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THE GENERAL PATHOLOGY OF SYPHILIS

BY

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CHAPTER XIII

THE GENERAL PATHOLOGY OF SYPHILIS

Syphilis is in many respects unique amongst the infective diseases of mankind. It combines the characters of a specific fever running a very chronic course with those of an infective granuloma. No other communicable disease is apt to continue its manifestations twenty or even fifty years after the original infection, and, when it would appear at an end, syphilis may leave its victims subject to chronic degenerative changes, especially of the central nervous system, not in themselves of a directly syphilitic nature. Further, it is a disease which is more clearly inheritable than any other known infection.

The Specific Nature of Syphilis. Nothing is more certain than the fact that syphilis is a strictly specific infection. The idea that it is a filth-disease, originating from unclean and promiscuous sexual congress, is entirely disproved by the data of exact pathology. How in the first place it arose is a matter of pure conjecture. We must presume that the infecting agent was in the beginning a harmless genital saprophyte, and that it has since acquired parasitic powers enabling it to invade the living tissues and induce widespread morbid reactions. Having in some way thus originated, we see the disease to-day spreading from case to case by direct infection, able to attack the chaste as well as the unchaste, should transfer of the virus take place from an infected to a normal person, irrespective of sexual intercourse.

The history of medicine abounds in examples of diseases long confounded with allied affections, but in the end, with the advance of clinical observation and experiment, gradually recognized as specific entities. All venereal diseases were at one time confused together. Gonorrhoea was at length recognized as an independent affection; later still, venereal sores were found to fall into two

groups—those which after weeks or months are followed by symptoms of constitutional infection, and those which produce no such results. There are few nowadays who doubt that the 'soft sore' is a distinct infection, which may indeed complicate true syphilis at the outset, but is in no sense a mere abortive form of that disease.

Syphilis now stands out as an affection well marked and separate from other venereal diseases. It would be rash to predict that no further differentiation amongst these infections will ever become manifest, but there is at present no hint that syphilis is other than a specific entity. Recent discoveries have indeed greatly strengthened this belief.

The Effect of Modern Discoveries as to Syphilis. The absence of exact knowledge as to the nature of the infecting agent in any given infective disease has always proved a serious bar to its scientific study. Even a graver hindrance is the lack of any susceptible animal suitable for experimental investigation of the infection. With Koch's discovery of the tubercle bacillus our knowledge as to tuberculosis at once began to increase by leaps and bounds, and is still advancing. But in the case of syphilis pathology seemed to have reached a limit. What morbid anatomy and histology could teach had been learned; experimental inoculation upon human beings was not justifiable upon the scale required. Chance clinical observations occasionally allowed of some new, though mostly tentative, conclusion to be reached, but the subject was almost at a standstill. Then came the announcement by Metchnikoff and Roux, in 1903, that syphilis was inoculable with typical results on the anthropoid apes, and in less typical fashion upon certain of the lower monkeys—a discovery confirmed on every hand. Again, two years later, came the evidence brought forward by Schaudinn and Hoffmann connecting the *Spirochaete pallida* with the causation of syphilis. This evidence, it is true, is circumstantial only, but it has been so abundantly confirmed that the spirochaete has gained widespread acceptance as the true causal agent in the disease.

It is difficult to say which of these two discoveries is the more important. Up to the present time the possibilities opened out

by simian inoculation have probably proved the more fruitful in direct positive advances in our knowledge. The inoculability is a tangible fact which cannot be gainsaid. It has already afforded the means for tracing the generalization of the syphilitic virus throughout the body, and has in many ways corrected the crude data which had been derived from clinical observation; it makes it possible to distinguish between a cured and a latent case of the disease, while the problems of immunity can for the first time be approached by those modern methods which have proved of such value in the case of other infections. We have, too, a criterion by which the reality of the alleged successful results of syphilitic inoculation upon other animals can be judged. The discovery of the spirochaete may, it is true, in the long run, prove the more important, but at present there are certain limitations to its value, some of which must remain until it has been found possible to cultivate the organism. So far it fulfils only the first of Koch's postulates, but it does this very fully. The technique of its demonstration is often difficult and uncertain, though less so with experience; nevertheless, the inoculation of apes appears at present a more certain test as to the syphilitic nature of any given material than the presence or absence of demonstrable parasites.

