c. for animals weighing from 2,500 to 3,000 grammes. It was found impossible to measure this accurately, as the animals showed different degrees of susceptibility. It may be taken, then, that the toxines obtained from the various cultivations with the very virulent organism were for all practical purposes of identical strength; the presence in the culture medium of a considerable percentage of the blood of the same species was not attended by the corresponding increase in strength which one might naturally expect.

A new fact now came out with regard to the action of the toxines. It was found that in animals previously treated with toxine the subsequent injection of the toxines themselves was followed by severer symptoms than in the case of normal animals. In the normal animal 30 c.c. of serum toxine proved fatal after a week or fourteen days, but in animals previously treated with smaller doses of toxine this amount of toxine caused much severer symptoms and death earlier. Also, 20 c.c. injected into animals previously treated with toxine caused in some instances death after ten or eleven days—a result never obtained in the case of normal animals. One such case is as follows: An animal weighing 2,170 grammes received 10 c.c. of toxine. After two days it again received 10 c.c.; its weight next day was 2,130 grammes and T. 103·4°. After two months

it received 20 c.c. of toxine subcutaneous. Its weight had by this time advanced to 2,710 grammes. Next day it was very ill, refused food, T. 105°, weight 2,620 grammes. The temperature kept high (about 105·4°) and the weight steadily fell to 2,290 on the tenth day. It died on the eleventh day and had slight diarrhœa. In one of the animals the toxine injection produced paralysis, which was also confined to the forelegs, as in the former case.

I shall next give the results of the action of the serum toxine administered in different ways to five animals, with a view to immunising. No. 1, weight 2,080 grammes, received 10 c.c. subcutaneous on the first day; after two days it again received 10 c.c. subcutaneous, the weight remaining the same. Next day the temperature was 103·2°. It was then allowed to stand over for six weeks, when its weight had risen to 2,760 grammes. It then received 15 c.c. of serum toxine intraperitoneal. Next day it was ill, had not taken any breakfast, and T. 103·4°. In a few days it recovered, and on the seventh day it again received 10 c.c. of toxine subcutaneous, weight at the time 2,710 grammes. Next day thet emperature was 103·4°. A week afterwards its weight had risen to 2,800 grammes. After two weeks the weight was 2,780 grammes. Altogether, this animal received 50 c.c. of toxine between 4th April and 1st June.

No. 2, weight 2,710 grammes, received 10 c.c. of toxine subcutaneous. Next day it refused breakfast, but its temperature was normal. After eight days it had quite recovered and its weight had risen to 2,960 grammes, when it again received 10 c.c. of toxine subcutaneous. Next day its temperature was 103·4°. After a week it was well and the weight had advanced to 3,120 grammes. After another week the weight was 3,150 grammes. This animal received, therefore, 20 c.c. of toxine between 1st June and 8th June. On 22nd June, twenty-one days after No. 1 had received its last toxine injection, and fourteen days after No. 2 was last injected, the weight of

the former being 2,800 grammes and of the latter 3,150 grammes, they were inoculated with pneumococci along with a control weighing 3,005 grammes. In all three a prominent swelling formed at the side of injection in the abdomen. On the second day No. 2 was dead and on the fifth day No. 1 was dead. In the control the swelling turned into an abscess, discharging pus externally. It ultimately recovered.

In these cases the dose of pneumococci was measured and it was purposely used of but a moderate degree of virulence. The remarkable fact is that the control survived, but at the same time it will be seen that No. 1 outlived No. 2 by three days, notwithstanding that it had received considerably more toxine. But, on the other hand, the last toxine injection of No. 1 was made a week previous to that of No. 2.

No. 3, weight 1,890 grammes, received 10 c.c. of toxine subcutaneous on 2nd June. It received no more, and on 29th June its weight was 1,980 grammes.

No. 4, weight 1,870 grammes, received also 10 c.c. of toxine intravenous on 17th June. On 29th June its weight was 2,230 grammes.

No. 5, weight 2,050 grammes, received 20 c.c. of toxine on 16th June. In three days its weight had fallen slightly to 1,995 grammes. On 29th June it had risen to 2,250 grammes.

These three, with a control weighing 2,150 grammes, were tested with virus (as in the former cases) on 29th June. In each a hard local swelling formed in the abdomen. Next day No. 4 was dead; after two days No. 3 was dead; in two and a half days No. 5 was dead, and on the third day the control was dead. Examination of the abdominal swelling showed a hard mass of fibrin and infiltration of the neighbouring tissues. In No. 3 there was a patch of pneumonia in the base of the right lung.

In these cases also the control survived longest, and

the most susceptible animal was No. 4, which received 10 c.c. of toxine intravenous thirteen days previously.

The toxine was next injected into fresh animals, beginning with very small doses : ½ c.c. subcutaneous, increasing by ½ c.c. every third day until the twelfth day, then 2 c.c. and so on, until the dose reached 5 c.c., and then final doses of 10 c.c. were given. One or two of the animals died quite suddenly during this period—a circumstance already alluded to. The others gained in weight. They were all (except one) tested by virus at varying periods from the twenty-first to the forty-second day. The result was the same as in the other cases : they succumbed before the controls. The excepted animal was permitted to survive two months after receiving the last injection. It weighed 1,900 grammes at the commencement of the injections on 12th October, and received 40 c.c. of toxine between that date and 21st November, when its weight had advanced to 2,730 grammes. On 24th January it was tested with virus of medium strength along with two controls. Next morning it was found dead and both controls living. On the following day one of the controls died. The second control survived for four days.

The last experiments I shall mention here refer to the results obtained a long period after the toxine injections. Nine animals which had received from 40 to 50 c.c. of toxine each, half subcutaneous and half intravenous, were kept for eight months. They then received, together with a control of the same average weight, a measured dose of virus. Next day all were dead except three and the control. On the following day the control and two more were dead. On the fourth day the last one died. In this case, then, one of the injected animals outlived the control. But in view of the general results this circumstance cannot carry much weight. It would therefore appear that the effects of the toxine remain for a very long period in the susceptible tissues of the animals.

Dr. Cartwright Wood, from whom I received most

valuable assistance in conducting these investigations, undertook to grow the virulent organism in veal bouillon rendered highly alkaline, as used for the production of diphtheria toxine.* Growth took place extremely well in this medium, and after ten to fourteen days the cultures were filtered. The results were not materially different from those produced by the serum toxine made alkaline with chalk. It proved fatal to rabbits in about the same doses, and Dr. Wood found that in doses of 10 c.c. intraperitoneal it proved fatal to guinea-pigs weighing about 500 grammes after the lapse of about twenty hours.

Meaning of the Experimental Results.

The most notable result of these experiments is the uniform occurrence of an increased degree of sensitiveness to the pneumococcus and its toxines in the animals previously treated with the toxines themselves. This phenomenon has bearings of great intricacy and importance, and claims close consideration. Another result of interest which may be alluded to is the occurrence of foreleg paralysis in two of the research animals—so far as I am aware, a condition hitherto undescribed. Paralysis occurring after pneumonia in man, though by no means common, has nevertheless been noted by a good many observers. Lately, this subject has been investigated by Janakief,† who recognises an early group and a late group of cases, the latter occurring quite at the end of the disease or during convalescence. The forms are variable: purely localised in an arm or leg, crossed, ascending, etc. The paralysis may also affect the palate and ocular muscles (internal and external). Some cases lasted a few weeks, others from two to twelve months. Death may occur from the bulbar involvement. As regards our experimental

* The bouillon is first rendered neutral to phenol-phthalein, then 5 c.c. of normal soda added per litre.

† *Thèse de Lyon*, 1900.

cases, there is reason to believe that the toxine has a selective affinity for the nerves of the upper extremities, which may or may not be related to the circumstance of the thoracic region being the usual seat of the pneumococcal infection. It is also to be noted that the paralysis lasted for months, and that some time after the apparent recovery of the animal a fresh dose of toxine caused its immediate recurrence, thus demonstrating a latent degree of weakness or degeneration in the involved nerves and their centres.*

Notwithstanding the high degree of virulence to which the organism was raised, the resulting toxines were correspondingly weak: the minimum lethal dose being about one hundredth part of the weight of the animal. Other observers have found that the toxines obtained by filtering the blood and exudates of animals dead of virulent pneumococcal infection are fatal to normal animals in about the same proportion.

Returning to the phenomenon of increased sensitiveness which the research animals exhibited both to the organism and its toxines, we have a problem exposed which in the light of our present knowledge is to some extent at least amenable to explanation. It seemed to me at first that the results obtained were merely the evidence of failure to properly adjust the doses of the toxine, as we are well aware of the occurrence of supersensitiveness as an occasional phenomenon under many conditions. It has been observed during the immunising process against diphtheria, against tetanus, against snake-venom, against plague, against the *vibrio Metchnikovi* and against hog-cholera, at least so far as the toxines are concerned, and the same underlying causes doubtless determine the reaction to tuberculin which tuberculous subjects display. But the constancy of its occurrence in the experiments herein described, and

* A woman (*æt.* 45) was lately shown me, by Dr. A. Morison, who had paresis and wasting of the muscles of the left hand and forearm, with pain at night, which dated from an attack of pneumonia seven years previously. In this case both flexors and extensors were more or less involved.

under all circumstances of dosage, seemed to be something novel and quite inexplicable.

Some time after these experiments were published I came across a paper by B. Issaeff, entitled "A Contribution to the Study of Immunity acquired against the Pneumococcus".* The investigation was made at the suggestion of Prof. Metchnikoff, and within his laboratory. The first part of it is devoted to a consideration of the contradictory views which various authors have set forth as to the causes of the immunity acquired against this organism. Thus Foa and Carbone, and afterwards Emmerich and Fawitzky, had alleged that they cured pneumonic septicæmia in rabbits and mice by the injection of the serum of animals vaccinated against the pneumococcus, and regarded the action of the serum as bactericidal. Krause and Pansini had seen a progressive diminution in the number of the organisms when mixed *in vitro* with the serum of vaccinated animals. Behring and Nissen had affirmed that in the serum of vaccinated animals the pneumococci grew well, but gradually lost their virulent properties, until they became inoffensive. Others again (Mosny, E. and F. Klemperer) found no diminution in the virulence of the organism when grown in the serum in question, and explained the immunity by the exercise of antitoxic qualities on the part of the serum of vaccinated animals, the serum directly neutralising the toxines. Thus three views had been advanced by different investigators: the bactericidal view, the theory of attenuation of the microbes, and the antitoxic theory.

After detailing the various experiences he had with the strength of the toxines and the results of passing the organism through a successive number of rabbits to exalt its virulence—experiences which completely correspond with those obtained in my own investigations—Issaeff describes the methods by which he immunised

* *Annales de l'Institut Pasteur*, 1893, p. 260.

rabbits against the pneumococcus, and the effects of the injection of toxines into rabbits so immunised. Briefly, he immunised some animals by the intravenous or intraperitoneal injections of the virulent blood (of rabbits dead of pneumococcal infection) which had been sterilised by heat or by chloroform water. Others were treated with the toxines obtained from the blood by filtration; others by the sterilised pleuro-peritoneal exudate; and yet others by successive injections of bouillon or serum cultures which had been subjected to heating. Animals prepared by these methods were always submitted to injections of the fresh blood of rabbits newly dead of the pneumococcus, beginning with two to four drops, intraperitoneal. These inoculations were repeated until in the course of four weeks nine injections of the virus had been administered. Most of the research animals received five injections of toxine and nine injections of virus.

After the animals had completely recovered from their illness they were experimented upon with the toxines of the pneumococcus, either obtained from bouillon cultures, sterilised in diverse fashions, or separated by filtration from the blood and exudates. From 20 to 35 c.c. were injected directly into the auricular vein, except in one instance, when the toxine was injected into the peritoneal cavity. Sixteen of the vaccinated animals were made the subjects of experiment, alongside an equal number of animals inoculated with pure bouillon (*i.e.*, control animals). The results of the sixteen experiments were alike. "*Notwithstanding variations in the individual receptivity, the vaccinated rabbits always reacted to the toxines in a more energetic manner than the controls.*" Several of the vaccinated animals died, the corresponding controls either surviving or dying some time after. "We are convinced," he goes on to state, "that rabbits which have been rendered completely refractory to pneumococcal infection remain sensitive in a high degree to the toxines of the microbe. Even weak doses of toxine (from cultures in bouillon) are unable to

be neutralised in the blood of vaccinated rabbits." And so the conclusion is come to, that no antitoxic property can be admitted as existing in the blood of animals vaccinated against the pneumococcus.

In further experiments Issaeff obtained results which lead him to state that the pneumococcus when cultivated in the serum of vaccinated animals has not lost the power of producing its toxines. On the contrary, the organism retains its pathogenic properties for about eighteen hours, and it is, according to this observer, the dispersal of the toxines throughout the body which in vaccinated animals provokes a positive chemiotaxis of the phagocytes to the seat of infection, resulting in the destruction of the bacteria.

Although the experiments of Issaeff are on different lines from those which I carried out, yet the two sets of results harmonise in the most perfect manner.

In Issaeff's experiments it was found that animals rendered completely refractory to the pneumococcus contained no antitoxine in their blood. The resistance must therefore have been conferred by other and more complex bodies, probably of the nature of bacteriolysines. Now we know that the latter bodies (by whatever name called) can only be produced by immunising with either the living or dead bacteria themselves, or, as in the case of the filtered fresh blood, with the products of their solution. In treating animals with Chamberland-filtered artificial toxines, as in my experiments, the only anti-bodies they could be expected to call forth are the antitoxines, which, as we have seen, they completely fail to do. Consequently the subsequent inoculation not only of these toxines themselves, but also of the virus, must necessarily be ineffective. Not only so, but the action of the toxines can only be a source of injury to the animals, and herein we find the explanation of their increased sensitiveness.

Experiments having shown that the immunising serum obtained from rabbits vaccinated against the pneumococ-

cus is not antitoxic, but bactericidal, or, in other words, according to the side-chain theory propounded by Ehrlich, it contains a body which has two haptophore groups, one which combines with the bacterial cell and the other or "grappling arm" that which attaches the ferment (from the serum) to which the solution of the cell is due: we see that it is the complex albumins of the bacteria themselves which, by specific action on certain cells of the organism, give rise to the immunising body or bodies.* The albumoses, or simple products of the bacteria, are only harmful and aid in no way, so far as at present known, in the immunising process against the pneumococcus. We may presumably connect the occurrence of leucocytosis in pneumonia with the formation of the bodies in question.

We find additional confirmation of this in the circumstance, first noted by Behring,† that the amount of antitoxine in the blood of an animal might diminish, while its resistance actually increased. Thus in horses, he found that the amount of diphtheria antitoxine in their blood might fall to a hundredth of what it once was, and yet the immunity of the horse be greater than it was before. Here the immunity must necessarily have been produced by anti-bodies of the nature of the lysines, etc.

On the other hand, Behring has also shown that the sensitiveness of an animal to a specific toxine may actually increase when there is abundant antitoxine in the blood, and instances horses, sheep and goats which he found to react to even the millionth part of that dose of tetanus toxine which had no action whatever on untreated members of the same species. The usual explanation of this phenomenon is that, owing to the slow action of antitoxine on toxine, the latter reaches the susceptible tissues first and

* It is stated by Foa and Scabia that a watery glycerine extract of dead pneumococci forms a good immunising medium.—*Gaz. Med. de Torino*, xcii., 13, 14, 16.

† *Deutsch. Med. Wochen.*, 1894, s. 251.

exerts its action upon them. But this view alone seems inadequate, as it does not seek to explain why the antitoxine should be able to neutralise the toxine in one case before it reached the tissues and not do so in another.

However, in the case of pneumococcus toxine it has been shown that the problem of hypersensitiveness is not complicated with the presence of antitoxine in the blood, and the questions, therefore, which naturally suggest themselves are, first, why no antitoxine is produced, and second, what is the immediate cause of the sensitiveness.

So far as our present knowledge goes, these phenomena must be regarded as mutually dependent. Again, on Ehrlich's theory, we must have an excessive accumulation of side-chains in the susceptible cells, and likewise the *failure to cast them off into the blood as antitoxines*. Such overloading of the cells would of course cause their injury and so render them more susceptible to fresh doses of the toxine.

But when we come to ask why it is that the side-chains are not cast off into the blood, we enter the realm of theory pure and simple. The only consideration which I would venture to suggest is this: according to the view which has been so elaborately propounded by Ehrlich, the haptophore groups of the toxines come into binding union with their appropriate side-chains immediately after injection into the body, whereas the toxophore groups (or those which cause injury to the cells) only come into action after the lapse of a considerable time, corresponding to the period of incubation of the illness. It is interesting now to note that those diseases which are characterised by the longest periods of incubation are, as a rule, followed by the most complete degrees of immunity. The period of incubation of pneumonia is extremely short, merely a few hours. It may therefore be legitimate to consider that the short time which elapses between the anchorage of the haptophore group and the coming into play of the toxophore group, in the case of the toxine of pneumonia,

may prevent the cell from acquiring the power of throwing off its side-chains into the blood in a sufficiently free manner.

In conclusion, this research, though only fragmentary, may help to an understanding of certain phenomena which characterise pneumonia in Man. Two facts may be explained. One refers to the frequency of its recurrence. Those who have once had pneumonia remain afterwards more susceptible to it. This proves the immunity to be of short duration. And our experiments prove that this immunity can only be caused by certain complex "anti-bodies" whose duration is also but short. On the other hand, the experiments show that the action of the toxine is injurious, and that this action is of very long duration, far outliving the presence of the immunising "anti-bodies". To this prolonged action we must ascribe the susceptibility to future attacks of the disease in the case of Man.

The second fact refers to the production of passive resistance. Hitherto it may be said that the serum treatment of pneumonia in Man has so far failed. Washbourn in particular made careful experiments in this connection with the serum of horses which had been under treatment for a prolonged period. But if the view herein taken be correct, that the immunising bodies are not antitoxines, we find a way out of the difficulty. For it is now recognised that the immunising sera produced by the specific actions of the bacteria themselves may be limited in their operation to individuals of the same species, as in these the "immune body" finds its appropriate "complement". Hence we should look for the successful treatment of pneumonia in Man by the administration of serum taken from immune human beings, or possibly from apes.

CHAPTER IV.

BRIGHT'S DISEASE.

First I shall describe the morbid changes found in the pia mater, then certain lesions of the Malpighian bodies; the causation of renal œdema next claims attention, and lastly I shall deal with some considerations based on anatomical data respecting the cause of the polyuria which is so constantly observed in the contracting form of Bright's kidney.

The Pia Mater.

I have been enabled to examine the pia mater of all brains removed in the *post-mortem* room during a period of eighteen months. In each case the membrane was carefully hardened in Müller's fluid and alcohol, then dehydrated, and soaked for some days in gum and sugar solution. From the resulting sections some valuable facts were obtained; and, in particular, I have been enabled to make out by means of high powers what seems to be the true nature of the hyaline-fibroid thickening of Gull and Sutton. As is well known, these authors contended that in Bright's disease the blood vessels throughout the body, and especially those of the pia mater, had their outer coats thickened by the deposition therein of a hyaline-fibroid material, probably derived from the blood. The muscular coat in such vessels they conceived to be atrophied, while the inner coat frequently, but by no means invariably, partook of hyperplastic change. This theory received a most damaging criticism from Johnson,

who strongly maintained the truly hypertrophic condition of the muscular layer, while the so-called "hyaline-fibroid" he alleged to be a delusive result of reagents, such as glycerine and acidulated mounting fluids. In 1873 Grainger Stewart pointed out that, while mounting media undoubtedly had some influence in producing the hyaline appearance, not a few cases exhibited a true fibrous thickening. Dickinson subsequently lent his adherence to this view, but the precise nature of the change is still a theme of discussion. According to my observations, it may be stated generally that in Bright's disease all the coats are thickened. In the vast majority of cases the inner coat shows endarteritis. This change seems very constant in fatty kidneys in adults, though it is occasionally absent in contracting kidney. As regards the muscular coat, there can be little room for doubt that Johnson's contention is so far correct, quite apart from an *apparent* hypertrophy due to contraction occurring at death. Further, it was maintained by this observer that a longitudinal layer of muscle cells could be observed alongside the hypertrophied circular layer in some of these cases. It was asserted by B. Waller that this was an impossibility, and that Johnson mistook the cellular strata of the thickened inner coat for a layer of muscle cells. Some of my sections clearly show that to the inside of the hypertrophied circular coat longitudinal muscular fibres exist, as their straining reactions differ *in toto* from the proximate layers of the thickened intima. There are, however, some cases in which the muscular hypertrophy is far from being a marked feature, and when the disease is advanced degenerative changes attack the hypertrophied fibres. In the case of the outer coat it is plainly shown from these preparations that it is thickened, and the question is, what is the nature of this thickening? Now, after eliminating the possibility of amyloid disease, high microscopic powers reveal, in sections macerated with picric acid and carefully stained, a fibrillar disposition of

the hyaline-fibroid substance, together with the existence of branched corpuscles with dividing nuclei embedded within it. It seems clear that this formation owes its origin to a slowly progressing inflammatory new formation of connective tissue. Not only so, but this corpuscular activity is manifest throughout the connective tissue of the pia mater generally, leading to a more or less general thickening.

From these observations it is to be concluded: 1. The hyaline-fibroid thickening of the outer coat of the vessels is not of the nature of an exudation or deposition of a foreign substance, nor yet a transformation of existing structures. 2. The effect of reagents is, after all, but unimportant. 3. The thickening of the outer coat is due to proliferation of connective tissue corpuscles embedded therein, leading to new formation of tissue; in short, is a slowly progressing periarteritis. 4. This change is probably general throughout the entire tissue of the pia mater. 5. The muscular and inner layers of the vessels show hyperplastic changes; latterly the muscular coat may become the seat of atrophy and degeneration.

In the case of the smallest arterioles their muscular elements were certainly increased in volume, if not also in number,* and their delicate investment of connective tissue was represented by a thick, homogeneous-looking cylinder. It is particularly to be noted, however, that their endothelial lining showed no deviation from the normal, in this respect presenting a marked contrast to the condition prevailing in the larger vessels. The diameter of the channels in these thickened arterioles suffered great diminution; not infrequently it measured just the diameter of the wall.

The Malpighian Bodies.

With regard to the lesions of the kidney itself in chronic Bright's disease, examination of a large number of kidneys

* Herringham states that the muscular coat of the arterioles within the *kidney* is atrophied.

has led me to recognise two main divisions. In one the lesions of the glomeruli and of Bowman's capsule are very marked, and overshadow the other lesions; in the other class the reverse holds good. Greenfield recognises the lesions of the capsule as pericapsulitis or cellular infiltration and tissue-formation occurring chiefly outside this structure, as hyaline thickening of the capsule itself, and as endo-capsulitis or the formation of concentric laminæ of cells and tissue inside the capsule, between it and the glomerular tuft.* Greenfield regards the cells lining the capsule to be capable of originating this formation. Now in acute glomerulitis it is undoubted that layers of epithelial cells are formed inside the capsule, derived from germination of its lining endothelium, and in chronic glomerulitis also concentric layers of cellular-like tissue are in many cases found, which seems so far to be a reduplication of the endothelial lining of the capsule. The appearances leave no doubt as to the derivation of this tissue from these cells, which are in reality epithelial cells. We are unable, therefore, to regard the formation as true connective tissue. On the other hand, one is struck with its general resemblance to the more superficial portion of the Malpighian layer of the epidermis. In the kidney formation, however, the cement substance between the cells is more abundant. It is in reality an epithelial formation, its lamellar disposition being largely due to pressure from within, *i.e.*, exudation round the glomerular tuft.