The evidence connecting the *Spirochaete pallida* with syphilis is fully discussed in another section of this work [Vol. I, p. 95–101.] While I accept it as in all probability the causal agent, I shall endeavour, in this article on the general pathology of syphilis, to confine myself as far as possible to such facts as would remain true even should it be proved that the spirochaete was not the cause of the disease. Though I shall frequently have to refer to the spirochaete, I shall, wherever possible, use the term 'syphilitic virus'.

The Properties of the Syphilitic Virus. Syphilis has always been recognized as a 'contagious' disease in the strict sense, i.e. one which spreads by direct infection only. The reason for this is clear: it depends upon the very low resistance of the virus outside the human body. Tested by inoculation upon apes, it remains efficacious only up to six hours after its removal from the body. It is destroyed by heating for an hour to 51° C. Hence it is that syphilis is so rarely conveyed indirectly. Where a cup

or tobacco pipe is used in common by a syphilitic and a healthy subject, so that still moist secretions may be transferred, infection may undoubtedly arise in rare cases. But in the overwhelming majority of cases the disease is transferred by immediate contact, usually in sexual intercourse (90 to 93 per cent. of all cases, according to Fournier), more rarely in kissing or suckling, or in the surgical examination of a case of active syphilis. The conveyance of syphilis by inheritance will be discussed later.

The Channel of Infection. Clinical experience proves the primary seat of inoculation in acquired syphilis to be almost invariably a surface covered by squamous epithelium. This is so in all cases of syphilis of the genital organs in both sexes, for in the male the urethra, beyond which primary inoculation does not occur, and in the female the cervix uteri, of which the same is true, are both covered by epithelium of this type. The mouth, tongue, tonsils, and pharynx are similarly coated. Practically the only instance to the contrary which can be cited is primary chancre of the rectum above the sphincter ani—an occurrence of such extreme rarity that it only emphasizes the general law laid down. It would seem as if squamous epithelium were the specific primary nidus of infection. In order to effect a lodgement, the parasite would appear, in the great majority of cases, if not always, to require some minute crack or abrasion in the epithelium. Whether infection ever occurs through intact epithelium or mucous membrane cannot certainly be decided, but it is at least clear that minute surface-lesions, such as are apt to occur during coitus, are conditions very strongly predisposing to infection.

Experiment has carried our knowledge to a still further point of certainty. Cutaneous inoculations are alone successful. There seems only one way of producing syphilis in apes and monkeys, namely, introduction of the virus into the scarified epidermis. It is strange but true that an organism capable, in the later stages of the disease, of flourishing in so many of the bodily tissues, should at its first introduction be capable of taking root in one tissue only—the epidermis, and that a damaged epidermis. In all the numerous experiments of Neisser and his colleagues, the rubbing of virulent material into the undamaged surface of the tonsil,

conjunctiva, and nasal mucous membrane produced no effect. They were uniformly unsuccessful in fifty-one cases in which subcutaneous inoculation was tried, though many animals so treated became cachectic and died. Equally futile was intravenous inoculation, which they attempted fifteen times. Intraperitoneal inoculation has also proved of no avail. These non-cutaneous methods may indeed lead to the formation of antibodies in the inoculated animal, but they do not cause recognizable syphilis. The only possible exception to the rule seems to be the testis: of two animals inoculated in the incised testis, one subsequently proved refractory to cutaneous inoculation, and the other, killed after fifty-six days, was proved to harbour the virus in its bone-marrow. Primary infection of the testis cannot occur under natural conditions, and the results of experiment upon apes tend to confirm clinical experience, that the acquired form of syphilis is propagated exclusively by cutaneous channels.

As regards experimental inoculations upon the relatively insusceptible lower monkeys, it would seem that success can be achieved only in certain regions of the body, namely, the genitalia and eyebrow. It has been suggested that this depends upon the greater vascularity of the skin in these parts ; Neisser states that he has never attained a successful result without such energetic scarification as to cause some haemorrhage.

The rule that cutaneous inoculation is alone successful does not apply to the inherited disease.