I wish, however, to note more particularly certain other changes which are found in connection with chronic glomerulitis. These are: 1. The epithelial cells covering the glomerular tuft proliferate, assuming a peg-top or columnar shape, and are desquamated into the peri-glomerular space, where they assume a rounded form. Afterwards they may enter into the formation of the concentric laminæ of cells already alluded to. 2. The

* New Sydenham Society's *Atlas of Pathology*, Fascic. ii., 1879.

capillary nuclei of the Malpighian tufts proliferate and give rise to a new growth of tissue between the tuft and the capsule, having an appearance quite distinct from the epithelial formation. This phenomenon has been questioned by Ziegler and some others, but I have been fortunate enough to come across a case which demonstrated it well. In this instance a band of connective

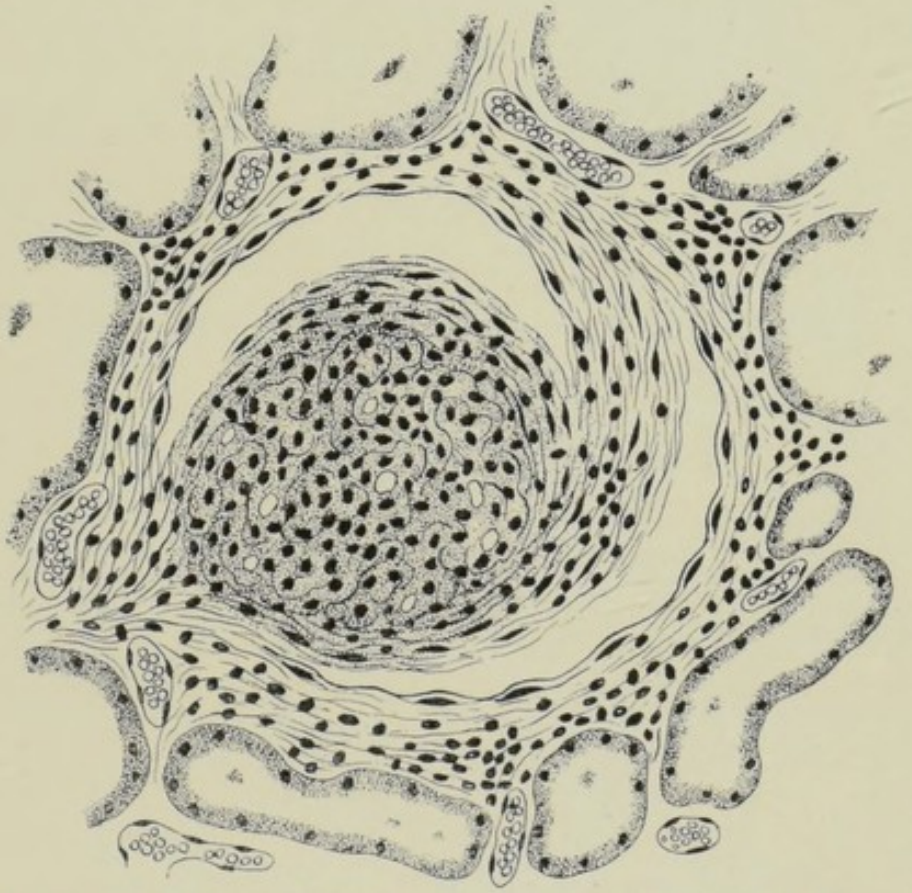

FIG. 6.—Glomerulitis, showing the formation of a band of new connective tissue between the glomerulus and Bowman's capsule.

tissue had formed between a partially sclerosed glomerulus and Bowman's capsule, giving the appearance represented in Fig. 6. To this band numerous epithelial cells had attached themselves, and similar cells were present in the spaces outside. (These are not represented in the drawing, for the sake of clearness.) The manner in which the nuclei from the tuft entered the band at its broadest part left little doubt as to its genesis. It seems not un-

likely that in such cases a fibrinous exudate in the peri-glomerular space fails to undergo absorption, with the result that it becomes organised by cells proceeding from the tuft. In other cases, however, organisation proceeds also from cells derived from the capsule and outside it, when it is impossible to differentiate the resulting lesions. 3. Not infrequently the capsule itself becomes slit up into several layers, giving the appearance of two or more capsules for part of its circumference. This dissecting process is accomplished by cells from the surrounding connective tissue. In other and more advanced cases, the capsule appears striated and concentrically thickened by new connective tissue which blends with the sclerosed glomerular tuft. It is seen, therefore, that in chronic glomerulitis we may meet with a formation of stratified epithelium within the capsule; with a formation of new connective tissue derived from the Malpighian tuft alone, or from both the tuft and Bowman's capsule; and, lastly, we may have a dissecting process involving the capsule, due to proliferation of its connective tissue cells, leading to a concentric thickening and often its amalgamation with the glomerular tuft.*

It is difficult to see why these lesions of the Malpighian bodies should occur in some cases and not in others; they are by no means confined to scarlatinal cases, and, moreover, in post-scarlatinal nephritis which has assumed a chronic form they are occasionally absent.

The Œdema.

The pathology of œdema, and of renal œdema in particular, has excited considerable interest and discussion since the experimental inquiry which is chiefly associated with the name of Cohnheim.†

* I purposely omit reference to hyaline degeneration and the other lesions of the glomeruli, as I have no observations to offer thereon.

† *Virchow's Archiv*, vol. lxix., p. 106: "Ueber Hydrämie und Hydrämisches Œdem".

With respect to the œdema of hydræmia, Cohnheim and Lichtheim found in their experiments that a simple hydræmia or even hydræmic plethora was insufficient for its production. It was necessary that a change in the capillary wall of a paralytic nature be superadded, tending in all probability to cause a loosening of the attachments of the endothelial cells of which it is composed. In one experiment they ligatured the iliac vein of a dog, yet this was not followed by œdema of the corresponding limb. Ranvier repeated the experiment, and in addition divided portions of the sciatic nerve. It was found that while section of the motor fibres of the nerve gave negative results, section of the vaso-motor fibres was followed by œdema of the limb. Salvioli obtained similar effects in dogs rendered artificially hydræmic. With respect also to the lymphatics, it is found that their complete occlusion is, at least for a time, unattended by œdema of the pertaining parts. In another experiment Cohnheim depleted a dog, and injected salt solution till hydræmic plethora ensued. The result was a great increase of the natural secretions—*e.g.*, saliva, bile, urine, and intestinal fluid; but not until the hydræmic plethora was of the most extreme kind was any dropsy manifested, and then in the form of ascites only. Not only so, but Fleischer,* after tying the ureters and adding urea to the injected liquid, failed to obtain anasarca, nor was the blood pressure permanently raised.

On the strength of these and such-like experiments, Cohnheim came to the conclusion that dropsy occurring in the human subject was caused, not so much by a hydræmia or hydræmic plethora, as by a morbid alteration in the walls of the capillaries favourable to an increased transudation of their fluid contents. This alteration he considered to be due to the direct action of a particular poison existing in the blood, the nature of which is

* *Sitzungsb. d. Physik. Medic. Societät zu Erlangen*, July, 1858.

problematical, but defined by some in the case of renal dropsy as the same specific agent which affects the kidney. Again, with respect to the locality of the œdema, it is found in disease, and especially in renal disease, that hydræmic plethora is chiefly associated with symptoms the very reverse of those occurring in Cohnheim's experiment—with œdema, namely, of the skin and superficial tissues of the body, and with a diminution of the natural secretions and excretions. In explanation of this various opinions have been advanced. Cohnheim himself supposed the skin in renal disease to be in a morbid state, its vessels debilitated, and more susceptible to the action of the poisonous agent which he believed to exist—a condition which, indeed, demonstrably obtains in the case of scarlatinal dropsy. It has also been supposed that a special vulnerability of the skin is, from its physiological relationship, to be apprehended in kidney disease.

In the case of chronic renal disease, the difficulties are lessened by the circumstances of an attendant chronic hydræmia or hydræmic plethora, together with a degree of anæmia often more or less profound—in short, in chronic parenchymatous nephritis we have the factors which tend to œdema-production in cases of anæmia and chlorosis. In acute nephritis the problem is much more complicated. Here there is no sufficient evidence of, or reason for, any increase of pressure in the veins and capillaries. This form of œdema may arise with comparative suddenness in persons who show no signs of anæmia, as in the case of young adults who have had scarlatina, etc. Now, so far as conditions of the venous pressure and hydræmia are concerned, such cases are exactly on a par with cases of obstructive suppression. In the latter dropsy is absent; therefore in acute nephritis a new and important factor must be operating.

In comparing these conditions it has always seemed to me that sufficient stress has never been laid on the fact that in cases of obstructive suppression the circulation is

passing through a healthy kidney. There are two considerations which have to be emphasised here. One relates to the destruction of toxic bodies, which in obstructive suppression is so far at least normally accomplished, even if only a portion of the kidneys remains healthy. The other refers to the possibility of an internal secretion on the part of the kidney, also produced, and exercising its effects on the bodily metabolism. It is to the absence of these two factors that the dropsy of acute renal disease must be ascribed.

We know that the injection of urea into the circulation, after tying the ureters, as in the experiment of Fleischer already alluded to, does not produce anasarca. In obstructive suppression the conversion of toxic bodies in the kidneys into urea normally occurs, and the urea so formed escapes into the circulation, but in acute nephritis this conversion fails to occur, or at least occurs but very imperfectly, and so leads to accumulation of the toxines. As regards the influence of an internal secretion, that can only be hypothetical, but its suppression can only favour the augmentation of poisonous substances.

In what way then do these toxic bodies produce œdema? Considering the fact that the body is so often gravely poisoned by toxines without any œdema-production, there must be something special, something peculiar, about the action of the toxic substances in renal disease.

It seems likely that the œdema is really compensatory, and to be regarded as a salutary occurrence. The skin in particular responds to the demand for an outlet on the part of the toxines, and this is borne out by the large percentage of extractives in the dropsical fluid. The blood, in point of fact, is washed out by the skin, and the toxic agents merely serve to supply the necessary stimulus to a heightened or vicarious function which the skin has, for the time being, assumed, and which is only called forth by the existence of the renal condition. So that, while it is true that the dropsy is caused by a poisonous

agent acting on the capillaries of the skin, the additional fact must not be lost sight of, that the capillaries themselves are a party to the process in the sense of its being restorative or compensatory.

In some cases, however, I have obtained direct evidence that there is a certain degree of inflammation present in the skin. After examining this structure in a number of cases, there were a few in which the derma was unusually cellular, clusters of leucocytes being scattered through its substance. In these the œdema was very pronounced. It is probable also that in these the amount of proteid in the dropsical fluid would be relatively greater than usual, though observations on this point could not at the time have been made.

The Polyuria.

Lastly, I propose to advance a few considerations respecting the cause of the polyuria which is such a characteristic symptom of contracting kidney—considerations based almost entirely on the histological appearances which this kidney presents. It is the custom to ascribe the excess of urine to one or other, or else a combination, of the following factors: Increase of the blood pressure with increased rate of flow through the available kidney substance (Cohnheim-Fagge hypothesis); inability of the tubular epithelium to absorb the water passing from the glomeruli, and increased permeability of the glomerular wall. On the sufficiency of each or all of these alleged causes the facts of pathological histology seem to me to cast grave doubt. As regards the second of these—the inability of the tubular epithelium to absorb the water—are we certain that such an absorption normally occurs? For, if it did, we should have the phenomenon of a cell simultaneously secreting and absorbing a waste product. Other arguments could be adduced against this theory, but it does not vitally concern my position. Consider first the normal secretion

of urine. It is accomplished by two great systems, from two great sources. One of these is the glomerular system, which secretes the watery part of the urine *plus* the salts; the other is the tubular system, which secretes a fluid rich in urea and extractives. This is conclusively proved by the experiments of Nussbaum on amphibians, and by the experiments of Heidenhain. With respect to the glomerular system, the view of Heidenhain is unquestionably the correct one, that the Malpighian body is in reality a secreting gland and not a mere filtrating apparatus, otherwise it is inconceivable how, after section of the medulla, the injection of sodium acetate into the blood is accompanied by a copious secretion of urine, which is of course unattended by any rise in the blood pressure. And, indeed, in the case of granular kidney, Broadbent has given cases in which the polyuria was marked without any rise in the arterial tension. The epithelium of the tuft is therefore pre-eminently a water-secreting epithelium. Now, what is observed on examining microscopically sections of granular kidneys? It is found that the glomeruli are agglomerated together in more or less wedge-shaped areas of sclerotic tissue, the intervening spaces being occupied by dilated tubules whose basement membrane has escaped much alteration, but whose vascular supply is abnormally abundant. Now, in the majority of cases 80 per cent. of the Malpighian corpuscles in these sclerosed areas are totally functionless. How, even admitting the Cohnheim-Fagge theory, can the few remaining tufts manage to secrete the large quantity of water which flows from the kidney, especially when, in addition, it is considered that the tubules from the patent glomeruli are not infrequently snared by the cirrhotic tissue?

Allusion may here be made to certain curious experiments by Bradford. He states that if in a dog a portion of one kidney be removed, or if, with the removal of a wedge-shaped portion from one kidney, the other kidney be entirely removed, a great and permanent (at least for

several months) increase in the urine is produced. If from each kidney a wedge-shaped portion be removed, the increase in the urinary water is still greater. No other marked effect is produced, provided the amount of kidney left approximates to one third of the previous total kidney weight. But if the quantity of kidney substance left be only a quarter of the previous total kidney weight, not only is the quantity of urine greatly increased, but there is also an abnormally great excretion of urea producing a state of marasmus and death of the animal within three weeks. This last result gives rise to the supposition of disordered metabolism leading to increased urea formation, independent of the excretory activity of the kidney. And it also suggests the probability of an internal secretion on the part of the kidney regulating this metabolism; a secretion which is insufficiently produced by a quarter of the total kidney weight. None of the above results were in any way affected by division of the renal plexus.

In view of the well-known fact that if one kidney be excised, the other undergoes compensatory hypertrophy, it seems strange (as alleged by Bradford) that in his cases the portions of kidney left presented no alterations after several months. Apart from the increased excretion of urine, the most notable fact in connection with these experiments was the entire absence of any of the symptoms of kidney disease. Even in the case of increased formation of urea there were no symptoms of uræmia preceding the death of the animals. It is likely that a condition of matters was set up resembling very closely diabetes insipidus in the human subject. In these experiments the urine was increased about twofold to threefold. In diabetes insipidus it may be increased tenfold (corresponding to the difference in kidney substance present). There is no particular reason to suppose that division of the renal plexus should materially alter matters, as we must believe their inhibition to be pretty

well discounted beforehand. In view of these considerations, no parallel can be legitimately drawn between the polyuria of contracting kidney and that produced by excisions of the kidney substance.

If then the view hold good that in granular kidney the few glomeruli left undestroyed are unequal to the task of secreting all the urine, where else, it may be asked, is the seat of its secretion to be sought? This, I believe, may be found in a peculiar modification or transformation of the tubular epithelium in the areas which have escaped destruction and show more or less dilatation of the tubules. It is a remarkable fact, acknowledged by all observers, that the normal glandular epithelium in this situation becomes converted in granular kidney into a thin, flat epithelium—an epithelium, in fact, resembling that normally lining the glomerular tuft. Is there, therefore, any reason to deny that this peculiar modification of the epithelium may be but a special adaptation of nature whereby the elimination of water is effected? Further, these epithelial cells have bright-staining nuclei, which proves them to be in an active state. If it be not conceded that this epithelium actually subserves a modified function—that of secreting a much larger percentage of water than normally—I think it at any rate cannot be denied that it more readily permits a passage outwards of water from the underlying blood vessels, that, in short, it ceases to become a "water-inhibiting" epithelium, as in the normal gland.

This view is supported by the anatomical appearances, by the constant diminution of the urine in cases of chronic Bright's disease wherein this epithelium is gravely injured, and by many of the kindred facts of pathology.

CHAPTER V.

HÆMATOGENOUS JAUNDICE.

A GREAT deal of evidence has accumulated in support of the view that jaundice is always of hepatic origin, and that a hæmatogenous jaundice is no longer admissible. We may have a non-obstructive jaundice, which is by no means hæmatogenous, except in so far as the hepatic disturbance is initiated by changes in the blood. But a true hæmatogenic jaundice, or that produced exclusively from the blood, is regarded as having been disproved by certain experimental investigations, physiologists now holding that all forms of jaundice are of hepatic origin or due to reabsorption of secreted bile.* In order to examine adequately this evidence it will be necessary briefly to recount and review the observations which led up to the hypothesis of a hæmatogenous jaundice. Before doing so, however, it may be well to mention that the presence or absence of bile acids in the urine as a means of diagnosis between different forms of jaundice has been shown to be untenable, and therefore the question need not be taken notice of any further. It may also be advisable to preface the fact—possibly lost sight of by some—that the bile does not pass directly into the blood vessels of the liver in cases of obstructive jaundice. It was shown by Kufferath † that if both the thoracic duct and the common

* Recently, the possibility of a hæmatogenous jaundice has been admitted by several observers (see also Hunter in Allbutt's *Syst. of Med.*, vol. iv.).

† *Du Bois Reymond's Archiv f. Physiol.*, 1880, p. 92.

bile duct be ligatured none of the constituents of the bile pass into the blood; and in an investigation by Vaughan Harley * it was strikingly shown that under similar conditions no biliary constituents are to be found in the urine, even after the lapse of two or three weeks. After the lapse of some days supplementary ducts formed below the seat of ligature. Hence the path of the bile into the blood is *viâ* the lymphatics of the liver and the thoracic duct.

The View that Jaundice may be Caused by the Reabsorption of Secreted Bile from the Intestine.

This is a view which modern investigation compels us to set aside. It was originated by Frerichs † (and supported by Murchison) who thought he had shown that the bile acids when injected into the blood become converted into bile pigments. As the result of such injections in dogs there was jaundice, and the urine contained bilirubin. Normally, according to this theory, the bile acids after absorption become first of all converted into bile pigments, and thence by oxidation into substances no longer endowed with the properties of bile pigments. An arrest of this oxidising process would, according to Frerichs, cause the accumulation of bile pigments in the blood, and so give rise to jaundice. Such he supposed to take place as the result of certain febrile processes.

It may be remarked that the pigments of secreted bile are reduced, and partly excreted with the fæces as hydrobilirubin, and partly by the urine as urobilin. The bile acids are mainly reabsorbed, not by the radicles of the portal vein, as some have supposed, but by the absorbents of the jejunum and ileum, and so pass into the thoracic duct. This reabsorption of the bile acids has a very pronounced effect on the secretion of the bile, as the

* *British Medical Journal*, 1892, vol. ii., p. 397, and *Du Bois Reymond's Archiv*, 1893, p. 291.

† *Treatise on Diseases of the Liver*, p. 91 *et seq.*

experiments of Schiff* have so conclusively proved. In dogs with biliary fistulæ, if the bile flowing from the fistula be introduced through a duodenal fistula, the secretion of the bile is soon notably augmented, and the same result is obtained if the portal vein be ligatured. A consideration of what follows will show that such reabsorption of bile acids is never, so far as we know, a cause of jaundice.

Kühne's Theory of Hæmatogenous Jaundice.

The phenomena observed by Frerichs after the injection of bile acids into the circulation received, as is well known, a very different interpretation from Kühne.† He maintained that the effect of the bile acids was to cause a dissolution of the red blood corpuscles within the vessels, and from the hæmoglobin thus liberated he traced the bilirubin excreted with the urine. This supposition also fitted in well with the discovery by Virchow of the identity of bilirubin and hæmatoidin, an observation which has received ample confirmation from modern research. Kühne extended his observations and also produced bilirubinuria in dogs from injection of hæmogoblin into the circulation, and Tarchanoff‡ showed that in dogs with biliary fistulæ the injection of either oxyhæmoglobin or bilirubin into the circulation is followed by a greatly increased secretion of bilirubin by the liver, in addition to its appearance in the urine. Others confirmed these results, and various poisonous agents were discovered to produce this bilirubinuria; for example, arseniuretted hydrogen, toluylendiamin, chloroform, etc. (icterogenic drugs). These experimental results were applied to explain certain obscure cases of jaundice in man, wherein no obvious obstruction could be made out; for example, acute yellow atrophy, pyæmic

* *Pflüger's Archiv*, vol. iii., p. 598 *et seq.*
† *Virchow's Archiv*, vol. xiv., p. 310.
‡ *Pflüger's Archiv*, vol. ix., p. 53.

jaundice, phosphorus poisoning, and the jaundice of certain fevers. In all such it was held that the red blood corpuscles suffered disintegration within the blood vessels (hæmocytolysis) outside the liver, the hæmoglobin passing into the plasma and undergoing conversion into bilirubin within the circulating blood. Hence arose, on what seemed reasonable enough grounds, the modern conception of a hæmatogenous jaundice.

Overthrow of Kühne's Theory: the Work of Minkowski and Naunyn.

It might indeed be supposed by a critical onlooker that such facts as have been stated could not be regarded as affording conclusive evidence for a hæmatogenous jaundice, seeing that the *rôle* of the liver under these circumstances was not minutely considered. For, although bilirubin was excreted in the urine, it was possible that the liver was not passing all its excreted bile into the intestine or fistula as the case might be. It was conceivable that under the altered circumstances a portion of the bile might effect an abnormal passage and enter the blood. And although the injection of bile acids or hæmoglobin caused bilirubinuria in the case of dogs, Naunyn,* Steiner,† and Legg‡ were unable to obtain this in the case of rabbits. By the injection of these agents into the circulation of rabbits, these observers found well-marked hæmoglobinuria, but no bilirubinuria.

But the fatal blow was given to Kühne's theory by the experiments of Minkowski and Naunyn.§ Taking advantage of the "renal-portal" circulation which obtains in birds, they found that the flow of urine continued after ligature of the vessels of the liver. It may be remarked

* *Archiv f. Anat. u. Phys.*, 1868, p. 410. † *Ibid.*, 1873, p. 160.
‡ *St. Bart.'s Hosp. Reps.*, vol. xii., pp. 28, 29.
§ *Arch. f. exper. Path. u. Pharmacol.*, Bd. 21, pp. 1-33.

that Sterne * had previously shown that in doves in which the vessels and bile ducts are tied, no biliary substances accumulate in the blood, while Moleschott † and others had long ago shown that extirpation of the liver in frogs was followed by entire absence of bile constituents from the fluids and tissues of the body. Leyden, however, after tying the common bile duct in frogs, obtained no jaundice after fourteen days.‡ But Minkowski and Naunyn advanced their experiments a stage further, selecting for their purpose ducks and geese. On causing these animals to inhale arseniuretted hydrogen for a few minutes, bilirubin soon made its appearance in the urine. In one duck the urine gave Gmelin's reaction in six hours, and continued to do so for some days. In another duck, just as this bilirubinuria was at its full development, they extracted the liver. The result of this was severe hæmoglobinuria and a distinct fall in the bilirubin excreted. This fall continued until after the lapse of five hours, when at the death of the animal there was no trace of bilirubin or biliverdin either in the urine or in 35 c.cm. of blood. Again, in the case of geese, they excised the liver in one, and after it had so far recovered from the operation, subjected both it and a control goose to the action of arseniuretted hydrogen. The control goose soon passed icteric urine, while the liverless goose discharged in half an hour hæmoglobin-urine. It died in three hours, and after death hæmoglobin-urine was found in the cloaca. In two other geese arseniuretted hydrogen was first administered, and in an hour or two the urine was icteric. The livers were then extracted, and the animals survived for about three hours. Before death the urine was free from bile in one case, but contained much hæmoglobin; while in the other the bile was fast diminish-

* *Arch. f. exper. Path. u. Pharmacol.*, Bd. 19, pp. 39-59.

† *Arch. f. phys. Heilkunde*, 1852, p. 479.

‡ *British Medical Journal*, December 3, 1892.

ing and could not be detected in the blood. These experiments, then, conclusively show that the jaundice which immediately follows acute poisoning with an icterogenic drug is not due to the formation of bilirubin within the blood, but is solely dependent on the liver.

The Observations of Städelmann, Afanassiew and Hunter.

In like manner Städelmann* and Afanassiew† constantly produced jaundice in dogs by means of toluylendiamin. In this jaundice there are two well-marked stages: First there is a polycholia or increased flow of bile, which lasts on an average from three to eight hours, during which the jaundice begins to make its appearance. This is succeeded by an acholia, the flow of bile gradually diminishing, until by about the second day it may apparently cease to be secreted. During this stage the jaundice is at its height, and is alleged to be due to an inspissation of the bile in the ducts. It is, in point of fact, an obstructive jaundice. Afanassiew, however, describes in these cases a sort of interstitial hepatitis, whereby the blood vessels and lymphatics are dilated and the fine bile ducts compressed and choked. Hunter,‡ from actual observation, denies this sequence of events, and he alleges the viscidity of the bile to be due to congestion and catarrh extending from the bile ducts down into the duodenum. This catarrh he considers due to the irritant action of a substance or substances excreted with the bile, and as a result the lumen of the duodenum is filled with a clear, viscid, inflammatory mucus, free from bile pigment. I may say that I have myself obtained corroborative evidence of this under certain circumstances, as will subsequently be alluded to, and I

* *Arch. f. exper. Path. u. Pharmacol.*, vols. xiv. and xvi.

† *Virchow's Archiv*, vol. xcviii., and *Ueber Icterus*, etc., 1891.

‡ *British Medical Journal*, August 20, 1892.

should consider the viscidity of the bile in the ducts in such cases to be due to the admixture of increased secretion from the glands of the ducts, as we know that bile when freshly secreted is always fluid, deriving its natural viscosity from the subsequent addition of a nucleo-albumin present in the secretion of the ducts and gall bladder. Hunter, however, seems to go too far in ascribing nearly all cases of jaundice to catarrh of the main ducts, and so underestimating important causes of disturbance high up.

A Non-Obstructive Hepatogenous Jaundice.

It will be seen from the foregoing remarks that poisoning by toluylendiamin causes, in dogs at least, an obstructive jaundice, but we have also to face the fact that this obstruction is not always found, for jaundice occurs during the polycholia in dogs, when the bile flows freely into the intestine, and in the case of geese, bile makes its appearance in the urine in half an hour after the administration of arseniuretted hydrogen. It is probable therefore that the disturbance induced by the poisonous agents is such as to cause a partial deflection of the bile over into the lymphatics, and so on into the blood. How else can the jaundice be accounted for? We may conceive, indeed, how the great demand made on the hepatic cell in respect of its bile-producing function would entail the arrest of glycogen formation. The equilibrium, so to speak, of the cell would be so disturbed as to lead to a dual current of the bile.

Here it may be remarked that the belief consequent on these experiments that all cases of jaundice were of hepatic origin, and due mainly to obstruction, has led, perhaps in an unwarrantable degree, to the adoption or readoption of various alleged mechanical causes as the explanation of certain obscure cases of jaundice in man—such are swelling of the hepatic cells, distension of hepatic capillaries, œdema of the capsule of Glisson (Birch-Hirschfeld),

desquamation of the epithelium of the ducts (Buhl, Cornil, etc.), mucous exudation into the ducts, etc. Any of these factors, in addition of course to inspissation of bile, would serve to hinder the descent of the bile through the finest ducts, and so precipitate jaundice.

In examining a large number of human livers I was, however, forced to conclude that these mechanical conditions (excepting, of course, inspissation of bile) are rarely found sufficiently distinctive to warrant their adoption as causes of jaundice. Œdema of the capsule of Glisson is not accompanied by jaundice, neither is swelling of the hepatic cells, nor yet dilatation of the hepatic capillaries. Ernest H. Starling * has convincingly shown, in experiments on dogs, that the great increase of lymph observed after obstruction of the inferior vena cava above the diaphragm is entirely derived from the liver. I am informed by Dr. Starling that the lymph so obtained is not stained with bile pigment, so far as he observed. Hence, if œdema of the liver were a cause of jaundice, the latter could not fail to be a marked feature of these experiments.

In this connection, mention may be made of the view which assigns certain cases of jaundice—for example, from mental emotion, icterus neonatorum—to lowering of the blood pressure in the portal vessels, the bile thereupon being induced to flow in the direction of least resistance, or into the blood. But this view, which originated with Frerichs, was supported by erroneous suppositions. He supposed, for instance, that the secretion of the bile was an act of filtration, which we know it is not, as the pressure at which the bile is secreted is, on an average, two and a half times greater than that of the blood in the portal vessels; and, again, the pressure of the portal blood is subject to much periodical variation, which is regulated chiefly by conditions of diet and fasting.

* *Journal of Physiology*, vol. xvi., p. 224.

The Author's Experiments: Acute Poisoning with Phenylhydrazin.

With the object of obtaining, if possible, a more definite idea of the phenomena, both general and microscopic, which characterise the action of an icterogenic agent, I undertook a number of experiments, advisedly using for this purpose rabbits. For, as previously mentioned, bilirubinuria quickly makes its appearance in dogs subjected to the action of toluylendiamin, or when bile acids or oxyhæmoglobin are injected into their circulation. It is a curious fact, however, that no such result is produced in the case of rabbits. A hæmoglobinuria results from acute poisoning with the latter agents, but toluylendiamin has not even this effect. Toluylendiamin does not seem to injure them in any obvious degree; they live and thrive under large and frequently-repeated doses. I tried them with metaphenylendiamin, but they seemed little the worse for it also. There is an agent, however, which I have found to act admirably in their case, for by it one can produce the most diverse results by simply altering the dose, and that is phenylhydrazin.

In the first place, by a fairly large dose, subcutaneously administered, an acute poisoning was induced, death occurring in from twenty-four to thirty-six hours. An intense hæmoglobinæmia is in this way produced, the urine being charged with hæmoglobin. No trace of bile pigment can, however, be detected in the urine. Examination of the liver revealed considerable distension of the gall bladder with hæmoglobin-stained bile, the latter being somewhat of a reddish colour (hæmoglobinocholia). This bile was perfectly fluid, and had a free exit into the duodenum, which contained a considerable quantity of bile-stained stuff. There was no appearance of catarrh. The intestines also contained a considerable quantity of this brown bile. On section, the liver exuded a thin serous fluid, which, though pale at first, soon acquired a red tinge from

admixture with blood oozing from the hepatic veins. The spleen was much enlarged, fairly firm, and intensely congested. It would seem, in point of fact, that this hæmoglobinæmia is characterised by a great determination of blood to the viscera.

Under the microscope the liver showed nothing of much moment; the nuclei of the cells seemed, however, to be much stimulated. The blood in the capillaries was hardly to be distinguished from normal blood. The spleen was intensely full of blood, many of the corpuscles seemed to be disintegrating within the cells of the pulp, and a certain quantity of pigment was present. The capillaries of the lung were highly swollen with blood. The kidneys showed extreme vascularity of the glomeruli, with occasional hæmorrhages into the capsular space. The lumina of several of the cortical tubes were filled with blood. The urine was, as stated, saturated with hæmoglobin, and it deposited epithelium, some red blood corpuscles, and red granular matter which I took to be fragments of blood corpuscles.

Subacute Poisoning with Phenylhydrazin.

In the next place, a subacute poisoning was induced by administering small doses of the drug from day to day for a period of about eight days. On one or two days no injection was given. In these cases the *post-mortem* appearances were as follows: The duodenum contained much green-stained stuff; the gall bladder was well filled with a dark olive-green, but perfectly fluid bile; and the hepatic, cystic and common ducts were likewise well filled with a similar bile; the duodenum was bulged into a distinct pouch just opposite the entrance of the common duct, and in one case, in which the animal had been kept exclusively on a diet of bread and milk, this pouch contained a bile-stained mucus of extraordinary viscidity, adhering with such tenacity to the wall that it could with

difficulty be torn away. Herein we find a corroboration of the observation of Hunter formerly referred to. The liver on section became bathed with a serous fluid which, as in the former cases, got tinged by blood from the hepatic veins. The spleen was much enlarged and fairly firm. The urine gave a distinct Gmelin's reaction. As the microscopical disclosures in these cases are of great interest and importance, I shall discuss them alongside those described by Minkowski and Naunyn.

Microscopical Appearances: Critical Comparison with those Described by Minkowski and Naunyn.

These authors have described and figured the minute changes in the liver, spleen and bone marrow in the subjects of their experiments. By special methods of preparation, chief of which is hardening of the fresh tissue in a 5 per cent. solution of corrosive sublimate for twenty-four hours, they found within the smaller blood vessels and capillaries of the liver large cells enclosing red corpuscles, and similar cells enclosing disintegrating corpuscles and the brown-red pigment of Langhans, or else this pigment in association with a bright or grass green pigment. They also found these cells in the spleen and bone marrow, but in these instances without containing the green pigment. The cells were not to be found in the general circulation. These cells in the liver, moreover, were rich in iron. The green pigment therein was either pretty uniformly diffused throughout the cell, or else it was confined to one portion of the cell, the rest of the protoplasm containing the Langhans pigment. They affirm the green pigment to be true biliverdin, and to be derived from the ultimate disintegration of the blood corpuscles within these large cells, expressly stating that the green colouration is not derived by imbibition of bile. By the sublimate method they allege that they could detect the hæmoglobin

passing into bile pigment. Sooner or later this pigment was excreted by the liver cells. Clumps and granular masses of biliverdin were conspicuously seen in the hepatic cells proper and in the bile ducts, and in that portion of the hepatic cell nearest the bile capillary were numerous granules, which gave a strong iron reaction. In dogs poisoned with toluylendiamin they also saw the corpuscle-holding cells, but in much fewer numbers, and without the green pigment. Finally they conclude that these appearances are merely an exaggeration of what is normally found in the liver of ducks and geese; in a normal goose which was the subject of a polycholia beyond that usually seen, they likewise found such cells to be present in the liver.

Now I shall describe the microscopic disclosures after subacute poisoning by phenylhydrazin in rabbits, where death occurred from about the sixth to the ninth day. For hardening I employed Flemming's solution, Müller's fluid, alcohol, and also the sublimate solution. For staining purposes the Biondi-Ehrlich reagent answered best, as by it the red blood corpuscles in particular were sharply differentiated from the various pigments resulting from their destruction, which retained their natural colours. In the small vessels of the portal vein within the liver I saw some leucocytes containing pigment particles, which were generally of a golden yellow colour, but sometimes of a greenish tinge. In addition to this, there was a considerable quantity of free pigment in the vessels. I never saw any cells contain blood corpuscles. In a great many of the capillaries were pigment masses, either golden yellow or bright green. These pigments were seen both existing together and likewise apart from each other. The stellate cells of Küpffer were not infrequently mapped out by the pigment. The hepatic cells themselves were well charged with pigment granules, always of a brownish-yellow colour. Their nuclei were large and not infrequently showed mitotic change. The liver cells, moreover, showed no marked

degenerative changes; they were apparently actively secreting, and the bile ducts contained bile. The spleen was vastly charged with blood, and great numbers of the endothelial cells of the pulp, and apparently also leucocytes, were crammed with pigment and disintegrating red corpuscles. In many of these cells the pigment was of a grass-green colour. The cells of the bone marrow gave in a great majority the methyl-green tint with Biondi's reagent, but little pigment was found, not more than was compatible with a normal condition of affairs. No pigment was observed in the kidney.

In comparing these results with those of Minkowski and Naunyn, I think one is justified in holding that they represent very much the same state of matters. The only differences consist in the blood-corpuscle-holding cells in the liver and the alleged absence of green pigment from the spleen in their cases. I do not know if these are to be accounted for by the considerable difference in the duration of the poisoning or by the difference in species.

The Seat of the Blood Destruction.

In judging of the quantity, character, and situation of the pigment found within the liver, and comparing the same with that found within the spleen, the conclusion which irresistibly forced itself on my mind was that the liver was deriving all its pigment from the spleen. In the latter the pigment was so greatly in excess of that found in the liver, and the fact that the spleen was also visibly manufacturing pigment at a great rate left but little room for doubt in the matter. I do not deny the inclusion of red corpuscles by cells in the hepatic veins in Minkowski and Naunyn's cases, but have these observers shown whence these corpuscle-holding cells are derived? On the other hand, in the present experiments, while no active dissolution of corpuscles could be detected in the liver, this was plainly manifest in the spleen. It has commonly been supposed that the pigment is formed in

the general circulation, the spleen and liver merely serving as traps to catch up the pigment or pigment-carrying leucocytes as they pass through. This is erroneous. The pigment is not formed within the circulating blood at all. I may go further, and affirm that under similar circumstances pigment is never formed within the circulating blood. It is formed in the spleen. Great numbers of the endothelial cells of this organ may be seen holding the corpuscles in all stages of downward metamorphosis. Hunter, in his well-known researches on pernicious anæmia, has clearly underrated this function of the spleen, but Dr. Hunter has kindly drawn my attention to certain subsequent investigations he made on blood destruction,* wherein I find that he has abandoned his former position, and gives practically the whole credit to the spleen. He has proved this by toluylendiamin experiments. With small doses of this substance the "morphological changes indicative of hæmolysis are confined solely to the spleen and the blood of the splenic vein," while "after removal of the spleen the destructive action of toluylendiamin on the blood of rabbits, in doses both small and medium, is completely abolished". So he says, "I cannot interpret these facts in any other way than by concluding that the spleen has been the chief seat of this hæmolysis, and that the sole part the liver took in it was to dispose of the products". There can therefore be no longer any doubt that the hæmocytolysis (as I should prefer to call it) is effected by the spleen, and the products are carried over to the liver to be excreted by that organ as bile pigments. In these cases of Minkowski and Naunyn's, as likewise in my own, the great increase of work thus thrown on the liver is the cause of the unusual production of bile, by the inspissation of which or otherwise a jaundice was brought about. It now remains to be seen whether this is the conclusion of the whole matter.

* *British Medical Journal*, December 3, 1892.

The Effect of Prolonged Poisoning with Phenylhydrazin assisted by Metaphenylendiamin.

Having determined the action of large and moderate doses of phenylhydrazin, I finally endeavoured to induce a prolonged poisoning with this agent. The best results, however, were obtained by first administering fairly large doses of metaphenylendiamin for about a week or ten days. An inconvenience attendant on the subcutaneous administration of this agent sometimes occurs in the shape of necrosis of the skin at the seat of the injection. Barring this, it is not followed by appreciable ill-effects on the health of the animal. It causes, however, as Hunter has shown in the case of toluylendiamin (in rabbits), a considerable destruction of blood corpuscles in the spleen, though this is not followed by hæmoglobinuria (unless given in enormous doses), nor yet by the presence of bile pigments in the urine. After the treatment by metaphenylendiamin, the phenylhydrazin was given in small daily doses, occasionally omitting a day or two days. Generally in from eight to twelve days the symptoms became serious, œdema being not infrequent, seen conspicuously about the head. By sinking vessels in the floor of the receptacle in which the animals were confined, the urine was generally regularly obtained for examination. Two or three days before the urine gave Gmelin's reaction the conjunctivæ were seen to be somewhat jaundiced in one case. By this method of poisoning, after the lapse of about eighteen days the urine will begin to give Gmelin's reaction, but considerably less marked than in the cases of subacute poisoning after eight days. Typically, the *post-mortem* appearances in such cases were as follows: On opening the body, there was considerable œdema, generally at least in the form of some ascites. The blood had a marked "laky" appearance and consistence, and quickly coagulated, both in the vessels and outside of them. In the case of the liver, coagula were sometimes found in the

portal veins which were evidently formed *ante mortem*. Under the microscope these thrombi in the liver had a hyaline appearance; there was no ordinary fibrin to be seen.* Further examination revealed but a small quantity of bile in the gall bladder, which gave a flaky precipitate. No obvious catarrh of bile ducts or duodenum. The contents of the duodenum were bile-stained, but not viscid. A good deal of serum oozed from the liver on section—in fact, the organ generally seemed swollen from œdema. The spleen was greatly enlarged and extremely firm. The urine drawn from the bladder was generally of a dark brown colour. It gave the reactions for blood, albumin, and bile pigment. The sediment consisted of epithelial cells, granular casts, and cohering masses of granules.

Under the microscope the spleen was found to be enormously charged with pigment of a golden yellow colour. Even the Malpighian corpuscles were invaded by this pigment. Not a few of the cells, however, showed active hæmocytolysis still going on in their interior, and they gave a marked iron reaction. In the liver the portal vein and the capillaries were highly coloured by this pigment, carried over, as already shown, from the spleen. Many of the endothelial cells of the vessels, and likewise

* Thrombosis is a well-known tendency of laky blood, and due, as Wooldridge[1] has demonstrated, to the excessive liberation of fibrinogen from the broken up stromata of the red corpuscles. The hæmoglobin contains no fibrinogen. The hyaline or homogenous condition of the thrombi has been described in particular by Recklinghausen[2] as a peculiar modification of fibrin which occurs most typically after transfusion of blood from one species to another, as in the cases of lambs' blood transfusion into dogs and men given by him. The thrombi in question he ascribes to a local change in the walls of the vessels induced by the altered blood. In Wooldridge's experiments the portal vein was always the first seat of this clotting. The œdema also is to be explained by the results of Wooldridge's experiments. He found that injection of fibrinogen into the circulation of dogs causes extensive œdema of the leg if the femoral vein be ligatured, whereas in the normal dog ligature of the vein has no obvious effect.[3] This œdema he attributes to a disturbed relationship between the blood and the vascular wall.

[1] *Chemistry of the Blood*, 1893, p. 167.
[2] *Handb. d. allgem. Path.*, pp. 134, 135, 413, 414.
[3] *Ibid.*, p. 350.

the cells of Küpffer, were clearly mapped out by the deposition of the colouring matter; but the liver cells themselves were quite devoid of pigment; they were pale and in a condition of fatty degeneration, the protoplasm of the majority of them being transformed into fine oil or fat globules. On the other hand, the blood of the hepatic veins contained much pigment, and in the kidney these pigment granules were seen amongst the cells of the convoluted tubes, whilst *the lumina of the straight tubes in the pyramids were frequently choke-full of the same yellow pigment.* Here then it was indisputable that the granular pigment brought to the liver from the spleen was carried over in abundance into the general circulation, and, if so, can there be any doubt that pigment existing in soluble form in the blood plasma was also carried over?

The Idea of a Hæmatogenous Jaundice not to be Discarded.

Now, whereas in the experiments of Minkowski and Naunyn, as also in the second series here described, the liver was found to be most actively engaged in disposing of the products of the blood destruction, we have just seen that a further stage may be reached in which the liver apparently refuses any longer to deal adequately with those products, its cells undergoing degeneration. The result of this is, that the pigments of reduced hæmoglobin will be carried beyond the liver into the general circulation, stain the tissues, appear in the urine, and so bring about a true hæmatogenous jaundice. In order, then, to the production of such a jaundice, two factors are brought into play. One is an excessive destruction of blood in the spleen, a destruction which has advanced to a stage and to an extent far beyond that found in a mere temporary hæmoglobinæmia, such as that produced in liverless geese and ducks, and in which the hæmoglobin

passes into the urine as such. The second factor is an inefficient or paralytic condition of the liver cells so far as the excretion of bile pigments is concerned. We may even conceive, however, of a partial action of the liver which, nevertheless, does not prevent the escape into the circulation of a large proportion of hæmochromogen and its decomposition products. Thus we might have presumably a combination of the two forms of jaundice.

The result of the destruction of red blood corpuscles in the spleen has its parallel so far in the case of the icteric phenomena following extravasations of blood. In either case the pigmentary products of the hæmoglobin, which are identical, or almost so, with bile pigment, gain access to the general circulation. At any rate, examination of the urine in these experiments proved the jaundice to be due to bile pigment, so that we may leave out of account the presence of urobilin in excess.

It seems to me, therefore, that we cannot regard the experiments of Minkowski and Naunyn as finally disposing of the doctrine of a hæmatogenous jaundice. They have done a great service, however, in disproving the hitherto recognised hypothesis of such a jaundice. They have also been of indispensable assistance in helping on to a different conception of what a true hæmatogenous jaundice may be, should there be anything in the observations herein described.

CHAPTER VI.

ADDISON'S DISEASE.

My researches on the suprarenal gland were begun in the latter part of 1893, and in May, 1894, a short paper was published giving some of the results obtained. In August of the same year, the part of the work relating to the function of the suprarenal medulla was brought before the British Medical Association, when the views presented, being so far in direct opposition to those which had until then prevailed, naturally did not escape criticism. But it was not very long until Schäfer and Oliver announced the discovery of an active substance, only to be found in the medulla, and according to the meaning attached to this discovery, it is either confirmatory of, or else does not materially affect, the conclusions at which I arrived. The observations and experiments were continued at intervals until 1899, and are here presented in continuity.

Comparative Development of the Gland.

The light which has been thrown on the functions of the thyroid and pituitary bodies by the study of their evolution naturally leads to the expectation that some clue to the function of the adrenal might in like manner be derived. Unfortunately this matter stands greatly in need of further investigation, the work already accomplished having left many important points undetermined. I purpose, however, to note some of the gleanings I have made, with occasional comments, necessarily very brief.

Bergmann in 1839, and following him Remak, Leydig,

and Kollicker, observed the close relationship which subsisted between the suprarenal and the sympathetic nervous system. The latter observer regarded the medullary portion as purely nervous, while the cortical was distinct both in origin and function, being a derivative of the mesoblast. Leydig, and subsequently Balfour, in researches on elasmobranch fishes regarded the segmentally arranged paired bodies in connection with the sympathetic ganglia as homologous with the suprarenal of reptiles and higher vertebrates. Balfour afterwards regarded these bodies as homologous only with the medullary portion of the gland, another structure, the "interrenal body," corresponding to the cortical portion. The paired bodies are situated on the branches of the aorta dorsal to the cardinal veins, while the interrenal body lies between the dorsal aorta and caudal vein in the region of the posterior end of the kidney, and is of mesoblastic origin.* It only remained for these bodies to be united, and so form the compound organ of higher animals. In *reptilia* and *aves* Braun† found that the elements corresponding to the medullary part, or those presenting the characteristic brown stain with bichromate of potash, were derived from the sympathetic ganglia, while the cortical portion he traced from the mesoblast. Finally, Mitsukuri‡ arrived at the same conclusions from an examination of mammalian suprarenals; in particular he endeavours to trace in the rabbit, apparently in a very careful manner, the entire medullary portion of the organ from the peripheral part of the sympathetic system.

But further investigation has thrown doubt on these statements. In particular, the work of Weldon§ is deserving of special consideration on account of the care in details and clear conceptions which characterise it.

* *On the Development of Elasmobranch Fishes.* 1878.

† *Arbeiten a. d. Zool-zoot. Inst. Würzburg*, Bd. 5, 1879.

‡ *Quarterly Journ. of Micros. Sci.*, vol. xxii., 1882.

§ *Ibid.*, vol. xxiv., 1884, and vol. xxv., 1885.

He claims to have examined younger embryos than either Braun or Mitsukuri, and justly complains that they give no account of the origin of the blastema which goes to form the cortical portion. Weldon, in point of fact, traces the suprarenal body to the most anterior part of the primitive kidney.

In like manner Gottschau * and Janosik † deny that the medullary portion arises from the ganglionic fundaments of the sympathetic nerve trunk. These observers maintain that only certain ganglionic cells and nerve fibres grow in from the sympathetic, but that the real medullary nerve cells arise by a metamorphosis of the cortical cells. A good many facts seem to lend support to this view.

Carefully examining the embryo of *lacerta muralis*, Weldon found that as the glomeruli of that region of the mesonephros which is co-extensive with the generative ridge are being formed, a localised proliferation of the cells composing the wall occurs opposite to the point of attachment of the segmental tubule. This mass, which always remains distinct from the endothelium of the vena cava outside, divides into two portions—the suprarenal rudiment which goes upward, and the connecting tubules between testis and epididymis which go downward, a severance by the interpolation of blood vessels afterwards occurring. After a time the medullary ganglion cells enter the mass. The same results followed an investigation of *pristiurus*.

Testimony is borne to this view in the "accessory" suprarenal bodies which Marchand, Gibbes, Pilliet, and others have described as occurring in the vicinity of the sexual organs, wherein it is conceivable that some of the cells of the suprarenal rudiment might be carried down with those destined for the sexual gland. Janosik and Mihalkovies ‡ also, though tracing the development from

* *Archiv f. Anat. u. Physiol.*, Anat. Abth., 1883.

† *Archiv f. Micro. Anat.*, Band xxii., 1883.

‡ *Internationale Monatsh. f. Anat. u. Histol.*, Bd. ii., 1885.

the epithelium of the body cavity somewhat differently, nevertheless admit the connection with the sexual cords.

In a comparative study of the adult organ, so far as known, indications are afforded not only of the origin but also of the function of the gland. We must have regard to a process of development and a process of suppression.