The General Course of Syphilis. Before pursuing in detail the progress of the infection throughout the body, or discussing the essential nature of the lesions which arise, it will be convenient to make a few general observations on the course of the disease.

Attention has frequently been called to the correspondence between syphilis and the specific fevers ; the difference is indeed mainly one of chronicity. An ordinary specific fever, such as small-pox or scarlatina, presents certain definite stages. After exposure to infection there is a latent period during which no clinical manifestations are evident : this is the stage of incubation. The specific agent is at work, but until it has so multiplied in the body as to produce a sufficient toxic influence, the body does not

respond by any clinically recognizable phenomena. The latent period may be short or long—a day or two in scarlet fever; a fortnight or so in typhoid. Then comes the bodily reaction against infection—in some cases abrupt, in other fevers insidious in onset. The popular idea dates the beginning of the disease from the first clinical manifestations, but in truth the process starts at the time of infection.

In most fevers there ensues a cutaneous eruption or exanthem, varying in character and time of onset with the nature of the disease. The exanthem may effect mucous as well as cutaneous surfaces. And finally, if recovery take place, the bodily reaction ceases, the temperature falls, the eruption vanishes, and health is restored. Nevertheless, in many cases the disease leaves some traces behind—a weakness, an anaemia, or a slowly progressive change in one or other organ which has been affected.

In all these respects syphilis corresponds with the ordinary specific fevers. There is an incubation period, followed by a rise of temperature and an exanthem, with general disturbance of the health. And when all this has subsided there remains a tendency to remote consequences of a very special character. But there is this difference between syphilis and the ordinary fevers: instead of running its course in a few weeks, its manifestations are spread over months and years. The incubation period is longer than in other fevers; the febrile reaction and rash may persist for months, and the ultimate sequelae may appear after ten or twenty years. Syphilis may justly be classed, from this aspect, as a chronic specific fever.

From another aspect it may with equal propriety be classed with the infective granulomata. An acute infection such as that seen in tissue-invasion by the pyogenic cocci, running its course in a few days or weeks, is met by a response on the part of the more labile factors in bodily defence—notably of the polynuclear leucocytes; there is no time for the more sluggish reaction of the cells concerned in tissue repair, though this is added during the later stages of healing. But in such chronic tissue-infections as that due to the slowly-growing tubercle bacillus the primary reaction is on the part of the endothelial and connective-tissue elements

of the body; the leucocytes take but a subordinate share in the process. The first result of the lodgement of tubercle bacilli in the tissues is, as a rule, the formation of a kind of granulation tissue, constituting the primitive tubercle. Such infections are hence termed 'infective granulomata', and they tend, on the one hand, to a degeneration and softening of the newly-formed tissue, and on the other to a fibrosis which helps to limit the spread of the infection.

The nature of the tissue reactions in syphilis conforms to this latter type. The primary seat of inoculation becomes occupied by a granulomatous growth—the chancre—which consists essentially of cells derived from the fixed connective-tissue and endothelial elements with an abundance of 'plasma cells', the origin of which is not yet certain, but which are clearly not among the more labile elements in tissue defence. Most of the cutaneous lesions of the eruptive stage of syphilis show similar aggregations of plasma-cells, which, though they may not organize into permanent fibrous tissue, indicate an analogous reaction. But it is in the later stages of the disease that the correspondence with the infective granulomata is most clearly apparent. When the eruptive fever is over, there remains, so long as the virus persists in the body (which may be almost for a lifetime), a tendency to local tissue-proliferations, or gummata, which present the closest analogy with tubercle. So similar is gummatous to tuberculous infiltration, that, though it is easy to indicate general differences, the histologist is not rarely in some doubt as to which process he may be observing. Syphilis in this stage appears as an infective granuloma pure and simple.

Last of all, the final and most remote effects of syphilis—the so-called 'parasyphilitic' lesions—are in their essence degenerative changes associated with overgrowth of the fixed connective tissue elements.

The Detailed Course of Syphilitic Infection.

Incubation Period. The essentially chronic nature of syphilis is seen even from the first. After the virus has been introduced into the skin, there ensues an incubation period of several weeks,

during which not even a local manifestation is apparent. In man this latent period may last from ten days to seven weeks, but on an average it is three weeks or a month. In apes and monkeys it is about the same : according to Neisser's figures the average incubation period is three or four weeks, with extreme limits, in exceptional cases, of twelve days and sixty days respectively. Neisser conjectures that the variations depend upon the number of parasites present in the inoculated material. During the incubation period we must believe that the parasite is gradually making good its foothold in the local tissues. The tardiness of the local reaction which it evokes depends upon the fact that it is a reaction of the fixed tissues. If the virus of gonorrhoea or of soft sore has been simultaneously inoculated, their manifestations are speedily apparent, but in due course are followed by the specific reactions associated with syphilis.

The Primary Lesion. The clinical characters of the chancre are dealt with elsewhere in this work. I propose here only to touch on its more general pathological features.

It is essentially a *cutaneous* lesion at the outset, spreading to the subcutaneous tissue and later to the local lymphatics. In cases where the virus has been deliberately inoculated in man, in which alone the earliest stages of the process are likely to come under observation, the first sign to appear is a slight and very local reddening of the skin, which slowly spreads and becomes a raised papule. As it increases in size, a slight crust of dried exudation may form on the surface, and beneath this the epithelium is apt to be superficially eroded, though, as a rule, no extensive loss of substance occurs.

With the spread of the inflammatory reaction to the dermis, which takes place at a comparatively early period, a marked degree of induration is, in most cases, apparent. In part this induration doubtless depends on lymphatic obstruction, but it is in the main due to proliferation of the fixed connective tissues and endothelium, with a local aggregation of lymphocytes and plasma cells. It varies considerably in its degree, but on the whole amply justifies the term ' hard chancre ' commonly applied to the primary sore. Many clinical varieties of the chancre have been

described according to the degree of induration ; they depend on the extent of the reaction on the part of the subcutaneous tissues. This varies in different regions of the body ; it is often less marked on the female than on the male external genitalia, and it is sometimes practically absent in extra-genital chancres.

The final stage of the primary lesion is one of gradual disappearance. The induration becomes less, and healing slowly occurs, as a rule with little or no scarring or permanent tissue change. The total duration of the chancre is from four to six, or more rarely eight, weeks. It is a striking fact that the initial manifestations of so dire an infection should be of such apparently benign nature. Almost painless, apparently local, accompanied by no constitutional disturbance, and tending to disappearance in a few weeks, the chancre offers little hint of what is to follow.

The Lymphatic Phenomena accompanying the Primary Sore. In spite of this apparent benignity, there is already one constant sign that the infection is not a merely local one. This consists in an enlargement of the lymphatic glands in the vicinity of the chancre—the ' indolent bubo ' so characteristic of the primary disease. ' Pas de chancre infectant sans bubon ' was Ricord's law, and Fournier declares that in 5,000 cases he has found it but thrice absent.

The lymphatic vessels passing from the site of the chancre to the nearest lymph-glands soon become recognizable as indurated cords, interrupted here and there by small nodular swellings—the so-called ' bubonuli '. The process is a chronic lymphangitis with local lymphatic infarctions. Even by the end of the first week after the chancre has appeared, certainly during the second week, enlargement of the lymphatic glands is clinically manifest, and there can be little doubt that glandular *infection* is practically concurrent with the development of the chancre itself. The gland or group of glands to which run the lymphatics draining the site of the initial sore, wherever this may be, become gradually enlarged and firm—a change usually unnoticed by the patient, since it is unaccompanied by pain or tenderness. Nor, even at this stage of the disease, is infection necessarily confined to the first group of glands to which the lymphatics in question pass. In

persons dying accidentally during the primary stage of syphilis in the genital region, there has been found, in addition to the ordinary inguinal bubo, a marked enlargement of the iliac and even of the aortic lymphatic glands. It is probable that this is no exceptional thing, though it cannot be determined during life.

The truly syphilitic nature of the glandular affection is beyond doubt. It runs the same sluggish course as the primary sore, spontaneously subsiding after a time. The *Spirochaete pallida* has repeatedly been demonstrated in the indolent bubo, and material from such glands has proved inoculable upon apes and monkeys with typical result.