Amongst myxinoids, the pronephros, or head kidney of *Bdellostoma*, has been carefully studied by Weldon. This structure is peculiarly modified so as to form a lobulated glandular body lying in front of the kidney proper, and functionally analogous to the adrenals. It consists of a lobulated arrangement of branched, intercommunicating tubes which open (some of them singly) on one side into the pericardium, and their cubical or columnar epithelial cells are continuous with the flat pericardial epithelium. Anastomosing with each other, these tubes pass without change in their diameter to a large central duct branched anteriorly. The latter is lined with a single row of columnar cells having large nuclei. A remarkable peculiarity of these cells is that they are crowded with granules, and their free extremities are produced into a number of pseudopodia, round which numerous granules are collected. The lumen of the duct is occupied by blood clot. Posteriorly the duct ends in a mass of tissue resembling that of a lymphatic gland, the epithelium of which forms the capsule of a large glomerulus which lies close to it. Blood vessels pass from this glomerulus into the lymphatic tissue, and thence into the duct. Weldon considers the appearances to indicate that the pseudopodous duct cells are actively amœboid, and eject secretion granules into the blood.

Balfour,* in his researches on adult ascidians and ganoids, finds that the head kidney is not, as Rosenberg supposed, the persisting larval excretory pronephros. The latter undergoes atrophy, and the so-called pronephros is, in point of fact, a mass of "lymphatic" tissue richly supplied

* *Quart. Journ. of Micros. Sci.*, vol. xxii., p. 12.

with blood vessels. Emery * afterwards showed that this lymphatic tissue was developed from the embryonic kidney by modifications affecting both the pro- and meso-nephros. Now in teleosteans and teleosteoid ganoids possessing this tissue no suprarenal organs are found, and hence it is to be concluded, with Balfour, that they are represented by this tissue. According to Balfour, also, this tissue must be engaged in the production of some of the elements of the blood.

Ascending higher in the scale, the suprarenal bodies give evidence of their development from the mesonephros, as is judged from their anatomical position in amphibians, and the derivation of their blood from the renal-portal vein. Thus we find evidence of successive modifications of portions of the primitive kidney, from the pronephros in myxinoids to the mesonephros in higher vertebrates; the same causes operating throughout, namely, specialisation of organs (pericardium, etc.) causing suppression of original renal pronephros, and gradual limitation of the seat of renal secretion, with co-advancing change of origin of the suprarenal.

Structure of Adult Mammalian Suprarenal.

In the connective tissue capsule are blood and lymph vessels, nerve ganglia, and nerves. I have observed large masses of ganglion cells immediately outside the capsule both in embryo and adult animals, and in man. In the embryo and newly born kitten, masses of cells are there seen taking on the deep brown stain with bichromate of potash, whose rich vascular supply is in striking contrast with that of the ganglion masses. Sometimes in this situation accessory suprarenals are found—the so-called "rests". Of the parenchyma itself, the outer or marginal zone (zona glomerulosa) is in great measure a reserve tissue. In rabbits

* *Atti dell' Accademia dei Lincei*, 1882.

and guinea-pigs it is composed of an almost solid mass of cells with but few developed acini. In the human subject I have seen an unusual development of the acini in cases of senile atrophy of the organ. The cells of the closed columns forming the greater portion of the cortex stain readily with eosin, and are usually quite filled with an oleaginous substance, which disappears after mounting in the usual way with Canada balsam. Each cell has a separate investment of connective tissue, and occasional small loculi may be seen between the cells. Their staining reactions and contents would assign to them but a subsidiary place. A single layer of capillary blood vessels passes down between the columns, forming frequent anastomoses. Reaching the inner or pigmentary zone these vessels break up into numerous large tortuous channels in which the blood pressure must be considerable. This zone is of great breadth in the guinea-pig, and pigment abounds. Some authors have erroneously described this layer in the guinea-pig as pertaining to the medulla.

In its most essential characters the medulla stands in marked contrast to the cortex. In all vertebrates it forms more or less distinctly alveolated or tubulo-alveolar gland. Speaking generally, the glandular cells are arranged in solid cylinders, which occupy the meshes of the network of blood vessels. This meshwork forms elongated and branching spaces in the outermost part of the medulla (that is, the part next the cortex), and more distinctly alveoled spaces in the central parts. In some animals—for example, sheep, rabbits—the alveolar arrangement obtains pretty much throughout, whilst in man it is more of a mixed character, but more distinctly alveolar than otherwise. As each cell is in contact with a blood vessel at one end, it follows that in the elongated cylinders the cells on longitudinal section will form double rows having a blood vessel on either side. The most actively secreting cells are situated in that layer of the medulla which lies nearest the cortex, that is, nearest the zona reticularis.

The arrangement of these cells and their appearances are very striking, more especially in the horse, in which they seem to form a special layer of branching tubes. Referring more particularly to man, the glandular epithelial cells of the meshwork are highly branched. Large gangliated nerve trunks and groups of ganglia traverse the medulla in abundance (Fig. 7). Isolated ganglion cells

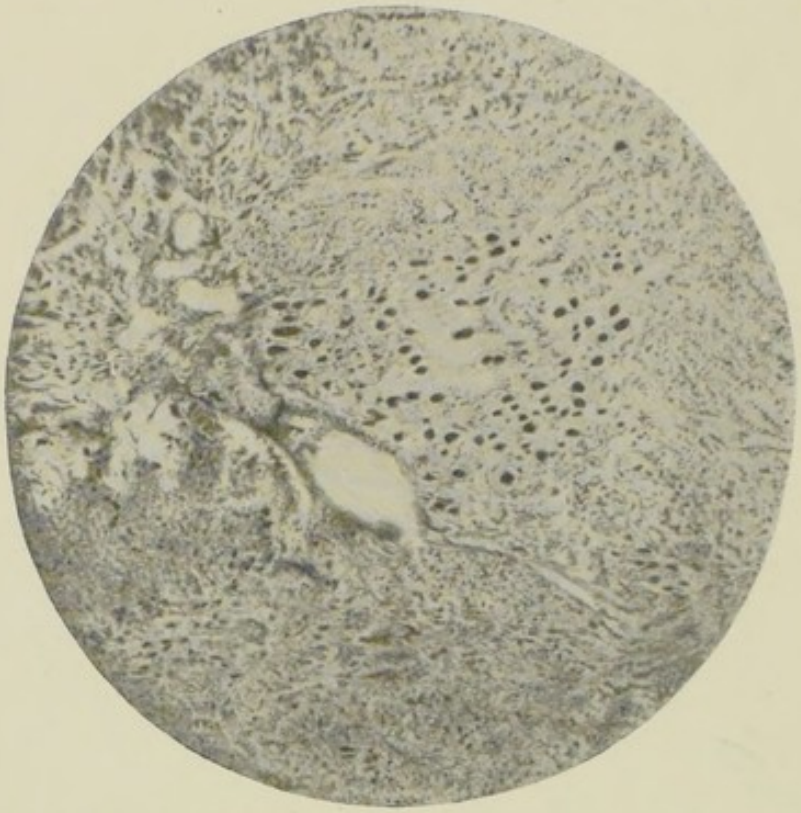

FIG. 7.—Normal Suprarenal, showing a large cluster of nerve-ganglia (micro-photograph).

are occasionally found occupying one of the smaller meshes, while branching nerve fibres course throughout its whole extent, lying underneath and in connection with the aforesaid epithelial cells which clothe the alveoli. The blood vessels consist of a rich plexus of narrower and broader sinuses and capillaries; the principal branches have muscular walls, but the walls of all the rest consist of a delicate nucleated intima on which, as stated, the glandular epithelial cells are immediately placed. The sinuses are collected into a large central vein whose wall is of extraordinary thickness and muscularity.

Isolated groups and processes of oil- and pigment-containing cortical cells are to be found in the medulla, while the central vein is immediately surrounded in part of its course by a reflexion of the cortex.

In the natural state and in sections prepared from alcohol, the epithelial cells in the medulla are of a lustrous whiteness as compared with the yellowish opaque cortical cells. Hæmatoxylin staining reveals the large and active character of their nuclei (some of which are of enormous dimensions) and their richness in chromatin. The protoplasm is finely granular and resists the action of eosin.

These epithelial cells or chromatophores, whose colour reactions are so well known (for example, brown by bichromate of potash, red by solutions of iodine, blue by ferric chloride, etc.), have been the theme of much discussion. Whatever their origin, I have now no doubt whatever that they are glandular in character. Both nucleus and protoplasm stain brown by the chrome salt, but as time goes on, some of them may lose this characteristic reaction, and appear as ordinary gland cells. Moreover, many of the cells of the cortex can be shown (especially in guinea-pigs) by the same reagent to be branched, and it is not unlikely that all the cells of the medullary meshes partake more or less of this character, the extremely delicate nature of the bichromate stain serving to distinguish some more than others. The branching processes of the chromatophores may often be seen embracing the nerve ganglia.

[In conducting these observations, some abnormal conditions of the gland were encountered. Of these, mention may be made of the occurrence of an adenoma (in man) circumscribed, and situated in the medulla, which it had expanded so as just to form a capsule round it. The proper tissue of the adenoma resembled that of the cortex, and was highly oleaginous. In the case of a Persian cat which died of suffocation on the eighth day from a rapidly-growing tumour in the larynx, the adrenals were converted

into white structureless bodies, of cartilaginous consistence, a hyaline form of degeneration which I have not found described hitherto as occurring in them.]

Function of the Cortex.

On making a fresh section of the adrenal body, the extremely vascular character of the inner cortical layer becomes at once apparent. It contrasts strongly with the delicate pearly-looking tissue of the medulla on the one side, and the opaque yellowish external portion of the cortex on the other. The blood seems almost entirely collected in this zone, and that the intravascular pressure is considerable is apparent from the welling forth of the fluid which occurs after section. Further examination reveals that the cells composing this layer are more or less pigmented, highly so in some cases, and but faintly so in others.

The existence of the pigmented cells has long been recognised, but their significance has not, so far as I am aware, been hitherto apprehended. Sections reveal the fact that large numbers of red blood corpuscles make their way into these cells, and are to be found (by suitable methods of staining) in their interior in all stages of regressive metamorphosis, from the completely-formed cell downwards. The englobed corpuscles are probably best seen by Biondi's reagent (after suitable hardening). Apparently by a chemiotactic action, certain of the red corpuscles are selected and attracted within the phagocyte cells (for such they may be called). They can be seen passing inwards, and at first cannot be distinguished in any respect whatever from those in the vessels outside. Gradually they assume a greenish-brown coloration, and thereafter begin to break up into larger and smaller particles. The nucleus of the phagocyte is usually much obscured by the pigment particles, but it is large, and

together with the protoplasm may show signs of formative activity.

These appearances seem to indicate that *one at least of the functions of the suprarenal gland is the destruction of a certain class of red blood corpuscles.* It is seen that not only do these cells separate pigment, but they absorb and destroy the stromata as well. In all probability such corpuscles are effete. Nothing can be made out or hazarded about the zona fasciculata, but its oily contents and staining reactions are such as to imply functions of a very primitive kind.

A brief reference may be made to the outer cortical zone (zona glomerulosa of authors). Its cells are but moderately eosinophilous—in this respect contrasting with those of the columns of the middle zone—and their nuclei readily absorb logwood. Although the acini are usually entirely filled with cells, I have seen under favourable circumstances a considerable central lumen which seemed to contain secretion. The appearance much resembles that found in the anterior lobe of the pituitary body.

Function of the Medulla.

It cannot be denied that the intimate structure of the medulla is alone a sufficient indication of an important function. Some have supposed this to be destructive in character; in particular, McMunn,* as the result of spectroscopic examination, concluded that its function was excretory, as he found the spectrum of hæmochromogen in solutions from the medulla, even after washing out the blood vessels. The same of course may be said of the liver, which also gives the spectrum of hæmochromogen. No doubt products of excretion may be found in the medulla of the suprarenal, as in other organs. In like manner, in a recent paper by Ewald of Berlin, a somewhat similar view is propounded. Now, I am far from

* *British Medical Journal*, February 4th, 1888, and December 1st, 1883.

denying that the medulla does not directly or indirectly profoundly influence substances which, if left to themselves, would cause a poisoning of the blood. Such a neutralising or reducing power is no doubt a province of the medulla. But the question remains as to how this power is exercised; and on the first view it is hardly conceivable that that portion of the gland which immediately guards the exit of the blood should be mainly excretory in character.

In making systematic examinations of the suprarenal in as many cases as practicable, a specimen presented itself which, though in all other respects perfectly natural, nevertheless showed a peculiar phenomenon in connection with the medulla. In several places the glandular cells were arranged so as to form acini of unusual dimensions, in the interior of which were larger or smaller spherical or oval masses of colloidal substance, or else the acinus was occupied by a single large mass. The gland cells lining such acini were reduced to a more or less flat epithelium. As regards their essential characters these masses did not differ, so far as I could find, from colloid elsewhere. They were perfectly homogeneous, and in unstained specimens of a faint yellow or greenish-yellow colour. They were readily tinted by eosin. In sections stained with carmalum and counterstained with acidulated picric alcohol they presented a brownish-yellow coloration. A similar colour is imparted by this stain to colloid substance elsewhere, for example, the thyroid. The colloid substance was also present in many of the blood vessels of the medulla, and these latter presented generally an unusual dilatation and frequency. This circumstance is all the more significant, seeing that the cortical vessels presented no such deviation. In all other respects, as already mentioned, both cortex and medulla were perfectly normal. The specimen occurred in a man, aged 30, who died from the effects of injuries. In another case, that of a man, aged 36, who died of stone-mason's phthisis, a great formation of colloid was present in the medulla of a gland

otherwise quite normal. Here also the blood vessels were markedly dilated. Examination of the suprarenals in many other cases showed that these colloid bodies were very frequent, especially in cases where a high bodily temperature had characterised the disease. In a case of acute tuberculosis, wherein a few minute tubercles had invaded the suprarenals, these bodies were large and frequent, while the secreting cells themselves were evidently in a high state of stimulation, judging from the size and appearance of their nuclei. As already mentioned, however, the colloid formation was present in the suprarenals in certain cases of perfect health.

The next thing which attracted my attention was, that the colloid was also present in what appeared to be dilated lymphatics. Unstained sections prepared from pieces of the organ hardened in bichromate of potash showed brown masses which were absolutely homogeneous, and seemingly forming moulds of the lymphatics or blood vessels. They were well seen in the sheep. Sections treated with alcohol did not show these coagula. Some months afterwards I saw a paper by P. Manasse in which a similar appearance was noted by him in a tumour of the suprarenal (in a man) and in the blood vessels of the gland in bovines.* This colloid-like substance naturally suggested secretion. It seemed likely that while under ordinary circumstances the secretion produced by the medulla passed into the blood vessels either direct or by the medium of the lymphatics, it nevertheless occasionally revealed itself amongst the gland cells, while the cases presenting the great formation of colloid, referred to above, were instances of abnormal functionating on the part of the gland. Other considerations supported this view. It was highly improbable that a gland otherwise healthy should exhibit in one portion of its structure alone what could be otherwise interpreted, while the abnormal dila-

* *Virchow's Archiv*, Band cxxxv., Heft 2, p. 263.

tation of the blood vessels, to whetever cause due, was evidence of abnormal activity.

Further Observations. [1896.]

After a long and varied series of investigations made on Man, horses, oxen, sheep, dogs, rabbits, etc., I arrived at certain definite conclusions respecting the secretion of the medullary gland cells and its path of entrance into the blood.

It was found possible to trace the continuity of the masses of coagula with the interior of blood vessels, and indeed some coagula had blood corpuscles imbedded within them. The delicate nature of these coagula, their speedy solubility in alcohol and characteristic staining, served to distinguish them completely from ordinary hyaline thrombi, described in particular by Recklinghausen,* as the result of certain pathological changes in the blood. It became evident, however, that the coagula resulted from the admixture of suprarenal secretion with the blood, and did not represent the actual secretion itself.

When about to become active, the cells of the solid columns become highly elongated, and the nuclei of any row recede to those of the opposite row, until in this way the nuclei of any two opposite rows meet, forming a double row of nuclei. On either side the protoplasm of the cells may be seen stretching to the vessels or capillaries, upon which (as described) they are directly implanted. In longitudinal section, the nuclei of the columns will thus be seen to form rows, and in transverse section, to form rosette-like masses in the centre of the cells (Fig. 8).

The protoplasm thereupon assumes a finely but markedly granular character, and the granules become disposed so as to form longitudinal streaks perpendicular to the wall of the blood channel; the ends of the cells become flattened

* *Handb. d. Allgem. Path.*, pp. 134, 413.

against the delicate membrana propria, through which the secretion is *absorbed directly into the blood*. Sometimes, indeed, the membrana propria is invisible in certain places, the blood and cells being apparently in direct contact.

Some appearances seemed to indicate also that sometimes a local secretion occurs amongst groups of cells, undischarged into the blood, and then we have a mass of secretion

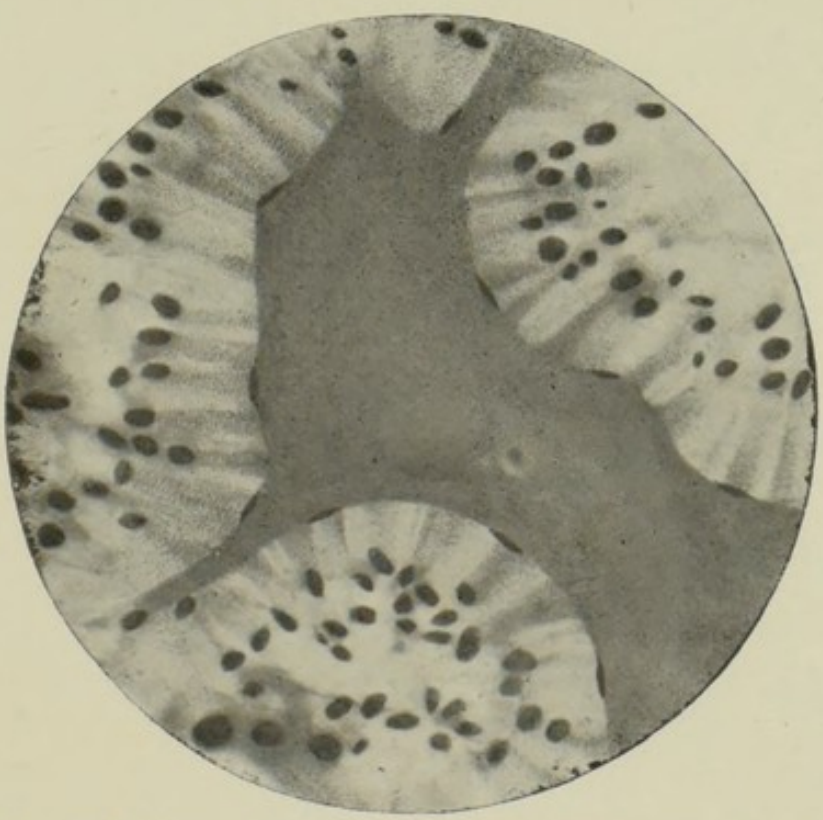

FIG. 8.—Medullary cells of the suprarenal secreting into a blood-space. The protoplasm becomes elongated and shows a streaming disposition. The interior of the blood-space is filled with homogeneous material. (Micro-photograph.)

lying amongst, and to some extent displacing, the cells (Fig. 9). This mass is apt to be confounded with the contents of blood vessels, but its shape, immediate contact with the cells, and especially its deep staining reactions, suffice to distinguish it from the coagulated contents of vessels.

The substance thus discharged into the blood is of fluid consistence, and is a chromogen possessed of a powerful

reducing action. The receptive blood gives the same characteristic colour reactions as the gland cells themselves. Blood in other parts of the organ, not immediately

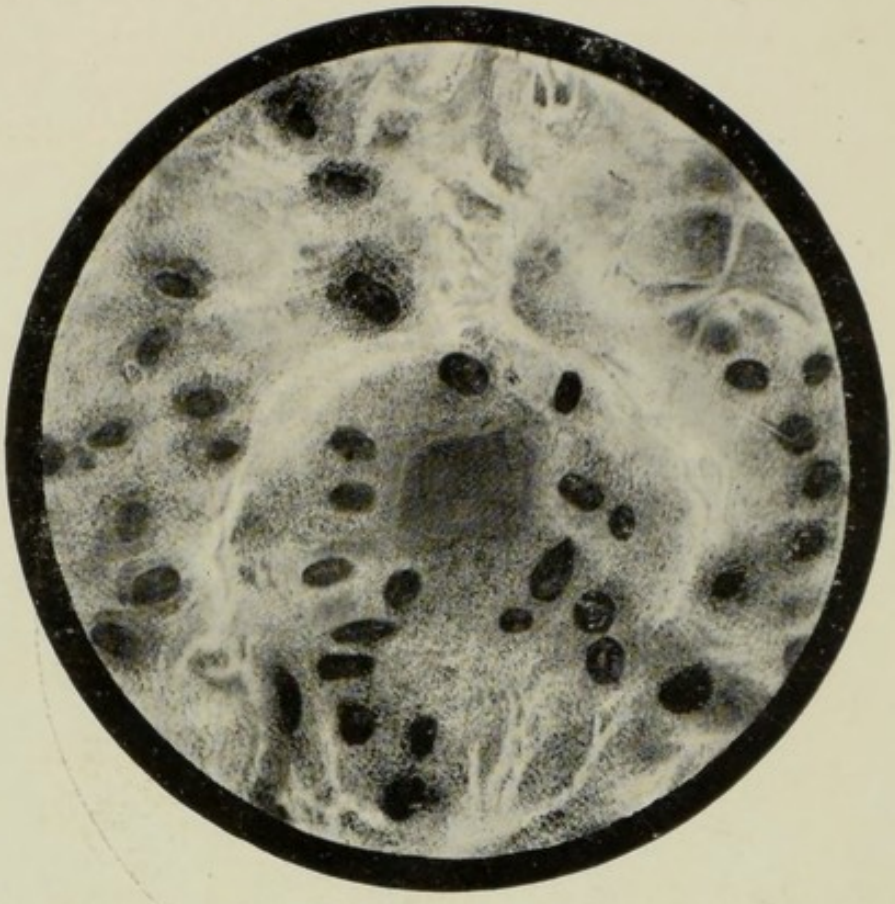

FIG. 9.—Suprarenal Medulla, showing in the centre of the figure, a mass of secretion surrounded by cells in a more or less resting condition. (Micro-photograph.)

connected with the cells of the medulla, gives a negative reaction.*

* The formation of coagula in the blood vessels—which stain of a deep brown with bichromate of potash, from the presence of the medullary secretion—is perhaps not difficult to understand. The blood is mixed with a secretion which is of course rich in fibrinogen. In the presence of the chromogen and possibly also incidental to its manufacture, a disturbed or peculiar relationship is to be apprehended as existing between the hæmoglobin molecule and the stroma in the red corpuscles. These factors would be highly favourable to the production of a coagulum immediately preceding death. I may add that in persons dead of acute pneumonia I have seen a widespread precipitation of fibrin in the medulla of the gland.

These observations seemed strongly to point to the conclusion, that in the medulla of the gland at least, a substance is elaborated which is transmitted to the blood. And here we are reminded of certain appearances formerly alluded to as occurring in lower forms, notably the case of the myxine in which secretion particles seemed to Weldon to be ejected directly into the blood. In the case of the human subject we have seen that in the zona glomerulosa of the cortex the blood is so far purified by filtration—large numbers of red corpuscles being visibly undergoing disintegration in the gland cells of that layer. The blood in passing on to the medulla is subjected to further and more refined tests of purity, inasmuch as it is mixed with a secretion which contains an exceptionally powerful reducing agent. In how far toxic substances in the blood are decomposed and rendered inert in the gland itself, or to what extent the secretion influences the body generally by passing into the general circulation, requires evidence of a different kind. There seems, however, little reason to doubt that this secretion has directly or indirectly the control of normal colour within certain limits, and that its arrest would form the principal etiological factor in Addison's disease, in which the blood clots with difficulty, the red corpuscles refuse to form rouleaux, and the body becomes pigmented.

Chemical and Experimental Work.

The foregoing observations were based entirely on anatomical data, and were made antecedent to the experimental work, which, in the hands of Oliver and Schäfer, and Abelous and Langlois, has been fraught with such interest and importance. If it should ever be shown that the active principle discovered by the former is indeed an internal secretion essential to life, it must be carefully recognised that it would only be a constituent of that secretion, and not the entire secretion itself.

It was shown by Moore that the active principle is distinct from the chromogen.* The destruction of the active principle in no wise affects the chromogen. This was very simply shown by extracting the medulla with strong alcohol. The alcoholic extract contains abundance of chromogen, but no trace of active principle (when physiologically tested).†

For several months much time was devoted to the chemical investigation of the medullary extract. I had so far isolated the active principle as to demonstrate its distinctions from pyrocatechin, and came to the conclusion (as reported to the Laboratories Committee) that it was an alkaloid. It is unnecessary to recount here the various steps of the work, but shortly afterwards, J. J. Abel‡ announced as the result of his investigations that the active principle was a base or poisonous alkaloid, having the percentage composition of C_{17} H_{15} NO_4, to which he gave the name epinephrin. Abel's work on this point is certainly the most important which has yet appeared.§ The free base cannot itself be isolated without altering its physiological effects, but if its benzoyl compound is heated under 3 atmospheres with dilute sulphuric acid and the product treated with sodium picrate, a picrate is formed of great activity [0·0011 gm. causes a rise of pressure = 46 mm. of Hg. in a dog weighing 6,850 gm.]. From this picrate an active bisulphate was

* *Journ. of Physiol.*, vol. xxi., p. 382.

† I found in the course of my work on this subject that the decomposition of a watery extract of medulla does not affect the colour reactions.

‡ *Zeits. f. Physiol. Chem.*, xxviii., S. 318.

§ He heats a water extract of suprarenals with benzoyl chloride and caustic soda, when all the epinephrin is thrown out of solution as a benzoyl compound, *viz.*: C_{17} H_{14} NO_4 COC_6 H_5. This is heated in an autoclave under 8 or 10 atmospheres with water alone, or else under 3 atmospheres with a 2 per cent. sol. of H_2 SO_4. In either case the benzoyl compound is decomposed, and in removing the benzoic acid and carefully neutralising the remaining product with ammonia, epinephrin itself is precipitated. But it is only when the autoclave product at 3 atmospheres with dilute sulphuric acid, *without first isolating the free base*, is treated with sodium picrate that a picrate is formed of great physiological activity.

prepared. The active salts are all transformable into one another. Treated with dilute alkalies, a volatile substance is produced possessing the odour of both conium and piperidin, and on acidifying the products of the reaction a dark brown acid is thrown out, in many respects behaving like the melanins. The last named reaction is of high interest in relation to the pigmentation of *morbus Addisonii*.

Fate of the active principle in the body. I made a considerable number of experiments in regard to this question, using an aqueous extract. The only point in these I need bring forward is this: When the extract was injected into a vein which had been clamped as high up as practicable, it was found, on releasing the vein after a few minutes, that a marked diminution of pressure was recorded as compared with that produced by injection into the free vein. In the case of the lower limb, six experiments were made, both by clamping the limb itself in its upper part, and also the particular vein, with the above result. Although not altogether free from disturbing factors, these experiments would indicate that the pressure-raising substance undergoes a process of destruction in the blood. I also found, as Schäfer pointed out, that extract and blood mixed *in vitro* and allowed to stand for some time in no way impairs the activity of the substance, but of course this is no parallel with the case of circulating blood.

It is alleged by Schäfer that this active principle is beneficial, and is probably stored away in the muscles. But that it is destroyed, not only in the blood but in the organs, and more especially in the liver, receives strong support in some remarkable experiments by P. Langlois. He found: 1. That maceration of suprarenal extract with hepatic tissue lessens its activity more so than maceration with any other organ. 2. That injection of a weak extract into the mesenteric vein remains without effect, although the same dose injected into the general circulation gives

a notable elevation of pressure. 3. That in an animal under the influence of the capsular extract the blood of hepatic vein is less rich in the active principle than the vein of any other organ. 4. That the suppression of the hepatic circulation causes a prolongation of the period of hypertension.*

Langlois's conclusions are, that the liver chiefly, but also the blood and other organs, rapidly destroy this substance.

Results of Extirpation of the Gland.

[1898.]

For these experiments I used dogs and cats. One gland was first removed. The cats soon recovered, and remained perfectly well and active. In two months' time the remaining gland was removed from one cat; in another the remaining gland was crushed and left *in situ*. The former cat died in twenty-four hours, and the latter on the second day. The excisions of the gland in dogs did not result successfully. Prof. Rose Bradford suggested to me that it might be advisable to keep the animals for some time longer after excision of the first gland, as in the case of a dog, one of whose suprarenal glands he had extirpated, death occurred quite suddenly in about three months (or two to three months) afterwards. I accordingly excised one of the glands in each of two fresh cats, but they were quite well and active five and a half months afterwards. The other glands were then removed, and the animals died in about thirty-six hours after the operation. Similar results have been obtained by other observers after excision of both glands.

After the second gland is removed, the animal lies on its side in a state of intense weakness, has a peculiar drowsy look, and refuses to move. In one of the animals I happened to see death supervene, which was preceded by convulsions.

* *Archiv. de Physiol.*, Jan. 1898, p. 24.

There seemed to be some compensatory hypertrophy of one of the glands last removed. In all four animals two phenomena were very apparent: (1) A very great hypertrophy of the thymus gland; (2) a considerable enlargement of the spleen. One thymus measured 5 inches long, 1 inch broad, and ½ inch thick. Pieces were hardened and subjected to microscopical examination. The most striking feature was an excessive vascularity of the medulla; otherwise the alveoli were enlarged and the nuclei very prominent. The concentric corpuscles seemed unaltered. What the precise significance of this hypertrophy of the thymus may be is indeed very difficult to affirm. It might be merely an ordinary result of disturbed blood relationships, such as is found under various circumstances, and in other lymphoid tissues. On the other hand there is no reason why it should not be specially compensatory to the loss of the suprarenal, and mean a performance of suprarenal work. If so, it would be instructive from one point of view, seeing that thymus extract is antagonistic, as regards its effects on blood pressure, to suprarenal extract. As regards the spleen its enlargement suggests increased hæmolytic function.*

Conclusions.

Experimental and chemical investigation have proved that an alkaloid of great activity, and possessing, even in small doses, poisonous qualities, is constantly present in the suprarenal medulla. The question is, in what capacity is it so present? Is it a constituent of a normal secretion, destined to pass into the blood and the system generally, fulfilling a function of a high importance, or is it, on the other hand, present merely as an intermediate product in the decomposition of toxic substances by the suprarenal —substances which, left to themselves, would cause an

* These results have since been corroborated by Boinet (*Gaz. hebd. de Méd et de Chir.*, March, 1900).

autointoxication? Now it seems impossible to doubt that the rapidly fatal issue in animals deprived of their capsules is due to a toxæmia. Even on the theory that death is solely due to lack of suprarenal secretion (as represented by the active principle) we cannot escape from the view of an intoxication resulting from profound vitiation of the bodily chemistry, as otherwise we cannot conceive of a cause of death, and especially death occurring so quickly. On the latter hypothesis (absence of the active principle) the symptoms should be removed, or at least retarded, by the administration of this substance. Not only is this not so, but such treatment, according to some observers, seems even to aggravate the condition.*

Granting then that in any case there must be an autointoxication in Addison's disease, the failure of suprarenal extract to influence this toxæmia causes the weight of probability to shift to the other side, *viz.*, that the toxic body or bodies are normally destroyed in the gland itself. To allege, as Schäfer has done, that on such an hypothesis this toxic body should be present in the blood of acapsulated animals (or in cases of Addison's disease) as the identical vaso-constricting substance found in the suprarenals, is opposed to the well recognised processes of physiological chemistry. It is much more natural to suppose that the toxic agent in the blood is the physiological forerunner of the alkaloid found in the suprarenals. The additional circumstance that the active principle has not been found in the suprarenal vein has also to be considered in this connection, and, lastly, there is the production from epinephrin of an acid body behaving like the melanins.

* Moore and Purinton (*American Journ. of Physiol.*, vol. iv., p. 51) have observed in one or two cases clots in the right auricle shortly after extirpation of both capsules, which they suppose to be formed *ante mortem*, and due to a great fall in pressure from absence of any "active principle". But in this case we should the more certainly expect administration of suprarenal extract to be efficacious.

We are thus forced back to the conclusions formerly suggested, that the work is largely done in the medulla itself and that this work is of a twofold nature. Toxic bodies are reduced or destroyed, and fresh qualities are imparted to the blood through a specific secretion containing a chromogen. The alkaloid (active principle so-called) is very easily oxidised, and this seems to be effected before it passes out by the suprarenal vein. It seems likely indeed that all this is accomplished on the spot, and herein we find a clue to the failure of suprarenal treatment. In a gland like the thyroid, the specific secretion passes by lymphatics into the general circulation as from a reservoir, while the blood vessels of the gland are comparatively few, detached from the gland cells, and serve merely trophic functions. A very different process occurs in the suprarenals. They are composed of a dense meshwork of blood vessels which are immediately surrounded on all their sides by glandular cells, and it is the blood *in situ* which is chemically altered, the general circulation being thereby influenced in a secondary manner only. Such chemical interactions necessitate the action of the living gland. Examination of the suprarenal vein shows the blood to have the characters of oxygenated blood. To supply a secretion which is pumped into the general circulation at any point, let us say, is a very different matter from dealing with the raw material on the spot.

The thyroid gland is an appendage of the respiratory system, and the study of its evolution shows that its original function is essentially concerned in the gaseous interchanges of the blood and tissues, "the phenomena following its destruction by disease or experiment being at bottom a disturbance of the gaseous metabolism and mal-assimilation of oxygen by the bodily tissues" (Andriezen). The pituitary gland is an appendage of the central nervous system, and, as the same observer points out, it is originally engaged in providing a secretion carried by oxygen-bearing water, which passes through its duct

to the central nervous system, while its destruction is followed by a nutritional failure in the nerve centres. Of the suprarenal gland, it may in like manner be said that it is an appendage of the renal-vascular system, being at the same time also in intimate connection with portions of the nervous system. Its original functions, so far as the examination of the pronephros of *Bdellostoma* indicates, are: (1) excretory or depurative, as suggested by a lymphatic glomerulus through which the blood passes to the central duct; (2) secretory or trophic, evidenced by particles passing from the lining epithelium into the blood-containing duct whose branches open into the pericardium. Both these functions are indicated as the result of our investigations in the case of the higher animals.

CHAPTER VII.

ATHEROMA.

[By Prof. COATS and THE AUTHOR.]

INTRODUCTORY.

IN examining the literature of this subject, it will be found that considerable variation exists as to nomenclature, and that this variation is an expression of differences of opinion as to the nature of the condition. It could not fail to be noticed by all persons experienced in pathological anatomy that the arteries are frequently the seats of thickenings or nodular protuberances on their internal surfaces. In accordance with the prevailing custom, these were at first described and named according to the general appearance of the lesion. Thus Hodgson,* who wrote in 1815, describes under three headings the condition of the internal coat, distinguishing first a cartilaginous condition, secondly a pulpy structure which Scarpa had named steatomatous, and lastly an atheromatous or purulent condition—the more specific atheroma. All such thickenings and new formations were customarily described as deposits, and so we find Craigie,† the first edition of whose book was published in 1828, distinguishing calcareous deposition, atheromatous deposition, and steatomatous deposition as three forms of disease in arteries. These observers, as well as Crisp, saw the lesions, but did no more than describe them, and were not aware of any connection between them.

* *A Treatise on the Diseases of Arteries and Veins*, London, 1815.

† *Elements of General and Pathological Anatomy*, Edin., 1828 and 1848.

Coming to the time of Rokitansky, whose "Handbuch" was completed in 1846, we find that a great advance has been made, in respect that these various conditions are now united into one, and described as a hypertrophy of the internal coat. At the same time, the idea of a deposit still remains. It is worth while to quote from Rokitansky's "Lehrbuch" his summary of the condition under consideration, as it gives a very succinct account of the conclusions which this observant and experienced pathologist had reached. He says:* "2. *A thickening of the internal coat by growth of the same into a pseudo-membranous new-formation*, which is sometimes, though far from always, induced by inflammation, *i.e.*, by absorption of exudation. This condition is, along with consecutive disease of the media and the adventitia, the usual foundation of the spontaneous aneurysm, besides being the foundation of ossification of arteries, of many obliterations, and in general of the most frequent diseases of arteries." Rokitansky thus recognised the unity of the disease, correctly distinguishing it as a thickening of the intima, and stating as the two secondary changes, an atheromatous degeneration and a process which he called ossification, and which at least implies calcareous infiltration. There still lingers in Rokitansky's mind the idea of a deposit as the cause of the thickening.

Then came the preponderating influence of Virchow† with the fundamental idea that all new-formed tissue arises from existing tissue, and not from any deposit or exudation in the tissues. The thickening of the intima in this case is, on these principles, a true increase of the connective tissue of which the intima is composed, and the atheromatous process or the calcareous degeneration is a secondary result, the former being chiefly a fatty degeneration and the latter a deposition of lime salts.

* *Lehrb. der path. Anat.*, dritte Auflage, Wien, 1856, bd. ii., s. 305.

† Virchow, *Gesammelte Abhandlungen*, 1856, s. 492, and *Cellular pathologie*, 1858.

Looking to the causation of this proliferation of the connective tissue, Virchow regards it as the result of irritation, and so recognises the process as an inflammation. He would, therefore, designate the disease as an inflammation of the intima of the arteries, comparing it strictly to chronic inflammation of the endocardium. Hence he introduces the term endarteritis chronica, on the analogy of endocarditis. As the disease leads to the formation of raised patches, and to other deformities of the surface, he uses qualifying adjectives to indicate these facts, and so the full name is *endarteritis chronica nodosa*, or *deformans*.

The views of Virchow have dominated the question ever since, but endeavours have also been made to introduce other designations. Of these the principal one is arterio-sclerosis. The introduction of this term has apparently arisen from a feeling of uncertainty as to the correctness of Virchow's view of the inflammatory nature of the process. Arterio-sclerosis seems a kind of neutral term, not committing one to any view as to the nature of the condition. Unfortunately, besides other objections, it again introduces a separation of conditions which are really one. The objections are prominently brought out on the perusal of Ziegler's remarks on the subject.* He heads his description, "Die Sklerose und das Atherom der Arterien," and endeavours to give a description of these two conditions, to some extent separately. But the condition designated sclerosis is frequently only the predecessor of that called atheroma, and the two conditions cannot be separated in the actual cases. There is the further objection to the term arterio-sclerosis that it emphasises a mere hardening of the tissue, and takes no account of the new-formation of tissue which is the fundamental fact in the process.

In regard to the term atheroma itself, there are doubtless great objections to its use to designate the process as a

* Ziegler, *Lehrbuch d. path. Anatomie*, 8te Auflage, 1895.

whole, whilst there are also certain advantages. No doubt the term originally referred to the fact that fatty degeneration is very common in this disease, and that it frequently results in the formation in the substance of the lesion of little collections of matter, which have been compared to porridge or pus. The term atheroma had long been applied, according to Virchow, to sebaceous cysts of the skin, or wens, whose contents consist of a fatty débris, and it was from this analogy that it was used for the condition under consideration. The atheromatous process is therefore, strictly speaking, the fatty degeneration which leads up to the atheromatous condition ; and hence the term atheroma is not strictly applicable to a disease of which the atheromatous process is merely a secondary and by no means a necessary incident. At the same time, there are advantages in the use of the term. It is short and involves no theory, and in its use we do not certainly depart more from the etymological signification than we do in using the term inflammation for such conditions as that under consideration, in which there are none of the cardinal signs of inflammation, much less the redness and heat which the term in its original use implied. The use of the term atheroma in the designation of the disease under consideration is therefore not altogether unwarranted, and it may be conveniently used as equivalent to endarteritis deformans, which is the more correct term.

General Description.

There can be little doubt as to the general facts in regard to atheroma. In a large percentage of persons dying in the period past middle age we find, in the arteries, obvious changes, which are limited in the first instance to the tunica intima. The lesions are usually most visible in the aorta, and they occur chiefly in the form of abrupt patches, which are at first of a grey colour and somewhat translucent. They are, in this early period,

hard, sometimes almost like cartilage (hence the term arterio-sclerosis). They are very prone to degenerative changes, of which fatty degeneration is the chief but not the only form, as we meet with the so-called hyaline degeneration and with calcareous infiltration, the latter mostly supervening on one of the other forms. If one of the patches be cut into perpendicularly to the surface of the vessel, even if it be a comparatively recent example, it will nearly always be found that, deeply in the patch there is a yellow layer indicating a fatty degeneration already present. By the advance of the fatty change the patch may soften, or the fat may give way to calcareous deposition. In many cases calcareous deposition is widely extended and exceedingly abundant. The presumption in these cases is, that the deeper layers of the lesion readily undergo hyaline degeneration, or, what is probably the same thing, obsolescence or necrosis, and so give occasion to the calcareous impregnation.

The disease is of very frequent occurrence in the aorta, which in many cases is, in its thoracic portion, almost continuously involved, although still showing indications of the original local patches. It is also frequent in vessels of a smaller calibre, more particularly the cerebral arteries, where the fatty change is very marked and the calcareous infiltration is rarely or never met with, and the coronary arteries of the heart, which are liable both to the fatty and to the calcareous change. The condition is by no means limited to the vessels mentioned, but is found in the arteries in every region of the body. It is frequent in the arteries of the lower limbs, less frequent in those of the arms. It is seen in the arteries within the abdominal cavity, sometimes attacking the splenic, renal, mesenteric, and other arteries. There are cases in which the condition is very widespread throughout the body, affecting at intervals almost all the arteries down to those of comparatively small calibre. There are cases also where there is a distinct localisation, and we may

have advanced atheroma in one set of arteries with very little in the system generally. It is true that, when atheroma exists, it is usually present in the aorta, but apart from this, we may find it very marked in the cerebral arteries, or in the coronary arteries, or in the arteries of the lower limbs, and absent or nearly so in the remaining arteries of the body.

The disease, however, is one especially of the larger arteries. This is indicated by the fact that its most frequent seat is the aorta, and that, if we except perhaps the cerebral and the coronary arteries, it may be said to diminish in frequency from the larger to the smaller arteries. Again, if we take a case where atheroma is very marked in the cerebral arteries we shall find, on a survey of the arteries of the brain, that the patches diminish in frequency very rapidly on passing from the main stems at the base and in the fissures to the branches which lie in the sulci, and that they are very infrequent in the finer arteries which run in the substance of the brain. It is true that the disease is more serious in its consequences in the smaller arteries, causing sometimes obliteration of their calibre and consequent lesions of the brain substance; but in regard to actual distribution it is less frequent in them. The same applies to other arteries. In the aorta it usually diminishes as we pass from the arch to the thoracic and abdominal parts of the vessel, and so forth. In cases of extensive atheroma, although it may extend to such small vessels as the radial artery, yet it is always very slight in such vessels, and is very seldom in the form of localised patches, presenting itself rather as a general thickening of the intima.

The pulmonary artery is to be mentioned as one of the vessels in which atheroma is not infrequently present. It scarcely occurs however, except in cases in which the right ventricle is much hypertrophied. The patches in the vessel are but slightly raised, they are usually opaque and yellow, and are, therefore, readily distinguished.

Distinction from Endarteritis Obliterans.

The fact above referred to, that endarteritis deformans is a disease chiefly of the larger arteries, and tapers off towards the finer ones, raises a question which may at once be answered in a few sentences. The minute arteries in the organs of almost all parts of the body are liable to a chronic inflammation, which some are inclined apparently to relate to atheroma. This is the condition variously designated *endarteritis proliferans*, *endarteritis obliterans*, *endarteritis productiva*. In respect that both conditions may be regarded as chronic inflammations characterised by new formation of tissue, they resemble each other, but there are such obvious differences in causation, distribution, and in the phenomena themselves, that we regard the conditions as properly distinguished from each other. The principal points of difference are related to the difference in causation. Endarteritis obliterans is an inflammation of the finer arteries, chiefly those of microscopic size, brought about as a rule by some general irritant which affects the arteries along with the connective tissue of the organ generally. It has thus no independent position, such as that of atheroma. Its most characteristic example is that seen in chronic inflammation of the kidneys where, with an increase in the fibrous tissue of the organ generally, there is a fibrous thickening of the intima, which, in the small arteries engaged, often amounts to an obliteration of their calibre. It is also seen in the neighbourhood of tuberculous and of syphilitic lesions, and in different localised forms of chronic irritation. Another point is, that the condition is one affecting the finest arteries, and tapering off towards the larger, precisely the reverse of atheroma. Further, it is not a senile change, its incidence depending on the occurrence of the primary lesion which induces it. There are thus obvious differences in causation and general circumstances, so that we do not hesitate to relegate this

condition of the finer arteries to a different category from that of the disease under review.

Age. Senility.

It has already been mentioned that atheroma is most commonly a disease of the period of life past middle age. This statement has to be made with a certain degree of reservation. If we regard the condition in the light of a senile change, then we must recognise in this as in other senile conditions great differences in the age at which they occur. Baldness, greyness of the hair, and arcus senilis are the familiar examples of senile changes visible to all. It need hardly be said that these conditions have no fixed age at which they occur, and that individual proclivities, determined doubtless by inheritance, have a ruling influence. It may be said also that the presence of one of these senile changes seems to have no relation to that of the others. Baldness and greyness of the hair by no means occur simultaneously and uniformly in the same person, and are even, to a certain extent, mutually exclusive. Although both conditions are atrophic, yet it is not common to meet with early baldness and early greyness in the same person. Following out this analogy we should not infer that external evidences of local senility, such as arcus senilis, or alopecia, or greyness of the hair, give any presumption of the existence of senility in the arteries. In confirmation of this view, the observations of M'Crorie* and others show that the absence of arcus senilis is no indication whatever of the absence of atheroma, or *vice versâ*.

It is also important to remark that, contrary to the analogy of greyness of the hair and alopecia, other forms of senility in the arteries very frequently coincide with atheroma. The most common of these is *calcareous*

* M'Crorie, "Atheromatous Disease of Arteries," *Glasgow Med. Journ.*, 1892, vol. xxxviii.

infiltration of the middle coat. This, as is well known, is an exceedingly frequent lesion. It affects, chiefly, vessels of medium calibre, such as the femorals and their branches, where it often brings about a partial petrification of the walls. The lime salts are deposited for the most part in the muscular coat and in the muscle fibre cells themselves. It is noteworthy that this form of senility scarcely occurs in the aorta, where the muscular tissue is but slightly developed, but is very common in such arteries as the brachial and femoral, where there is much more muscular tissue and much less elastic tissue. The process of calcification, however, is not limited to the muscular tissue in every case, but may affect the elastic substance. The calcification in one of our cases affected, in some arteries, the muscular substance of the media, whilst in others there was a very definite localisation of the impregnation to the membrane of Henle. The membrane of Henle, in almost the entire circumference of the vessel, was marked out by the calcareous impregnation which in most places formed merely a thin band representing that membrane, but sometimes formed more considerable nodules.

In regard to this matter of senility it is further to be remarked that the state of the circulation, as influenced by the occupation and habits of the individual, is no doubt an important element in determining its incidence. If a person follows a strenuous occupation, in which the heart is frequently excited to vigorous effort, and the blood pressure subject to frequent increase, then we may expect that any tendency to early senility will be brought out. A similar effect may be produced by disease. If the left ventricle of the heart be enlarged and hypertrophied from disease of the valves or otherwise, so that the systole is made with excessive force, then the tendency to senility will result in the early development of the senile changes. It is consistent with this that the pulmonary artery is not infrequently the seat of atheroma

in cases of hypertrophy of the right ventricle, the disease being otherwise rare in this vessel.

To sum up it may be said that atheroma is only one manifestation of senility in the arteries. Calcification of the middle coat is also a frequent manifestation, and it is very often present along with atheroma. When the latter is present in the aorta, we very often find the former in the femoral and in other arteries of medium size. Atheroma and calcareous infiltration are often present in the same vessel, but they do not seem to have any direct connection with one another, affecting, as they do, different parts of the vessels. Thus in the femoral we may have patches of atheroma in one place and calcification of the media in another. Calcification of the membrane of Henle is a more unusual manifestation. There seems no doubt that the state of the arterial circulation is a strong determining element in regard to the development of these various conditions, occupation or disease having their various influences on the heart's contractions and the blood pressure.