Clinical evidence is at one with histological observation and with animal experiment in pointing to the lymphatic system as the main channel by which the virus of syphilis passes from the primary lesion into the system. Whether it is the only channel is open to question ; there is as yet no clear proof of primary absorption by the blood-vessels, though it would be difficult to disprove such an hypothesis. But the facts already cited as to the early infection of the local lymphatics offer a complete explanation of the well-known truth that even free excision of the primary chancre, when it first becomes manifest, has no influence whatever in preventing constitutional syphilis. It has been seen that the response to primary infection is a very tardy one, with a latent period of some weeks. The response to lymphatic infection may be assumed to be equally slow, and the constitutional disease itself has a latent period which overlaps, or coincides with, the objective phenomena of the primary stage. Slowly the virus spreads from point to point, and the sluggish response of the fixed tissues follows too late on its trail for measures of interception to be efficacious.

The Phenomena of Constitutional Syphilis. During the earlier stages of the disease which have so far been described, there is no general disturbance of health—no response on the part of the body as a whole to the infection which has taken place. This is the so-called ' primary ' stage of syphilis, during which it is an apparently local affection.

Now ensues a stage when the body as a whole begins to react

against an infection which has manifestly become general; this is commonly known as the 'secondary' stage of syphilis. The phenomena of constitutional syphilis are very varied, and will here be considered only from a general point of view. The incubation period of the constitutional symptoms is, on an average, six or seven weeks from the first appearance of the primary sore, or between two and three months from the date of infection. Doubtless general infection has taken place some weeks before any outward signs are apparent.

The phenomena of the general bodily reaction are widely different from those of the initial infection. In place of a localised granulomatous formation we see a succession of rashes spreading over the cutaneous and mucous surfaces—widely diffused, though slight, enlargement of lymphatic glands—a chronic febrile condition with anaemia and general disturbance of health—aches and pains in the bones and a tendency to obscure inflammatory changes in many of the internal organs. It is not too much to say that no part of the body is exempt from the manifestations of secondary syphilis, though in any given case but few organs may be affected. Multitudinous though they be, the symptoms tend to preserve a certain general order in their evolution, and they may extend over a year or two unless controlled by active treatment.

The phenomena of secondary syphilis may be divided into general and local, and the local lesions must be regarded as metastatic—i.e. of the nature of local reactions against scattered accumulations of the parasite. Each papule in a cutaneous eruption must mean a local aggregation of the virus in the skin; an iritis in one eye implies a special incidence of the poison upon that rather than upon the opposite iris. Nevertheless, during this stage of the disease, the reactions tend on the whole to be distinctly symmetrical in their distribution. There would seem no reason why a virus generally diffused throughout the body should be unilateral in its effects, though slight and obscure predisposing causes may even at this stage determine the affection of one eye or one testis rather than the other.

In this respect of symmetry of lesion there is a marked contrast

between the earlier and the later stages of constitutional syphilis, for in the latter there is commonly no symmetry at all. There is another general difference between the lesions of these two stages, namely, in their local gravity. As a rule, to which, however, there are exceptions, secondary syphilis has much of the benign character seen in the primary stage of the disease. The consequences of secondary iritis may indeed be serious, but the majority of the local lesions of this stage tend to clear up, leaving no permanent trouble behind. Far otherwise is it with tertiary lesions, in which extensive tissue-destruction is common, and irreparable local consequences may ensue.

Lastly, it must be noted that secondary lesions tend to manifest an infective power little if at all inferior to that of the primary sore. It is a notorious clinical fact that the secretions from affected mucous surfaces (syphilitic sore throat, condylomata, &c.) are infectious to a very high degree: the disease is probably far more often conveyed to others during the secondary than during the shorter primary stage. This is confirmed by the results of inoculation upon apes and monkeys: the inoculation of material from secondary lesions is just as successful as where material from the primary lesion is employed, so long, at least, as the disease is in an advancing condition. During retrogression of the secondary lesions much more variable and uncertain results follow inoculation: the virus now appears to be scanty and localized. In correspondence with the above facts is the readiness with which the spirochaete has been found in secondary lesions of all kinds, often in large numbers. In this respect of infective power the manifestations of early constitutional syphilis offer a strong contrast to what is seen in the later stages of the disease.