As affording an illustration of these points, the following case may be cited which has been already referred to in connection with calcification of the membrane of Henle. A sailor æt. 46. He was affected with incompetency of the aortic valve, and great hypertrophy and dilatation of the left ventricle. The arterial system had thus been exposed to great stress by the regular powerful contractions of the enlarged and dilated ventricle. The aorta was highly atheromatous, the arch and thoracic portion continuously so. There was some endarteritis deformans in the arteries of medium size, but in many of them, with or without this condition, there was a marked calcification of the middle coat. In most of the arteries so affected, and especially in the femorals, this calcification took the usual form of transverse markings in the media, indicating calcification of this coat, but an unusual appearance was presented by some of the smaller branches of the femoral. Here there was the very striking but irregular calcification

of the membrane of Henle already referred to. The calcification caused this membrane to be demarcated, the high refraction of the lime salts when seen under the microscope bringing out the altered membrane as a dark wavy band, sometimes expanding into a more rounded mass, which had a crystalline appearance. The calcified membrane gave the usual reaction with mineral acids, namely, disappearance of the lime with evolution of gas. The arteries generally, down to those as small as the radial, presented thickening of the internal coat. In the case of the femoral, the atheroma sometimes coincided in position with the calcareous infiltration of the media, and sometimes did not.

Normal Structure of Arteries.

As a preliminary to our examination of the lesion in the arteries, it will be proper to describe their normal structure. The walls of all arteries are conveniently regarded as triple structures, consisting of inner, middle, and external coats. These layers are found in their simplest form in the smallest arterioles. In these the inner coat is no more than a single layer of flat cells—endothelium. Outside this is the muscular or middle coat (media), consisting of a single layer of muscle cells disposed circularly round the vessel. The external coat is a delicate connective tissue membrane, containing longitudinally placed nuclei.

Ascending towards the large vessels we find that these layers acquire greater thickness and complexity of structure. The endothelial layer is spread over the interior of all the arteries, and shows no variations; its cells are somewhat lanceolate, their longest diameter being directed transversely across the vessel. But connective and elastic tissues are superadded to the endothelium, causing the entire inner coat to appear as a delicate, colourless, and transparent elastic membrane, which, though friable, may be peeled off from the middle coat. The muscular coat acquires much thickness, and the outer coat is strengthened by the addition of elastic fibres.

Beginning with the inner coat, or *tunica intima*, we find, immediately underneath the endothelium, connective tissue, commonly called the subendothelial connective tissue layer. This tissue is that specially implicated in the process of atheroma. It is composed of an unusually homogeneous basis substance, enclosing many branched spaces,

in which lie correspondingly branched corpuscles. These spaces and their contained corpuscles are disposed so as to lie parallel to the long axis of the vessel; that is to say, in sections perpendicular to the surface of the vessel the corpuscles appear sharply oval, while in sections parallel to the surface the protoplasmic plates, with radiating processes, are brought fully into view. Although the connective tissue is usually homogeneous (and is said to yield gelatin), in the larger arteries a finely fibrillated appearance is not uncommon. Fine elastic fibres are said to pervade this layer in many arteries, but we are not fully persuaded of this.

The outer portion of the inner coat consists of an elastic layer or layers, and in the medium-sized arteries forms the principal bulk of the intima. It varies considerably in its arrangement. In most of the arteries it is seen as a thick, homogeneous, elastic membrane, usually corrugated from contraction of the vessel. The fibres of which this structure is composed are reticulated and longitudinally disposed, so as in many cases to form a membrane containing minute elongated openings—*the fenestrated membrane of Henle.* In the larger arteries the fenestrated membranes may be double or threefold. The position of this membrane is not quite determined, as some regard it as belonging rather to the media than to the intima. As will be seen afterwards, the aorta has many similar membranes in the media, and has no proper elastic membrane in the intima.

Kölliker pointed out that the tunica intima of certain arteries contained smooth muscle. We have been able to confirm this; and, referring more particularly to the aorta, find that muscle cells are sparsely distributed amongst the elastic tissue, having a circular or oblique disposition. This circumstance acquires some importance in connection with the subject of atheroma and aneurysm.

The middle coat, or *tunica media*, is, in the smaller and medium-sized arteries, composed of plain muscle fibre cells, circularly arranged round the vessel. In larger arteries, elastic fibres are intermingled with the muscular tissue, either in the form of irregular, finely reticulated fibrils, or else as fenestrated membranes, which latter alternate more or less regularly with the muscular bundles. A very small amount of homogeneous connective tissue unites these elements. The individual muscle cells are unusually short, and towards the intima we meet with oblique or even longitudinal nuclei. Certain other arteries likewise show this : an inner longitudinal layer is found in some of the arteries of the pia mater (Auld). Small blood vessels derived from the external coat are found in the outer portion of the media, and occasionally capillaries are seen extending to near the inner coat.

The external coat, or *tunica adventitia*, is a vascular structure,

consisting of trabeculated connective tissue bundles, intermingled with elastic networks or membranes. The corpuscles of this tissue are disposed similarly to those of the intima. In the largest arteries the elastic membranes are numerous where this tunic impinges on the media. A small proportion of variously placed muscle cells are likewise present in this situation. The external coat acquires its greatest development in the middle-sized arteries, tapering to a single layer of nucleated cells in the smallest vessels, and on the other side getting relatively finer until in the aorta it is reduced to very small dimensions indeed. Great variations however exist, and Ballance and Edmunds * point out that the external coat is thickest in those arteries which are subjected to the pressure of movements of joints, muscles, or viscera; thus the outer coat of the nutrient artery of the tibia is much the thickest where the vessel is external to the bone, and the same holds good with respect to the central artery of the retina outside the optic nerve, etc. It only remains to be said that the *vasa vasorum* form a branching plexus in this coat.

The aorta, which is the artery with which this research is most concerned, presents certain noteworthy modifications in respect of all its coats.

The intima is relatively thick, due to the development of fine elastic fibres and connective tissue. In the arch, in addition, laminæ of elastic fibres are found. These fibres are richly developed near the media, on which they directly abut, and the fenestrated membrane of Henle, as found in smaller arteries, is absent. The media, however, is composed mainly of elastic tissue in the form of regularly arranged thick membranes, structurally corresponding, in all respects, to Henle's membrane. These membranes alternate with the circular rows of the muscle cells, and are interconnected by a very fine branching plexus of elastic fibres. The muscle cells and fine elastic fibres are embedded in a delicate, nucleated, homogeneous connective tissue. Allusion has already been made to the presence of muscle cells in the intima, and the relatively great tenuity of the adventitia.

* "On Ligation of the Great Arteries," *Med.-Chir. Trans.*, London, 1886, vol. lxix., p. 443.

CHAPTER VIII.

ATHEROMA (*continued*).

Condition of the Intima in Atheroma.

It has already been indicated that the condition may in general terms be described as a thickening of the intima. The idea that this was really a deposit on the intima had hardly disappeared as lately as 1856, when Rokitansky issued the second volume of his "Lehrbuch". In this volume he writes: "On the inner surface there lies a peculiar substance, laid down in the form of prominent nodules, sometimes thin, sometimes thick". He had by this time given up his original idea that the atheromatous patch actually arose by deposition from the blood on the surface of the intima, this view having become untenable when Risse in 1853 had shown that the endothelial layer was preserved over the atheromatous patch, and that the latter must therefore be a thickening of the intima under the endothelium. Rokitansky's newer view was that the condition consisted in a hypertrophy of the intima, and he indicates the opinion that the cause of the overgrowth of the intima is usually to be found in local or general mechanical conditions, by which the arteries are exposed to excessive functional strain.

In Virchow's view the increase in thickness of the intima was, as already indicated, regarded as inflammatory.* He regarded the new formation of tissue as arising by

* Virchow, *Wien. med. Wochenschr.*, 1856, Nos. 51, 52; *Gesammelte Abhandlungen*, 1856, s. 492, etc.

multiplication of the cells in the intima itself, just as in any ordinary inflammation. It is due to Virchow that the name chronic endarteritis has arisen, and there has since then scarcely been any serious question that the process is to be included amongst those of an inflammatory nature. There was a slight revulsion in favour of deposition from the blood at the time of the domination of the idea of the emigration of leucocytes as the essential item in inflammation and as the source even of inflammatory new formations, but this also has subsided, and Virchow's doctrine of an inflammatory thickening of the intima is that generally accepted.

We have studied atheroma in sections of vessels from various parts of the body, such as the aorta, the coronary arteries, the femorals, tibials, radials, cerebrals, and we have had opportunities of seeing it in various stages and degrees.

It is customary to distinguish two forms of the disease, one in which it is widely and to a large extent continuously distributed, and another in which it occurs in localised elevations. Thus the forms endarteritis diffusa and nodosa are described. These are not to be regarded as two separate or separable forms. The node or patch, which is such a common lesion in the aorta, is very often merely an exaggeration of a more diffused and extended thickening. It is the same also in other vessels. The intima may be more or less thickened throughout the vascular system, down to the vessels of a comparatively small calibre, whilst in certain of the vessels, especially the larger ones, there are the localised nodosities. It seems that the process is the same in both, and that the one is merely a local exaggeration of the other.

In the *cerebral* arteries thickening of the intima is found inside the membrane of Henle; the new tissue of the patch is often seen to be in two layers, a more superficial which shows the structure of the tissue, and a deeper which gives the results of degeneration in the patch. The

more superficial layer is highly fibrous in character. The cells lie parallel to the surface, and are contained in spaces between the fibres. The fibres have the general aspect of those of connective tissue, and are sometimes distinctly wavy. This fibrous structure is brought out prominently in sections treated with Biondi's stain. The cells are at moderately frequent intervals, and the spaces in which they lie form elongated splits in the tissue of the patch. The deeper portion of the patch is merely a degenerated mass, frequently occupying about half the thickness of the lesion. The structure is completely obscured, and there are indefinite spaces occupied by irregular masses of fatty débris. There may still be some fibres visible and a few cells.

The media is undoubtedly thinned beneath the patch. It is distinctly encroached upon only in specimens in which the membrane of Henle is interrupted. Here the internal layers of the media become definitely interrupted and broken down, the degenerated part of the patch bursting in on these. This, however, is exceptional, and there is mostly a mere thinning of the media.

Generally speaking, in cerebral arteries we have found thickening of the intima inside the membrane of Henle. This thickened intima contains cells having the same characters as those described above, and there is a similar fibrous intercellular substance. The degeneration of the deeper layers of the patch, with accumulation of fatty débris, is also a usual occurrence, and the fat not infrequently is in such quantity as to form crystalline masses. The condition of the membrane of Henle varies. In lesser degrees it is intact, but it may suffer interruption by the impact of the patch. The adventitia sometimes shows signs of inflammation, in the presence of numerous cells, but as this is in some instances entirely absent, it is to be regarded as secondary. The media is affected passively, if at all. It suffers encroachment from within by the thickened intima, but only where the membrane of Henle

is interrupted is it actively interfered with. It is sometimes infiltrated in its outer layers by leucocytes, in cases where inflammatory manifestations are visible in the adventitia. This invasion of cells sometimes penetrates to the intima, and the degenerated deeper layers of the patch may be to some extent occupied by round cells. A calcareous infiltration of the middle coat, such as is so common in some other situations, was not observed in any case in the cerebral arteries.

In this study of the cerebral arteries what we have learned may be briefly summarised as follows:—(1) The endothelium is virtually unaffected, at most showing a slightly greater prominence. (2) The disease is a thickening of the subendothelial layer of the intima, the tissue consisting of elongated flat cells with a fibrous, intercellular substance—connective tissue. (3) The media is unaffected or only passively involved. If the membrane of Henle is interrupted the inner part of the media beneath that membrane suffers. (4) The adventitia is frequently unaffected, but it may show signs of inflammatory reaction in the form of round cells infiltrating the tissue. These may pass into media and even into intima.

In the smaller arteries of the *limbs* we do not usually see such extreme atheroma as is common in the cerebral vessels even of the same calibre, but the beginnings of the process may be the better demonstrated. There is here, as in the cerebral artery, a new formation of connective tissue between the endothelium and the media, in other words, the subendothelial tissue of the intima.

Taking for further illustration the femoral artery, we find the process similar to that described above, but it is not usually so extreme as in the cerebral vessels. In some cases the thickening of the intima was found to be continuous, but with occasional local elevation, so as to form nodes or patches. In other instances there has been little general thickening, the lesion having mostly a local character. The membrane of Henle is intact in many

cases, whilst in others the patch in its deepest parts coincides with a breach of this lamina. Again, the disease in the femoral usually occurs along with calcareous infiltration of the media, but although these two are coincident in the same vessel they by no means concur in the part of the vessel in which they manifest themselves. The patch more frequently avoids the area of calcification than otherwise.

In illustration of the disease in the femoral a figure is given (Fig. 10) where a defined patch occupied about a third

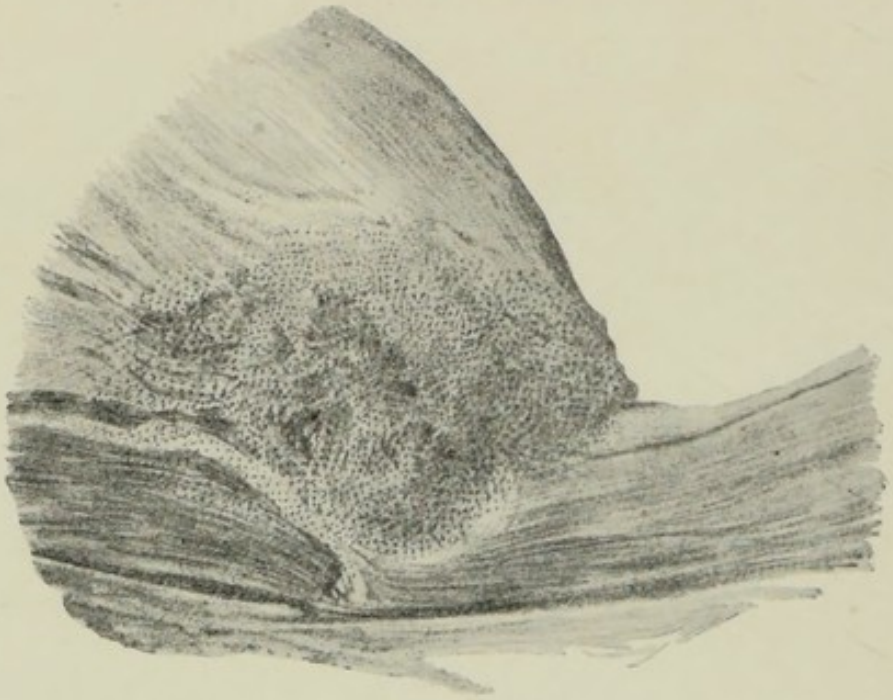

FIG. 10.—Section of Femoral Artery showing patch of endarteritis deformans, which rises abruptly. The membrane of Henle is ruptured and the media much encroached upon. A highly cellular granulation tissue fills the breach and extends into the patch. (Micro-photograph.)

of the circumference of the vessel. At one side it is almost absolutely abrupt, the intima at that side forming an exceedingly thin layer very nearly up to the border of the patch. On the other side there was slight thickening tapering from the edge of the patch along the vessel, but the patch itself was quite abrupt, forming an acute angle with the intima beyond it. The relations of Henle's membrane are here interesting and important. It is

broken, however, in two places, which are near the two extremities of the patch respectively. One of these ruptures with the accompanying conditions is represented in the figure. It is here seen that the membrane of Henle can be traced a short distance in from the border of the patch, but it is then interrupted for a short interval, to be resumed (as a rather broader and partly double dark line in the figure) a short distance farther in. In this place where the membrane is broken, the media is markedly impinged on and interrupted. The lesion in the media is broad towards the intima and tapers outwards, the apex reaching nearly to the external border of the media, but with still a narrow layer outside it.

Looking more closely at this lesion it is seen to have a distinctly inflammatory character. The tissue of the media is infiltrated with cells, and in the inner parts these are so abundant as to form a round-celled or granulation tissue. The cellular infiltration also extends into the patch itself. In the figure it is seen that the parts of the patch next to the breach in the media have similar characters to the structures occupying the breach, and here we have, as in the latter, a granulation tissue. Superficial to this we have the degenerated tissue of the patch, which is also, to a slighter extent, infiltrated with cells. The appearances thus presented seem to us to indicate that the rupture of the membrane of Henle and the consequent interference with the structures of the media have had the usual effect of a traumatic lesion of continuity. They have excited a mild inflammation with formation of new tissue, which in this case has not gone beyond the form of granulation tissue. It is to be noted that at the other end of the patch, where the rupture is very small, there is little or no appearance of secondary inflammation.

The question here occurs, what is the explanation of this rupture of the media? There can, we think, be little doubt that it is due essentially to the mechanical impact of

the raised patch against the media. This effect is most likely to occur towards the borders of the patch, where the abrupt thickening will, during the distension of the vessel by the pulse wave, have a much greater disturbing effect than over the middle parts of the patch, where there will be a more homogeneous and distributed impact. Further, the lesion of the media is in no sense, in this particular instance, to be regarded as an extension of the process from the intima, or as a degeneration induced by the degeneration in the patch. The deeper layers of the patch, in this vessel as in others, are markedly degenerated, the tissue broken up and largely replaced by fatty débris. But in every part, except at these two small areas, the media remains unaffected, although the degeneration is quite as great in other parts as at the two extremities.

The aorta.—In the aorta the atheromatous process is apt to be more complicated and difficult to unravel. The disturbance produced by the strong impetus of the blood is so great in the aorta, especially when the left ventricle is hypertrophied, that the general disturbance of the wall is apt to be much greater than elsewhere, just as atheroma itself is more frequent and more extreme in the aorta. Bearing this in mind we have to seek to disentangle the true atheroma from any secondary results of the process.

The simple patch or node in the aorta is similar to that described in the other vessels. The deep boundaries of the intima are not so definitely limited by a membrane as is the case in the smaller arteries, but it is not usually difficult to distinguish on account of the elastic laminæ which characterise the media. In the simple form of the lesion there is an elongated patch tapering at both ends. It is very sparsely cellular, and the cells are elongated and enclosed in spaces in the matrix, which again is fibrous in character. In the deeper layers of the patch, but not with any definite limitation, there are very marked appearances of degeneration and necrosis. These areas take on

a dull blue staining with logwood, and they contain no definite cells. These degenerated portions are sometimes in direct contact with the media, but the latter is little, if at all, affected.

Sections of the patch made parallel to the surface give very instructive results. They show that the lesion is really a new formation of tissue identical with that of the intima. The characteristic branching cells of the intima are seen embedded in a dense matrix. There are, in addition, a considerable number of round cells, such as we should expect to find in a tissue where new formation is actively progressing.

In regard to the processes of necrosis and fatty degeneration, different cases show great varieties, and even in the same case different patches, otherwise similar in form, show great differences in this respect. The fatty degeneration occurs in the flat cells of the thickened intima, and in sections made on the flat in the fresh state it is often possible to see these cells well mapped out by the fatty process. This condition is followed by disintegration of the intercellular substance, so that spaces are formed in which are contained fatty débris, the conditions being precisely similar to those which obtain in the cerebral arteries. The fatty change usually begins in the deeper layers of the patch, and may extend to the surface, but this is by no means a universal rule. There may be fat in the cells throughout the patch, or it may be more manifest in the superficial layers, or it may affect areas sometimes deeper and sometimes more superficial. In the more extreme cases of this process we have the so-called atheromatous ulcer, which is merely an extension of the process of disintegration to the surface and a solution of continuity there. As mentioned, the degeneration is usually most extensive in the deepest layers of the patch, where it impinges on the media. This coat is considerably thinned by the thickened and degenerated intima, and there are places where the fatty change has involved the

inner part of the media continuously with the process in the intima.

But there is in many such cases another condition, namely, a new formation of tissue of an inflammatory nature, such as we saw in its earlier stages in the femoral artery. At the base of the patch where the media is interrupted and involved, a new tissue is formed which is

FIG. 11.—Rupture and atrophy of media. This illustration shows a patch of atheroma, in the deeper part of which and to the left is a black mass of necrosis. Underneath this is a cellular tissue which extends into a rupture of the media. Blood vessels are seen passing from the adventitia into the gap in the media, accompanied by numbers of young cells. The curling of the ends of the ruptured fibres of the media is also indicated. [A good illustration generally of the descriptions in the text.] (Micro-photograph.)

neither media nor intima. It is connective tissue, such as characterises chronic inflammation, and it is signalised by the presence of new-formed blood vessels. The new-formed tissue and vessels extend into the media, and they may also extend into the deeper layers of the thickened intima.

This process, which we regard as one of repair, is seen in Fig. 11. There is the usual appearance of the pro-

nounced patch, elevated above the general level. The media shows an interruption and this is occupied by vessels which are passing inwards towards the intima. They extend through the media, which is parted at either side, and are accompanied by abundant round cells. The cellular condition extends into the intima.

Vascularisation of the intima, and its replacement by new-formed tissue, may occasionally reach a very high degree, as shown in Fig. 12, where the deeper parts of the

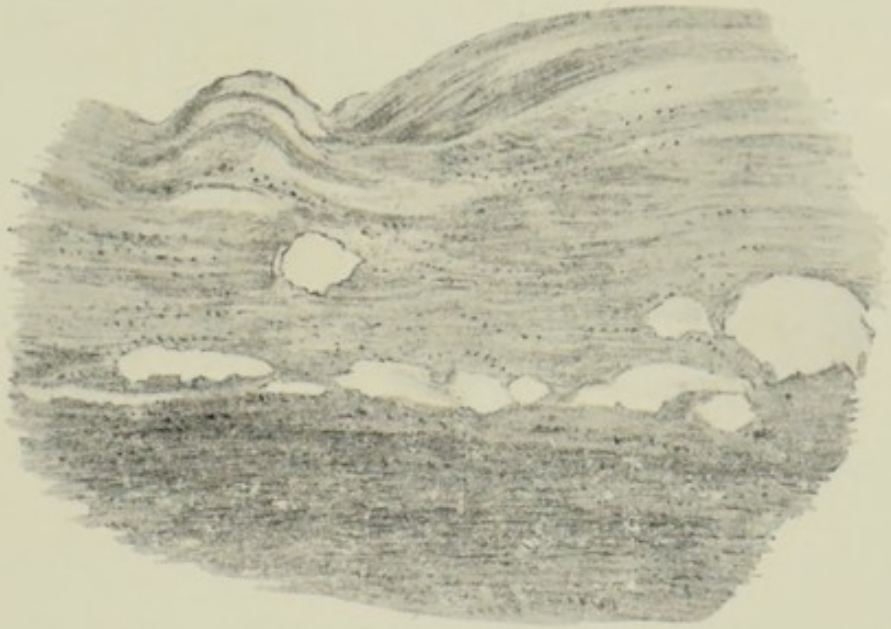

FIG. 12.—Shows well-formed blood vessels developed in the atheromatous patch. The media at this point is unaffected, but in many places it was extensively interrupted by vascular connective tissue. (Micro-photograph.)

patch are penetrated by large well-formed capillary blood vessels, which have a distinct endothelial lining. The patch indeed in this case seems to be largely replaced by the new-formed tissue.

The sections illustrate somewhat fully atheroma and some of its more general concomitants. We have the following phenomena:—(1) The patch formed by a thickening of the intima, the new tissue presenting a striking tendency to degeneration. (2) An impingement on the media, with some necrosis and destruction of its proper

tissue. (3) A new formation of vascularised connective tissue, which partly fills the gap in the media and partly extends into the intima, replacing the degenerated tissue, and in some cases even to a large extent replacing the patch. The whole bearing of these observations is to show that the order of procedure is that indicated in our enumeration of the lesions, and that the new formation of tissue and its penetration into media and intima are phenomena secondary to the lesion in the intima.

The inflammatory phenomena which we have regarded as secondary are not limited to the internal layers of the media and to the intima. It is not uncommon, even in cases where there is no new-formed tissue in these situations, to find the vessels of the media and of the adventitia surrounded by cells, and other evidences of chronic inflammation are also met with; one such case may be described.