The General Constitutional Symptoms of Secondary Syphilis. The general health may be little affected during the eruptive stages of the disease: a man may present a well-marked exanthem and yet feel perfectly well. For some reason which cannot yet be explained, the female sex seems to suffer more than the male. Fever and anaemia are commoner in women than in men, and especially in young women.

Syphilitic Fever. A raised temperature in the course of secondary syphilis is far from constant, yet by no means rare. The fever is usually transitory and not of high degree. Slight prodromal or initial fever may at times be observed before and during the eruptive stage, but the more common type of secondary fever appears to be independent of other symptoms. It occurs especially during the earlier months of the secondary period, and, according to Fournier, may be intermittent, continued, or irregular in type. It is associated with malaise, acceleration of the pulse, and other concomitant phenomena in proportion to its degree.

The Anaemia of Secondary Syphilis. In no respect are the constitutional effects of syphilis more constantly shown than in the anaemia which it induces during the secondary stage. The first and slightest degree of the blood change is seen in a fall in the haemoglobin-percentage, habitually seen even before the appearance of the secondary rashes. The haemoglobin may fall to 75 per cent. of the normal without any noteworthy loss in the number of red corpuscles. A somewhat graver degree of anaemia is associated with the outbreak of the cutaneous eruptions. The number of red corpuscles now falls, though rarely to any marked extent; the average count may lie between 4,000,000 and 5,000,000 erythrocytes per c.mm. The relative fall in haemoglobin is greater than this, so that the colour-index is less than unity: in other words the anaemia is of the chlorotic type, and this is said to be especially pronounced in young women. The ordinary anaemia of secondary syphilis does not, then, differ from the secondary anaemias seen in other conditions. It reaches its greatest intensity with the height of the cutaneous eruptions and tends to disappear with these. In the later stages of the disease blood changes may be almost absent, though severe anaemias may be seen at times in the tertiary stage.

As examples of a far more severe type of anaemia in constitutional syphilis, the cases recorded by F. Müller are commonly quoted. Here the red corpuscles and haemoglobin became extremely reduced—in one case to 720,000 erythrocytes per c.mm, with 18 per cent. haemoglobin—the colour-index being thus

greater than unity; poikilocytosis was present, with nucleated red corpuscles—even megaloblasts—the condition resembling pernicious anaemia. Such cases are certainly of extreme rarity in acquired syphilis, but in the congenital form of the disease very severe anaemias are far from uncommon, and may be fatal, though they do not, in their essence, differ from other grave secondary anaemias.

There is one consideration in regard to anaemia in syphilis which must not pass without remark. Mercury, so inevitably administered so soon as the diagnosis is made, is itself a drug tending to produce anaemia. How much, then, of the supposed anaemia of syphilis is due to this cause? The answer is not difficult: the anaemia is truly syphilitic. Not only is it present before the administration of mercury, but, for a time, when the mercurial treatment is first commenced, the blood condition markedly improves. Mercury has indeed been called 'the iron of syphilitic anaemia'. Only when the drug has been given for some time does its deleterious effect upon the blood become manifest—a fact which affords good reason for suspending the treatment from time to time.

Leucocytosis in Secondary Syphilis. All observers are agreed that in the eruptive stage of the disease some increase in the circulating leucocytes is present. The increase is usually of only moderate degree, but leucocyte-counts as high as 20,000 per c.mm. have been recorded. There is, further, a general agreement that this increase is not due to the polymorphonuclear leucocytes; it contrasts in this respect with ordinary septic or inflammatory leucocytosis. It is a rule of wide application that a circulatory leucocytosis tends to correspond in its character with the local leucocytoses seen in the lesions of the disease in question. This is so in syphilis. The polymorphonuclear leucocytes play little or no part in the local lesions of the uncomplicated disease: it may be assumed that the syphilitic virus, like that of tubercle, exercises no chemiotactic influence upon this cell. The most abundant cells in the local lesions of syphilis are the lymphocytes and the plasma cells which are by many believed to be closely associated in their origin with lymphocytes. In correspondence

with this, the chief element which appears concerned in the circulatory leucocytosis of active secondary syphilis is the lymphocyte. In this connexion may be noted an interesting fact recorded by Ravaut. During the secondary period he found a marked lymphocytosis of the cerebro-spinal fluid, running *pari passu* with the cutaneous eruption; in the case of extensive papular syphilides he found the cerebro-spinal fluid quite turbid with lymphocytes. This was not seen in the tertiary stage unless the eye or the central nervous system were affected.

It has also been stated by Loos and others that a circulatory eosinophilia may be present in secondary syphilis in proportion to the intensity of the cutaneous eruption. The combination of lymphocytosis and eosinophilia is alleged to be suggestive of this stage of the disease.

In the anaemia of hereditary syphilis lymphocytosis is common, as in the other anaemias of infancy, and myelocytes may be present. The following table, calculated from blood-counts quoted by Drs. Drysdale and Thursfield, may be taken as fairly typical of ordinary congenital syphilis:

Haemoglobin	76 per cent.
Red corpuscles	4,224,000 per c.mm.
Leucocytes—	
Polymorphonuclears	6,952 ,,
Lymphocytes	5,440 ,,
Large mononuclears	850 ,,
Eosinophils	54 ,,
Myelocytes	67 ,,

There is nothing here which is in any way remarkable or different from what might be seen in any moderate secondary anaemia in infancy. Lymphocytosis is so habitual a feature in infantile anaemias that one cannot lay much stress on it. It is impossible to name any one feature in the blood-count which is distinctive of syphilis.

The Local Phenomena of Early Constitutional Syphilis. These, which constitute the general symptomatology of the secondary stage, are fully described elsewhere in this work: only their general features can be considered here.

Whilst the lymph-stream is the path by which, in the main, the virus enters the system, its ultimate diffusion throughout the body must be by the blood. Nevertheless it would appear that the blood itself is not in any way a favourable soil for the multiplication of the parasite, and experiment proves that the circulating blood but rarely yields positive results on inoculation. The blood of active cases of the disease has indeed produced syphilis when inoculated upon human beings, but the far more extensive experiments which have become possible since the susceptibility of apes has been established prove that the virus is present in the blood in small and inconstant amount. Positive results on inoculation are recorded, but they are few in number. In Neisser's extensive series of experiments blood-serum yielded a uniformly negative result : Hoffmann succeeded three times in producing the disease with human blood, once with blood from a case of six months' duration. In accordance with this is the rarity with which the spirochaete has been demonstrated in circulating blood (some fifteen times only). In blood taken from the spleen, or from syphilitic rashes, success has more often been achieved, but in such cases there is, necessarily, admixture with local tissue elements and juices.

It is thus clear that, although the blood may be the channel by which the virus is diffused throughout the body, syphilis is in no sense a septicaemic disease even in its constitutional phase. The type of infection is essentially 'metastatic'. The virus has affinities with certain tissues, and in these, conveyed thither by the blood, it can settle and multiply. Thus arise its characteristic local manifestations, and the known distribution of these affords an index of relative proclivity to the virus on the part of the various tissues.

It has already been seen that primary infection with the disease can occur only by cutaneous channels ; squamous epithelium appears almost the necessary initial nidus, indicating some special proclivity on its part to the parasite. It might be urged that the primary disease must of necessity be so conveyed because the body is everywhere covered with squamous epithelium. But apart from the already mentioned failures to convey the disease

artificially by other than cutaneous inoculations, the phenomena of secondary syphilis afford convincing evidence of this special affinity of the virus for squamous epithelium. Although, when diffused throughout the system, the parasite has every tissue in the body at its mercy, there is none which is so uniformly and characteristically attacked as the integument. So constant and conspicuous are the rashes of secondary syphilis that they have long occupied a foremost place in the symptomatology and diagnosis of the affection. The only other tissues which can compare with the skin in frequency of attack are the lymphatic tissues and perhaps the blood-vessels, but these are structures of universal distribution, taking their part in the local reactions in whatever organ these may be induced by the virus.