The sections were made from the aorta of a man, æt. 37, who was affected with aortic valvular disease. The left ventricle was much enlarged, and the heart weighed 680 grms. (about 24 oz.). The aorta presented numerous atheromatous patches, of which sections were made. The patch is seen to rise almost suddenly from an intima which is nearly normal. The thickened intima is composed of cells elongated in the usual way, parallel to the surface of the vessel, and of a somewhat dense intercellular substance. The superficial layers of the patch present the cells described at somewhat regular intervals, but in the deeper layers there are few cells, and the tissue is degenerated and partly necrosed. In most of the patch the boundary of internal and middle coats is well preserved and perfectly distinct, but about the middle of the patch the media is broken through and its elastic fibres interrupted. There is thus an irregular gap in the media, the elastic fibres ending irregularly at intervals. With a high power the broken ends of the elastic fibres can be plainly seen, sometimes slightly clubbed. The gap thus produced is

occupied by a rather cellular connective tissue, which extends somewhat into the intima. There are blood vessels in this tissue, and one of them curves downwards so as just to reach the intima. Besides this there are, in various parts of this artery, indications of inflammatory new formation in the media and adventitia. There occur in the midst of the media occasional strands of vascularised connective tissue, highly cellular, approaching to granulation tissue in character. These do not, however, interrupt the continuity of the elastic tissue in the manner of the one described. One of these, a rather larger one than the rest, is prolonged out into the adventitia, where it is more expanded than in the media, so that there is a kind of wedge-shaped piece of cellular connective tissue with its base in the adventitia and its apex in the media. In addition to all this there is in the vasa vasorum in the adventitia a pronounced endarteritis obliterans, indicating a chronic inflammation in this coat.

We have therefore, in this case, what is in a sense a *general chronic arteritis*, whose effects are visible in all the three coats. It is to be noted, however, that these appearances are in addition to the regular phenomena of atheroma, and are to be regarded as concomitants or secondary results. The presumption is, in this case, that the chronic inflammation is partly the result of the atheroma and partly a concomitant, arising in connection with the same cause, as will be discussed more fully hereafter.

Such a chronic arteritis affecting all the coats was seen in some other cases of atheroma, although it is not of constant or even frequent occurrence as compared with the simple atheroma limited to the intima, or with some rupture and chronic inflammation in the immediately underlying media.

Pulmonary artery.—In order to conclude our description of atheroma reference may be made to this condition in the pulmonary artery. Atheroma of the

pulmonary artery is of frequent occurrence, but it is almost limited to cases in which the right ventricle is hypertrophied. The most frequent case is that of mitral disease of the heart, where, in order to overcome the mechanical interference, the right ventricle enlarges and becomes hypertrophied. The pulmonary artery has a structure somewhat similar to that of the aorta. The principal difference is that the media is much thinner.

As a typical instance of atheroma in the pulmonary artery the following case may be taken in which the lesion was microscopically examined:—

A woman, æt. 36, died after a prolonged history of heart disease, with breathlessness, dropsy, etc. The mitral and tricuspid valves were affected with chronic endocarditis, and there was marked mitral stenosis. There were many yellow patches in the pulmonary artery. Microscopic examination showed the patch to be composed of elongated flat cells, such as are visible in this disease in other vessels. There are also indications of the elongated processes of these cells. There is a marked degeneration in the patch, chiefly in the deeper portions. The media is slightly narrowed opposite the patch, but otherwise it is unaltered. There are no signs of inflammation in the media, whilst in the adventitia there is a slight aggregation of cells round the vessels, which however is scarcely more than normal.

General Conclusions as to Nature of Endarteritis Deformans.

Conclusions may now be offered as to the nature of the disease under review, and explanations suggested for the phenomena observed. These inferences and conclusions may be considered under the following heads:—

(1) *The relations of atheroma to hypertrophy and inflammation.*—In reviewing the facts brought together, by the examination of the disease under consideration in

various arteries throughout the body, perhaps the first conclusion we arrive at is that the lesion is one essentially of the intima. In its simplest forms, as seen in the cerebral arteries and in the femoral, it consists simply in a thickening of the intima, without any involvement of the media or adventitia. This is also frequently seen in the aorta, but there is here also frequently a lesion in the media and adventitia, which is generally to be regarded as secondary.

The lesion in the intima is a reduplication of its own tissue. The intima beneath the endothelium is, as already described, composed of a homogeneous basis substance, in which are branched spaces containing similarly branched cells. These spaces and cells are flat, and their flat surfaces are parallel to the surface of the vessel. As most sections are made perpendicular to the surface, the cells are seen in profile and appear as oval bodies. But when sections are made parallel to the surface their characters come out more distinctively. The tissue is, in its essentials, a reduplication of the tissue of the normal intima. It is so in essentials, but it frequently shows considerable divergences. It is more abundantly cellular, and the cells are by no means altogether of the typical character of those of the normal intima. The tissue is also very prone to degeneration, and chiefly to fatty degeneration. This manifests itself in whatever arteries the lesion occurs in, being often seen in the most exaggerated degree in the cerebral arteries. This degeneration often obscures the structure, and finally may lead to disintegration by softening of the tissue. The tissue is nonvascular, like the normal intima, so that in this respect also it is a reduplication of the original structure.

Such being the general structure of the new-formed tissue, we have next to consider what may be the essential elements in the production of the disease, and what position it may occupy as a pathological process. In regard to the cause, there are two factors which are to be considered, namely, the weakness of the wall, implied in the fact that

the disease is one of senility, and secondly the influence of the blood pressure. The fact that the disease is an expression of weakness has given rise to the idea that the new formation of tissue may be reparatory in its nature. It is probably in this sense that Rokitansky designated the lesion a hypertrophy of the intima. Again Thoma, in a very elaborate series of papers,* insists on the idea that the process is entirely compensatory, designed to make up for the weakening and over-stretching of the media. The nodes or patches so frequently found are, according to this author, designed to fill up depressions in the media and so restore the outline of the artery. It may be remarked that such a conception of the process could only arise from its study in such large vessels as the aorta. It is inconceivable as an explanation in its exaggerated forms, as seen in the cerebral arteries, where the protrusion inwards of the thickened intima often produces the most serious limitation of the calibre of the vessel.

The influence of the blood pressure in producing the lesion is capable of a twofold interpretation. It is calculated, when in excess, to weaken the wall of the vessel. We have, indeed, seen reason to believe that, in diseases characterised by hypertrophy of the left ventricle, the exaggerated impulse of the blood is a frequent cause of an early development of atheroma, as if a premature senility of the arteries were thus producible. On the other hand, mechanical irritation is a recognised cause of inflammation, and, more especially, of chronic inflammation, and we have to consider to what extent the disease is to be regarded as inflammatory in its nature.

In this reference we may at once advert to and dismiss the views of Köster,† who regards the process in the intima as an inflammation, and not only so, but as merely part of a general affection of the artery : inflammation of the media and adventitia rather preceding and determining the lesion

* Thoma, *Virchow's Archiv*, 1886, Bde. civ., cv., cvi.

† Bonn Dissertation, 1876.

in the intima. The whole bearing of the present observations is in the direction of a primary lesion of the intima, and although it cannot be denied that the media may be overstrained, and its fibres ruptured by excessive stretching, yet, in the majority of cases, the lesions in the media and adventitia are consecutive to those in the intima.

We have, then, two views before us: first, that the thickening of the intima is a compensatory process, or a hypertrophy designed, by a new formation of tissue, to strengthen the vessel weakened by senility, or excessive stretching by the blood; and, secondly, that the thickening is inflammatory, due to the mechanical irritation of the waves of blood. It seems to us that these two views are not mutually exclusive, and that it may be possible to regard the process as an inflammatory hypertrophy.

It may be proper here to indicate the sense in which we use the term inflammation, and more particularly chronic inflammation. We would include in the term inflammation those processes brought about in the tissues by the action of an agent of whatever sort, which irritates the living structures. In acute inflammations there is an obvious agent at work, but in chronic inflammations the causal agent is usually more obscure. It is, however, plain that a prolonged, mild excitation of the tissues leading to new formation of tissue, chiefly in one or other of the forms of connective tissue, especially the formation of fibrous tissue and of bone, is a frequent result of such irritation. Attempts have been made to separate such formative processes from inflammation, and to assign them a place as in a sense restorative or curative. While not denying a curative action in many cases, it is nevertheless hardly possible to carry out any such distinction. Even in the case of acute inflammation the attempt to distinguish between the direct effects of the irritant and the restorative efforts of the tissues must end in failure, as we cannot determine which of the phenomena necessarily belong to the one and which to the other. In the case of chronic inflammations it

cannot be held that the formation of connective tissue is always reparative. On the contrary, it is often, as in cirrhosis of the liver, destructive; and it is more satisfactory to regard the fibrous new formations as a part of the inflammatory phenomena, although in some cases they are undoubtedly beneficial, and in other cases hurtful.

In the case before us we are directly met with the fact that the lesion may be in part compensatory, but it is undoubtedly hurtful, and it is quite impossible to draw a line of distinction between the two. Perhaps the less we make any such attempt the better.

Objection may possibly be taken to the view that this process is inflammatory, on the ground that the tissue produced has a special structure. The tissue of the intima reminds one to a considerable extent of that of the cornea, with its clear matrix and branching corpuscles, and we know that in chronic inflammation of the cornea there is not, so far as we are aware, any new formation of the proper corneal tissue, but rather an ingrowth of ordinary connective tissue with blood vessels, such as is the general rule in chronic inflammations. However this may be, we are not left without an analogue to the production of a specialised form of connective tissue as a result of chronic inflammation. Bone, the structure of which is also in some respects analogous to that of the intima of arteries, is a regular product of chronic inflammation, under a remarkable variety of circumstances. It is not at all uncommon to meet with it even in the walls of arteries in which the media has become impregnated with lime salts. The presence of the lime seems to determine the formation of bone rather than of ordinary connective tissue, when, by means of chronic inflammation, the dead mineral matter is replaced by living tissue. In this reference, the analogy which Virchow has drawn between endarteritis deformans and chronic rheumatic arthritis, more particularly in the special form of arthritis

deformans, may be referred to.* Both diseases are senile manifestations, and both are characterised by the formation of a specialised form of connective tissue, bone in the one case and the tissue of the intima in the other.

The atheromatous process, therefore, is in its nature inflammatory, and properly designated by Virchow's term endarteritis deformans, but the idea of a compensatory process is not thereby excluded. It is evident that the thickening of the intima, especially if at all general, would render the vessel wall more rigid, and so far prevent over-expansion. This view is enforced in observations made by Roy,† with a view to determining the relative influence of the media and intima in resisting the distensile force of the blood. He found that the aortas of animals dying in a state of marasmus or fever marasmus, as also those of persons advanced in years, have acquired a permanent set, causing them to remain abnormally wide, indicating a marked diminution in their elasticity. "In connection with the subject of rupture of the vessels and the production of aneurysm," he remarks, "the resistance of the different layers of the aorta is found to have undergone quite a change in this respect, in persons of advanced years." While in young and healthy persons but little difference was found in the elasticity curve on removal of the intima (in traverse strips), "in these (*i.e.*, in elderly persons) removal of the intima did not leave the resistance of the traverse strip unchanged; removal of the intima caused the curve to fall more rapidly than before, especially with light weights". There was no evident structural change in the intima at the part taken, though there were patches of atheroma on the vessel elsewhere. Removal of the adventitia had but a slight influence. Where structural change existed, however, the change in the elastic properties of the aortic wall were even more marked than those above referred to. It would appear, therefore, that

* Virchow, *Gesammelte Abhandlungen*, 1856, s. 492.

† Roy, *Journ. of Physiol.*, London, vol. iii.

the presence of atheroma would greatly augment the resisting power of the aorta to over-expansion by the pressure of the blood.

(2) *The relation of atheroma to lesions of the other coats.*—In this part of our subject we are on surer ground. In considering this matter there are two elements to be considered, to each of which due weight must be given. We have in the first place the direct influence of the atheroma, and in the second place, the action of the cause which has led to the atheroma, and which may also lead to changes in the other coats. If atheroma be the outcome of weakness in the wall of the vessel, then that weakness will be liable to manifest itself in other lesions both of the intima and of the other coats. A weakened vessel, liable to be stretched beyond its powers of resistance, is apt to undergo partial tears and ruptures of its fibres. This is much more likely in the aorta, where the thickness of the wall is much less, in comparison with the calibre, than in other vessels. The frequent evidences of inflammation to be seen in the wall of the atheromatous aorta are partly to be traced to this source, although also to some extent dependent on the atheroma itself. An aorta subjected to the stress of a hypertrophied left ventricle, or exposed to the frequent rises in blood pressure incident to a strenuous occupation, is likely to sustain small injuries to its coats, which will lead to inflammatory manifestations in numerous small local centres. These phenomena in the middle and external coats are much less marked in the smaller vessels. Amongst the smaller vessels they are more frequent in the cerebral arteries, whose walls are less supported from the outside than those of the limbs. They are scarcely visible in the case of the femoral artery and the other arteries of the legs, although atheroma is frequent in them.

Atheroma itself, and especially the atheromatous patch, exercises an important influence on the other coats of the vessel, and more particularly on the internal layers of

the media. This is well illustrated in the case of the femoral artery, of which an illustration is given. The local patch or node is a hard, solid body, as it were, embedded in the wall of the vessel. It is often of almost cartilaginous consistence, and even when degenerated it is still a substantial piece of matter. This cannot fail to exercise a serious influence on the underlying structures, more particularly as at each systole of the left ventricle the wave of blood forces it outwards. We are in the habit of observing the conditions after death, when the blood pressure has entirely disappeared. On the removal of the blood pressure the node will move inwards towards the calibre of the vessel, as it is no longer supported in that direction.

In order to estimate to some extent the influence of the blood pressure, an endeavour was made to replace the latter by filling the aorta with an injection before hardening the vessel. Paraffin wax was used for this purpose, injecting it in the fluid state and allowing it to cool under pressure. After cooling, the vessel was hardened in alcohol with the paraffin retained. By this means, while the paraffin was in process of cooling, it would continue to exercise pressure, but all irregularities of the surface which persisted under the pressure would be preserved forming indentations in the wax. Two such injections were made in cases of atheroma of the aorta. From the examination of these, it is plain that the atheromatous patch exercises considerable pressure on the media outside it, and that it has sometimes a most disturbing influence. In one of these the description runs as follows:—In its deepest layers the patch protrudes against the media, its boundary forming a considerable arc of a circle, with its convexity outwards. The media here is markedly thinned, and there are inflammatory manifestations, in the form of cellular infiltration, partly separating the fibres of this coat. Even when the patch is not an abrupt one, and is degenerated and softened in its deeper

parts, these preparations show that the media is thinned and pushed outwards opposite the thickest part.

The intrusion of the patch is thus to be regarded as having a most important influence on the middle coat, especially where the thickening is abrupt. In some cases it causes rupture of the fibres of that coat, as has been shown, and consequent gaps in the continuity of its proper tissue. The effect is not limited to the media, but is liable to extend to the adventitia. A solid body continually protruded against the wall will have results extending through the wall. As shall afterwards be seen, these local injuries have an important influence in the causation of aneurysm.

CHAPTER IX.

ANEURYSM.

[By Prof. COATS and THE AUTHOR.]

THE pathology of aneurysm and its connection with atheroma are subjects which may be studied from various points of view. It is the present object to consider them in their anatomical and histological aspects, and for this purpose a considerable amount of material has been examined. But it is fully recognised that pathology is not limited to these aspects, and that when the view is thus curtailed, false or imperfect conclusions are frequently reached. It may be proper, therefore, at the outset, to consider briefly some points in the general pathology of aneurysms, and their relation to endarteritis deformans, or atheroma.

CAUSATION OF ANEURYSM AS INDICATED BY AGE OF OCCURRENCE.

One of the points to be considered is the age at which atheroma and aneurysm respectively occur. It may be said in general that atheroma is a disease of advanced life, but that the age of its incidence varies greatly, not only in regard to the individual persons affected, but in regard to the particular vessels in which it occurs. Comparing, for example, atheroma of the aorta with atheroma in the cerebral vessels, we shall find that it occurs at a much earlier age in the former than in the latter. In the aorta it is not uncommon to meet with it as early as the thirtieth

year of life, whereas in the cerebral arteries we must go on for at least a decade before we are likely to encounter it. These differences are doubtless determined chiefly by the circumstances of the particular arteries concerned. As the aorta is more exposed to variations in the blood pressure and to excesses in the impetus of the blood than any other artery, and as these are the principal determining causes of atheroma, so we have this disease occurring at an earlier age here than in other vessels.

For the purposes of comparison the statistics of M'Crorie * may be cited, which are comparable with our own in regard to aneurysm, as they concern the same population. M'Crorie's numbers are small, but they are striking, and probably in general correct. He found atheroma in the arteries at the following ages:—

Age 0-40	1
„ 40-50	8
„ 50-60	8
„ 60-70	5
„ 70-80	2

There is thus only 1 case under 40, and 15 out of 24 cases were over 50.

Turning to aneurysm we find that the age of its occurrence is distinctly earlier on the average than that of atheroma. In other words, aneurysm, although nearly limited to the period of life in which endarteritis deformans occurs, yet occurs chiefly in the earlier years of that period, and the average age of its occurrence is therefore distinctly lower than that of atheroma. A just comparison as to age can only be instituted in the case of aneurysms of the aorta, because they are sufficiently numerous to eliminate, in some degree, sources of error. Taking the various decades the ages determined in 33 cases were as follows:—

Age 20-30	1
„ 31-40	15
„ 41-50	10
„ 51-60	7

* M'Crorie, *Glasgow Med. Journ.*, 1892, vol. xxxviii., p. 110.

It will thus be seen that aneurysms, not merely at the time of the onset, but at the time when they have led to a fatal issue, have their maximum frequency between the ages of 30 and 40. This circumstance seems an interesting and important one. A condition which under 30 years of age is exceedingly rare, suddenly between the ages of 30 and 40 attains its maximum. There must surely be something in the conditions of life at that age which determines this curious circumstance. So far as working communities are concerned, the explanation is no other than that this decade includes the period of life of maximum physical vigour. Occupations calling for severe physical exertion can only be efficiently followed during the vigorous period of life, and it is recognised amongst us that this period is a distinctly limited one. With a view to the elucidation of this matter some inquiries were made from a man of great experience as an ironmaster. In the making of iron there is necessary, at certain stages, severe and continued active exertion so as to manipulate the iron while it is hot. Our correspondent writes as follows:—"Ironworkers as a rule are able to hold on to severe work up to about 50; a few 5 years longer, but more under 50 than over it. About this age they begin to have little ailments, but very seldom serious disease. I have noticed, especially in the case of men working at large steam hammers, that about 50, their movements of work are less certain, not from a want of muscular strength so much as from a want of quickness and definite action. About this time of life they perspire more, and the action of the heart seems to fail them, and very soon they have to give place to younger men. At this time I have observed that they begin to have shortness of breath, readiness to catch cold, and a want of recuperative force."

These remarks indicate that the period of life in which vigorous exertion of the greatest intensity is possible scarcely extends beyond 50. It will be noticed, in the

table given above, that of 33 cases no less than 26 were of that age or under it, and only 7 above it.

Sex.—The question of sex is also an interesting one, in respect to the matter considered above. It is well known that aneurysms, although by no means confined to the male, are greatly more frequent in men. Thus Bizot* states that in 189 cases there were 171 in males and 18 in females, and Hodgson,† in 63 cases, found that 56 were in males and 7 in females. Of the specimens of aneurysms of the aorta in the museum of the Glasgow Western Infirmary, the proportion of the sexes is very similar to that given above, namely—

Men	30
Women	4

There is a marked and instructive contrast in this respect between aneurysms of the cerebral vessels and those of the aorta, pointing to a difference in the causation of the two. In the same museum, of aneurysm of cerebral vessels, which number 8, there were 7 in women and only 1 in a man. But the extreme difference between the sexes in this case is accidental, and an analysis of recorded cases (Coats) shows that the incidence of cerebral aneurysm is nearly the same in both sexes.‡

Structure and Relations of Aneurysms at their Beginnings.

In this part of the investigation a large number of specimens have been available, chiefly of the aorta, but the number of cases of aneurysm of the cerebral arteries is also considerable. In one case of about 200 occurring in the regular work of the *post-mortem* room, the cause of

* Bizot, *Mém. Soc. Méd. d'Obs.*, Paris, 1837, tome i.

† Hodgson, *Lectures on Diseases of the Arteries and Veins*, 1815.

‡ With regard to syphilis as a cause of aneurysm, I am able to state that, so far as Prof. Coats is concerned, he did not share the view as to the relationship of these conditions which is adopted by many.—A.G.A.

death has been found to be the bursting of an aneurysm in one of the larger cerebral arteries. The material in regard to other aneurysms has, however, been small.

In examining the specimens, thin sections with the microtome were made in the usual way. Various methods of staining were employed, chiefly logwood, lithium-carmine, and alum-carmine. A method of staining described by Manchot * has also been made use of. This author stains the sections for half an hour in a strong watery solution of fuchsine. He then transfers them to a watery solution of glucose of syrupy consistence, to which three or four drops of ordinary sulphuric acid have been added. The preparations lose much of their colour, and finally the red colour of the fuchsine is confined to the elastic fibres of the media. This coat can therefore be readily traced. The sections are finally mounted in sugar solution without acid. This method was modified by treating the sections with a solution of methyl-blue instead of the sulphuric acid and sugar. The methyl-blue expels the fuchsine from all except the elastic fibre, and it gives a certain blue colour to the nuclei, which, however, is apt to become faint.

In studying the causation of this disease it is not the fully formed aneurysms which are the most important: it is rather the beginnings of them; and to these special attention is directed. In most cases of aneurysm of the aorta, when the vessel is carefully scanned, apart from the actual existing aneurysm there are nearly always small pouches discoverable; these are the beginnings of aneurysms. They may amount to nothing more than a slight depression below the surface which can be felt by the finger, or they may be in the form of actual pouches visible as convex projections externally. These beginnings of aneurysm are, however, not limited to cases where actual aneurysm exists. They are to be found in cases of

* Manchot, *Virchow's Archiv*, 1890, Bd. cxxi.

atheroma without aneurysm. In order to test this point the aorta was carefully scrutinised in 300 consecutive post-mortem examinations, and these little beginnings of aneurysm were found in no fewer than 8 cases. Amongst the 8 there were 3 cases of actual aneurysm.

Looking closely at these little depressions or pouches, they are seen to present a difference in colour from the general tint of the aorta. The latter is well known to have a yellowish colour due to the elastic tissue in the media, but the little depressions have largely lost their colour. On holding the vessel to the light, also, there is a distinctly greater translucency, especially in the bottom of the pouch, than in the general aortic wall.

It may be stated at the outset that in all the specimens examined at this early stage in the formation of aneurysm in the aorta there have been two common features, namely, the presence of atheroma in the localised form of atheroma nodosum, and an atrophy or destruction of the media in proportion to the projection of the pouch.

In order to introduce the subject, and to carry forward the observations already made in regard to atheroma, a fuller account of a case may be given here which seems in all respects illustrative, as it gives a picture of the chief lesions found in these investigations.

The case was that of a man, by occupation a slater, who died at the early age of 29. There was a large aneurysm of the thoracic aorta, which projected against the bodies of the vertebræ. Death occurred by rupture of the aneurysm into the pleural cavity. Besides the aneurysm there were numerous atheromatous patches, and there were several incipient aneurysms in the form of depressions, translucent in the middle, described above. Sections were made to illustrate the atheromatous condition as well as the commencing aneurysms.

In the simple atheromatous patches we find at the edges that the internal coat is unduly cellular, the cells as usual parallel to the surface, and with the spindle-shaped

outline as seen in section. There is intercellular substance, which gets more abundant in passing into the patch, and as the patch becomes thicker the cells begin to get fatty. In the fully developed patch fatty degeneration of the cells is very pronounced, and this condition is not limited to the deeper layers, but is tolerably uniform in the whole thickness of the patch.

Even in sections which do not involve a pouch it is obvious that the media is in most cases interfered with. Tracing the deep boundary of the patch the internal outline

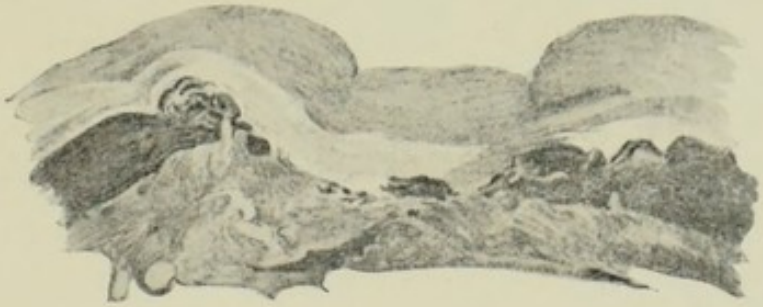

FIG. 13.—Section showing the very beginning of an aneurysm. [The upper part of the section is the atheromatous intima, and should be concave; the convexity is produced by the contraction of the elastic fibres of the adventitia when sections are made.] Under the atheromatous patch the media has disappeared except for a few traces, represented by the dark bits. It is also apparent, on the right side, that the media is irregularly wasted under the atheroma, while its contour on the side of the adventitia is nearly even. (Micro-photograph.)

of the media is irregular, and, in sections stained with logwood or alum-carmine, the media in these parts gives a dull homogeneous staining without differentiation of nuclei. With a higher power these parts of the media give, between the elastic laminæ, the appearance of a homogeneous or finely granular condition, not of a pronounced fatty degeneration, but rather of a necrosis with partial fatty change. Besides this it is seen in all the sections that the atheromatous patch impinges on the media by its actual bulk, and narrows it. In some of the sections it goes even further than this. The internal layers of this coat are opened out and partially disintegrated, and the spaces so formed are occupied by connective

tissue, which is in part continuous with the deeper layers of the patch. This connective tissue, however, is in part, if not wholly, derived from the media itself, being vascularised and apparently cicatricial in its nature. The sections which show the beginnings of aneurysm are illustrated in Fig. 13. There is seen to be an obvious dip in the outline of the internal surface of the vessel. A substantial atheromatous patch extends over the entire surface of the depression, its structure being similar to that of those described above, but less fatty.

The most striking feature is the extraordinary destruction of the media in the small pouch. It will be seen that on either side this coat tapers away, and at the bottom of the depression is, in more places than one, actually interrupted, so that no elastic structure of media separates intima from adventitia. This destruction of the media by no means corresponds with the amount of the depression, and is not a mere thinning by stretching of the coat. The depression is very slight, whilst the loss of substance is great. The media is broken up and separated in various ways, there being gaps and interruptions, which in many cases isolate portions of the coat. In some places small bits of the media, plainly distinguishable by the definite characters of the elastic tissue, especially when displayed by the fuchsine method, are completely isolated. In these instances, where an actual isolation or separation has taken place, the elastic laminæ and the elastic fibres cannot fail to have sustained a rupture, and in some instances the torn ends are visible, occasionally with a curling of the extremities.

An examination of the sections from this case shows clearly that the interference with the media has been from within. Following the internal outline of the media there are irregularities and interruptions chiefly along this border. There are, however, occasional ruptures of the media slightly removed from the internal surface, but usually in the more internal layers.

The tissue which occupies these gaps and interruptions in the media is not that of the atheromatous patch. It is a new-formed connective tissue containing blood vessels, and often abundantly cellular. This is clearly made out in one of our sections, in which it is seen that at a place near the edge of the depression the media is broken up, and that a tissue occupies the gap, which contains many round cells and shows sections of several blood vessels. This tissue along with the blood vessels extends partly into the deeper layers of the patch, replacing its tissue. The new-formed tissue, in some instances, is in connection with the adventitia, especially in the central part of the depression. In the adventitia itself there are not infrequent indications of inflammation in the form of cellular aggregations around the vessels. (May be studied in Fig. 14.)

It is not necessary to pursue the subject in other cases in such detail. The beginnings of aneurysm were carefully examined in 8 cases besides that given above. There is in every case the greatly thickened intima forming the atheromatous patch. There is usually the tapering away of the media with irregular interruptions of its continuity. The gaps are occupied by vascular, and usually somewhat cellular, connective tissue.

Whilst the atrophy of the media is usually gradual, the interruption is sometimes abrupt. In one specimen, for example, the media is abruptly truncated, ending in a rounded, almost bulbous extremity, as if it had suffered a complete severance. Minute examination in this case, however, shows some traces of media beyond the abrupt margin.

In all of the specimens also where there is this atrophy of the media, there is new-formed connective tissue filling the gaps and often penetrating into the atheromatous structure, although really foreign to it.

These being the general features met with in the first beginnings of aneurysm, it may be inferred that in actual aneurysm the media does not exist at all except at the

neck of the sac. This is the case even in very small aneurysms. In one such, in which, besides some small depressions such as have just been described, there was an actual sacculated aneurysm, but of small size, there was a thick atheromatous patch visible before the neck of the sac was reached. In this part the media was greatly atrophied and its fibres were separated by vascular connective tissue. At the neck of the sac the media for the most part ceased, but a few fibres could be traced round, everted by the protrusion of the sac. The atheromatous intima also was hardly carried into the sac, whose wall was formed essentially by tissue produced in intima, media, and adventitia by the process of chronic inflammation.

We have spoken of atrophy of the media under the atheromatous patch, but it behoves us to refer more in detail to the nature and seat of this atrophy. There is, in the first place, a local atrophy of this coat immediately under the patch, an absolute loss of tissue due to pressure. As already mentioned, the atrophy so induced may reach to a very considerable extent, especially when circumstances are favourable to an inordinately forcible impact of the atheromatous nodule against the media. It is quite common under such circumstances to find the thickness of the media reduced to one-half, or even one-third of its natural amount, from this cause alone. Again, the media may show a local destruction underneath the atheroma, necrotic in character, due to involvement of its inner layers in the atheromatous lesion. This form of encroachment is of extreme frequency, and serves to augment the tendency to rupture of the fibres of the middle coat.

But there is a form of atrophy of the media differing from both of these in respect of its origin and distribution. We refer to a granular atrophy of the elastic fibres, found generally to a greater or less extent in cases of commencing aneurysm. This change is the more clearly evident as the growth of new and vascular (inflammatory) connective tissue proceeds apace in the media, and reveals itself

microscopically as a finely beaded appearance of the involved fibres. Broken up into shreds and irregular masses, these granular fibres dispose themselves in variable numbers between the fibrous patches and lamellæ, interspersed hither and thither with a few healthy fibres in the best preserved parts, but ultimately disappearing into occasional thin granular lines. This granular degeneration, it must be observed, is only found after changes secondary to the atheroma. Ruptures, on the other hand, occur on the whole at an earlier stage, and when we find abrupt separation of the elastic fibres, with, possibly, coiling of their ends, we conclude that rupture has occurred; the ruptured fibres themselves are not usually at first the seat of this granular change.

The loss of the elastic tissue so entailed is usually accompanied by destruction of the muscular fibre cells of the media, and their replacement to a greater or less extent with vascular connective tissue. In some cases, however, the muscle nuclei appear to persist after the destruction of the elastic fibres, and are plainly visible in the midst of the sclerotic tissue. This persistence of the muscle nuclei is, however, not to be confounded with another appearance, which shall presently be referred to.

Repeated allusion has been made to the fact that a new connective tissue fills up the gaps caused by ruptures and interruptions of the media. But apart from the actual sac or pouch constituting the small commencing aneurysm, which is exclusively composed of formed connective tissue, let us advert to portions of the arterial wall in which the changes tending to aneurysm formation are in active progress. In such it is usually found that new connective tissue grows extensively in the media, the proper fibres of which show the peculiar degeneration above described. In the extensively diseased aortas of elderly persons we often see, without any aneurysm formation, what is virtually a new wall, composed of this connective tissue, which may even exceed in places the thickness of the

original wall. It is evident that such a formation must be restorative or compensatory. In elderly persons the compensation so provided is usually sufficient, but in those who are subjected to severe bodily exertion the case is different. *It is the weak point in this line of defence which is liable to become the starting-point of an aneurysm.*

But we have another and more direct proof of a compensatory process at work, afforded in the occasional new growth of muscular tissue in both intima and media. This curious phenomenon has been apparent in the thickened intima in several of our cases, and in one or two others it was plainly seen in the media. The existence of smooth muscle cells has been asserted by some as a normal constituent of the intima of the aorta and certain other arteries, and the phenomenon referred to would seem to confirm this view. It is noteworthy that whilst in the normal state the muscle cells of the aortic wall are disposed in regular order between the elastic laminæ, the muscular growth referred to consisted of bundles running in various directions. This atypical growth is to be regarded as an instance of exceptional compensation, and is in all likelihood the expression of individual peculiarities.

If now we consider the facts of the case in the light of what we have adduced in regard to atheroma in general, and as to the conditions met with in the beginnings of aneurysms in the aorta, the matter may perhaps be summarised as follows:—(1) Atheroma frequently leads to atrophy and rupture of the media, and when this has occurred there is always a new formation of vascular connective tissue which fills the gap, and apparently strengthens the wall. (2) In the beginnings of aneurysm of the aorta, which are frequently met with in the form of slight dips or dimples, both in cases of actual aneurysm and in cases where atheroma exists alone, there was in all the cases examined an atheromatous patch continuous

over the small depression. (3) There was also in all these cases great atrophy of the media, and, even in the case of slight dimples, an actual interruption of the continuity of the media was frequent. (4) Along with this there is new formation of tissue, by a process of chronic inflammation, the new-formed tissue growing into the media, and in many cases on into the intima. (5) When the aneurysm is actually formed, its wall is virtually composed of this new-formed tissue, which is derived from the existing connective tissue of the adventitia and media, but especially the former.

Rupture and atrophy of the media, as we have seen, play an important part in the actual production of the aneurysm, and the question arises whether such rupture and atrophy may not be the primary lesion, and the other processes entirely secondary. This is the view held by a considerable number of pathologists, amongst whom we find the honoured name of Recklinghausen, with Eppinger, Manchot and others, and it will be referred to further on. Meanwhile one or two facts may be related which bear on this point.

There seems to be no doubt that the media may be, by constitutional peculiarity or otherwise, unusually weak and abnormally ready to undergo rupture or atrophy. This fact is illustrated by the following case.

A man was affected with aortic and mitral disease, and his heart was considerably hypertrophied and dilated. He died of pneumonia and pleurisy with effusion. In examining the aorta *post-mortem*, some patches of atheroma were found, but in the parts free from atheroma were "a number of small puncta which are slightly depressed and are translucent". Those puncta were found, on microscopic examination, to represent ruptures of the media. At the surface of the aorta there was a distinct rupture of the media, into which the intima had sunk so as to produce a depression. Besides this superficial rupture, there were visible ruptures situated in the substance of the media at

a distance from the surface. In some parts of the aorta there were many such ruptures, both superficial and deeper. Most of these seemed recent, as judged by the fact that there was seldom any appearance of inflammatory new formation in the gaps, but there were some where such appearances were present, showing that they had existed for some time.

The condition of the media under the atheromatous patches was instructive. There were no appearances of

FIG. 14.—Section of aorta from the case alluded to in the text. For description see under Fig. 11. (Micro-photograph.)

aneurysm, but the media presented, perhaps in an exaggerated degree, that atrophy and partial interruption which atheroma produces, whilst the gap was occupied by new-formed tissue. This is shown in Fig. 14.

In this case there had probably been a weakness of the media, increased by the acute illness of which the patient died. The hypertrophied heart acting on the weakened media has caused these many small ruptures, which were visible to the naked eye as small puncta. Again, the

unusual degree of atrophy of the media, under the atheromatous patches, strongly suggests a preceding weakness of that coat. Beneath the atheromatous patch (which, partly necrosed, is shown by the dark mass to the left) there is a distinct gap in the media. This gap is occupied by a highly cellular new-formed tissue, which extends from the intima, where it is widest, in amongst the fibres of the media as if between the ruptured ends of the elastic tissue. The case is of great importance as supporting the view that the changes in the media are secondary to those in the intima. Here a special weakness of the media is associated with these secondary changes in a high degree, *but this high degree is only presented under the patches.* The same applies to inflammatory changes in the adventitia. These are indicated by the unusual nucleation of the tissue at the lower part of the figure. It is only directly underneath the atheromatous patches that such inflammatory changes are found in the adventitia.

Another case which came under observation also deserves a passing notice. It was a case of cancer of the stomach, with secondary growth in the peritoneum, in a man æt. 70. The body was much emaciated, but it is noted that "the heart is slightly enlarged, weighing 11½ oz. The muscular substance is firm and tolerably healthy looking." The aortic arch presented a well-marked, more or less uniform dilatation, but no thinning of the wall was observed. Under the microscope no atheroma or atrophy of the media was visible; but in the dilated part of the arch there was a well-marked fatty degeneration of the media. This is visible in the tissue lying between the elastic laminæ, and affects either the muscle alone or the muscle along with the fine elastic fibres which run between the laminæ. There is slight fatty degeneration in the aorta, outside the bulged part and in the wall of the pulmonary artery.

In another case of cancer (in which the sigmoid flexure was the seat of tumour), without any bulging of the aorta,

is found some fatty degeneration in the media, and also to a slight degree in that of the pulmonary artery.

These cases are of interest as showing that an emaciating disease may lead to degenerative changes in the media, and may presumably render it more liable to atrophy. It is not unlikely that in cases where a person survives an emaciating disease, the presence of atheroma of the aorta, coinciding with degeneration in the media, may lead to such atrophy of the media as to form the basis of an aneurysm.

One Case of Popliteal Aneurysm.

Only one case of aneurysm in the arteries of the legs was met with, but so far as they went the appearances were confirmatory of the observations in the case of the aorta.

The case was one of aneurysm of the popliteal artery. The aneurysm was oval in shape, forming a fusiform expansion of the vessel, about $2\frac{1}{2}$ inches in length. The appearances were studied in the vessel above and below the aneurysm, at its neck and in the midst of its wall.

The vessel above and below the expansion showed marked atheromatous thickening, with an occasional area of calcification in the media. Here is the description of a transverse section of the artery, at a point more than an inch below the distal extremity of the aneurysm :—

There is an abrupt elevation of the intima into the regular atheromatous patch, which, in its thicker portions, shows well-marked fatty degeneration. The media, before the patch is reached and also to a less extent inside its edge, shows small patches of calcareous infiltration. The membrane of Henle is at first traceable under the patch, but it soon gets broken and interrupted. At the same time the media shows signs of inflammation, becoming permeated by vessels around which a cellular connective tissue is present. It is particularly noticed that, where

the membrane of Henle is interrupted, vessels extend into the deeper layers of the atheromatous patch, and that here there is a more normal and undegenerated connective tissue than that of the rest of the patch. Turning our attention to the neck of the aneurysm we find, both at the proximal and distal extremities, important changes both in the intima and media. There is pronounced atheroma, and, a considerable distance from the actual neck of the sac, the membrane of Henle is broken and the muscular tissue of the media is interrupted. As the media in vessels of this size has little or no elastic tissue, the principal visible evidence of atrophy is in the muscular substance. We find in the latter that the muscular fibre cells are dissociated, and that connective tissue enters into the composition of the media. As the neck is approached there is a pronounced thinning of the media. At the proximal extremity however, just at the neck of the aneurysm, there is a curious increase in the muscular tissue of the media, so that, at the ridge which forms the neck, the media is really thickened, as if the muscle formed a kind of sphincter. At this place, and for some distance proximal to it, the membrane of Henle suffers many interruptions, and it is not at all traceable beyond the neck. The rest of the media also, when the ridge of the neck is passed, suffers rapid atrophy, there being the usual formation of vascular connective tissue which extends into its substance and separates its elements.

In the aneurysmal wall proper, there is rarely any trace either of intima or media, but the tissue is a highly cellular connective tissue containing blood vessels. In some places the cells are spindle-shaped, the spindles lying parallel to the surface. There is a coagulum adherent to the internal wall, and the lining of the aneurysm forms a somewhat irregular boundary to the coagulum. It is, in some places, as if the connective tissue were partly growing into the thrombus.

An Aneurysm in a Cerebral Artery.

An aneurysm of one of the larger cerebral arteries (such as already mentioned is of somewhat frequent occurrence) presented conditions in some important respects different from those already considered.

The aneurysm was situated on the right internal carotid artery, and was about the size of a pea. It lay exactly between the two vessels, the anterior and middle cerebral arteries into which the internal carotid divides. The fork between these two arteries was thus replaced by the aneurysm, and the mouths of the two vessels were separated by a third mouth, that of the aneurysm. The aneurysm also looks like a truncated prolongation of the internal carotid, being directly in line with it. Microscopic sections were made which present four rounded bulgings, namely, wall of carotid, and opposite it the aneurysm, whilst on one side is the middle cerebral, and on the other the anterior cerebral artery. In the three arteries the structure is well preserved. There is the thick muscular coat, bounded internally by the membrane of Henle. In preparations stained in fuchsine and methyl-blue, by the modification of Manchot's method, the membrane of Henle is prominently visible as a red wavy line around the vessels. There is an occasional but very slight thickening of the intima. At the neck of the aneurysm the membrane of Henle, on one side, abruptly disappears, as does also the muscular substance of the media. On the other side the membrane can be traced a very short distance inside the neck, and the muscular coat is also slightly prolonged. The aneurysm, as a whole, is formed of dense, somewhat cellular connective tissue, from which intima and media are entirely excluded. It is as if a gap had been made in these coats of the vessel, and the space filled with dense tissue expanded into the rounded form of the aneurysmal sac.

General Conclusions.

We have seen that atheroma is a frequent disease when the middle period of life is reached, and that it is earlier in its appearance in the aorta than elsewhere. The disease consists simply in a thickening of the intima, and, as the intima is non-vascular, so is the new-formed tissue which constitutes the thickening. In many cases, both in the aorta and in the arteries, the atheromatous thickening is unaccompanied by any affection of the other coats of the artery. But the atheroma, more particularly when, as in the aorta, it is in the form of localised thickenings or nodes constituting the atheromatous patch, seriously disturbs the remaining coats, and especially the media. It does so, not only by continuous pressure on the inner layers of the media, but by its impact against this coat due to the force of the blood. By these means the elastic tissue of the media may be ruptured or caused to atrophy, namely, the membrane of Henle in the smaller vessels, and the various elastic laminæ in the aorta. Where such rupture or atrophy occurs, a new formation of tissue takes place, just as in traumatic injuries elsewhere, the tissue produced being a vascular granulation tissue which proceeds to develop into connective tissue. The adventitia is involved in this secondary inflammation, the new tissue partly sprouting from it. The vasa vasorum, whose principal position is in the adventitia, sometimes take part in the inflammatory process, so that we may have, not only a cellular proliferation outside these vessels, but also a thickening of their intima, constituting a true endarteritis obliterans. The new-formed tissue also frequently invades the intima, showing itself under the patch, and is distinguishable from the patch by its vascularity and by the absence of any degenerative tendency. In some cases the media is penetrated by bands of new-formed tissue, and the intima is considerably involved.

All this may occur, and does occur, in a multitude of cases without any aneurysmal protrusion. The new-formed tissue evidently strengthens the wall and helps to replace the lost tissue. But the wall, weakened by the atrophy or rupture of the media, is liable to be stretched and bulged by the force of the blood. It is so liable chiefly in persons whose occupations or habits expose them to sudden and severe exertion, in which the heart is stimulated to very forcible pulsations, and the arterial blood pressure is elevated. Hence, whilst atheroma is a disease whose incidence extends over a considerable period of life, aneurysm occurs mainly in persons who are under 50 years of age. It occurs also chiefly in men, and predominates in occupations which imply severe exertion. There must be many persons past middle life whose vessels present conditions favourable to aneurysm, but in whom it does not occur because the weaker heart and the general muscular inability precludes them from the excessive physical exertion of more youthful persons. The aneurysmal period is where the period of atheroma overlaps that of severe exertion, and the two causal agents may come into play. It may, perhaps, be said that were atheroma to occur even in a small proportion of cases amongst persons in their teens and twenties, then the prolonged forcible exertions of rowing, football, running, etc., would furnish numerous cases of aneurysm.

It may be further said that a congenital or acquired weakness of the media may predispose to aneurysm, and that in cases of recovery from severe illness, should the heart be restored to full vigour before the arteries have completely recovered, there may be the opportunity given for the formation of an aneurysm.

Atheroma, however, although by far the most frequent, is by no means the only cause of such interference with the media as to give occasion to aneurysm. In the case of aneurysm of the cerebral arteries we have seen that the aneurysmal sac is virtually a protrusion from a gap in the

media and intima, but it is doubtful if atheroma ever plays any part in the production of such aneurysms. We have seen an aneurysm of a cerebral artery in a vessel with atheroma, and with a part of the patch carried into the aneurysm, but this is rare and may be only a coincidence. In our belief, embolism is the usual cause of such aneurysms. In a large proportion of cases, aneurysm in the cerebral arteries is associated with disease of the valves in the left side of the heart. The researches of Ponfick and others have shown that a piece of solid tissue or exudation, carried away from the curtains of the mitral or aortic valve, may lead to aneurysm, if, when carried to the brain, it fails to completely plug the artery. By its continual projection against the wall by the pulse wave it will injure the intima and especially the media, just as the atheromatous node does. The media once compromised, the aneurysmal protrusion readily occurs here, as the soft tissues around afford little support to the vessel from without. It is in agreement with this mode of origin of cerebral aneurysms that their occurrence presents a totally different incidence as to sex, occupation, and age to that of aneurysms in general. In our small number of 8 cases the ages range from 15 to 70, the cases being distributed over a period of life which is much longer than that of aneurysms of the aorta, and which overlaps the latter period both below and above. The only circumstance which is common to these 8 cases is the occurrence, at some period of life, of a condition of the heart which has given rise to an embolism.

It is necessary here to refer to the fact that a different view of the relation of the conditions of the media and intima respectively has been held.

Recklinghausen * seems to have originated the idea that rupture of the media may be the starting-point of aneurysm. His own observations, however, only apply to the minute

* Recklinghausen, *Allgemeine Pathologie*, 1883, p. 84.

miliary aneurysms of the brain substance, which are so frequently the source of cerebral hæmorrhage. He says, in regard to these aneurysms: "In the fresh miliary aneurysms I was able to detect distinct cracks in the media, and Virchow has already demonstrated defects in their muscular fibres; I consider the cells and tissue growth which Charcot and Bouchard have found as something secondary". This sentence seems to have been a very fertile one. Recklinghausen's observations, which referred to a particular class of aneurysms, have been extended to aneurysms in general.

Eppinger,* in a voluminous monograph on aneurysms, takes up this view, and holds that in ordinary aneurysms rupture of the media is the primary lesion. He goes so far as to propose that the ordinary aneurysm should be called by the name traumatic aneurysm, on the view that it has originated by a traumatic rupture of the media.

Manchot,† working in Recklinghausen's laboratory, has further amplified the view. It is to be presumed that his paper may be taken as having in some degree the high authority of Recklinghausen. According to this author, "the dilatation is brought about by primary rupture of the elastic elements of the media". The inflammatory processes visible in the wall of the vessel and of the aneurysm are of secondary importance. The atheromatous thickening of the intima is in this way relegated to an entirely subordinate position. A perusal of Manchot's paper leads to the conclusion that this view is not a tenable one. The possibility of aneurysm arising from rupture of the media, apart from atheroma, is not to be denied, and the case of aneurysm of the cerebral arteries has been adduced as an example. It is possible, also, that in the aorta a traumatic rupture of the media may lead to aneurysm, as it seems to have done in the case recorded

* Eppinger, *Pathogenesis, Histogenesis und Ætiologie der Aneurysmen*, 1887.

† Manchot, *Virchow's Archiv*, 1890, Bd. cxxi., s. 104.

by Krzywicki, quoted by Manchot, but such a condition is admittedly rare, and furnishes the exception which proves the rule. It is an interesting commentary on these views that primary rupture of the intima and media in the aorta does not lead to the ordinary sacculated aneurysm, but to the dissecting aneurysm, which is quite a different pathological condition.

In any case the foregoing observations show the most intimate association between atheroma and the ordinary sacculated aneurysm. We have seen that the first beginnings of such aneurysms are associated with atheroma, the thickened intima in the form of an atheromatous node covering the small depression which is the commencement of the aneurysm. We have found also that in cases of aneurysm of the aorta, the other parts of the vessel are, virtually in every case, the seat of atheroma. It has also been pointed out how the age at which aneurysm occurs connects it with atheroma as one of the causal conditions. Were primary rupture of the media the cause of aneurysm and of atheroma, we should have both of these conditions frequently occurring in the years of early manhood.

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