The special predilection of secondary syphilis for the skin may legitimately be extended to include the epiblast generally. The alimentary canal affords a striking instance of this truth. Lined throughout nearly its whole extent by epithelium of hypoblastic descent, its upper and lower extremities are formed by invaginations of epiblast known as the stomodaeum and proctodaeum. The mouth, tongue, and fauces, together with the lowermost part of the rectum, share the skin's extreme liability to the manifestations of secondary syphilis; the oesophagus, stomach, and intestines are to all intents and purposes wholly exempt. The epiblastic invaginations which go to form the external generative organs are another instance in point, and it is tempting to push the idea further and quote the eye and central nervous system, into both of which epiblastic elements largely enter, as illustrating the same principle. The mesoblast, however, is chiefly concerned in the formation of the iris and choroid, which are the main ocular structures liable to involvement in secondary syphilis, and the brain is more commonly affected at a later stage. Without pretending to enunciate any absolute law, we may, however, safely assert that on the whole the epiblastic tissues are the most susceptible to the syphilitic virus, and the hypoblastic tissues the least susceptible; the mesoblastic tissues, while occupying an intermediate position, approach the epiblastic rather than the hypoblastic tissues in

susceptibility. Were one inclined to speculate as to the reasons for this, the suggestion arises that the parasite of syphilis has been evolved from a form which was primitively a genital saprophyte, and has hence ancestral predilections for squamous epithelium. When, in the course of its evolution, it began to acquire parasitic powers, the tissues to which it must first have become acclimatized were the mesoblastic structures of the cutis, and the lymphatic and haemal endothelium. To the hypoblast it must always have been a relative stranger.

The details as to the anatomical characters of the cutaneous eruptions of secondary syphilis belong to another section of this work. (Vol. IV.) They are epidermal and sub-epidermal in their ground-work, and the blood-vessels and perivascular lymphatics play an important part in their development. Their minute histology will be considered later. From the point of view of general pathology they may be regarded as local reactions induced by metastatic accumulations of the virus in a highly susceptible tissue. Their actual characters depend much upon their situation. On the dry surface of the skin they tend to be scaly : in moist situations, such as in the mouth and about the anus or vulva, they are covered by sodden epithelium, and constitute ' mucous tubercles ' or ' condylomata '. In the case of mucous membranes the inflammatory reaction may take on the characters of a diffuse acute catarrh, as in syphilitic rhinitis and the common sore throat of secondary syphilis.

Other general phenomena associated with the cutaneous eruptions may be briefly dismissed. There is a tendency to pigmentation of the rashes which may persist for some time after the rash itself has cleared up : while this is characteristic of syphilis it is by no means confined to that affection : many chronic inflammatory conditions of the skin are associated with pigmentary deposit. It is a common thing for the accessory structures of the skin to be affected : the lesions are sometimes localized about the hair-follicles (pilar syphilides), and the common diffuse alopecia of this stage of syphilis appears to be due to chronic inflammatory changes in the follicles. The nails, too, are apt to be affected by onychia and perionychia.

The Lymphatic System in Secondary Syphilis. The lymphangitis and indolent bubo which have already been described in connexion with the chancre are essentially phenomena belonging to the primary stage. They are local manifestations occurring before the clinical evidence of constitutional infection. During the secondary period, the predilection of the virus for lymphoid tissue is manifested by widely spread enlargements of the lymphatic glands. Such enlargements are rarely absent, and they occur as early in the secondary stage as the cutaneous eruptions. In the later stages they become more rare. For some unknown reason certain groups of glands are far more commonly affected than others; such are the anterior and posterior cervical glands, including the suboccipital group, also the cubital or epitrochlear glands. Although it is possible that these glandular enlargements are at times directly associated with, and secondary to, lesions elsewhere (e.g. the glands of the anterior cervical triangle in syphilitic sore throat), it is clear that in most cases they cannot be so explained. They usually bear no definite relation to the regions affected by the cutaneous eruptions: they may be present in the absence of any exanthem or other evident lesion: they may be absent in cases of severe cutaneous lesion. In general they probably represent the local reaction of a tissue for which the syphilitic virus has a marked affinity and in which it multiplies more readily than in most other tissues. These glandular enlargements in secondary syphilis run much the same course as the primary bubo: they are firm, painless, and indolent, lasting for weeks or months and tending ultimately to spontaneous resolution.

Far rarer than lymphadenitis in this stage of syphilis is a chronic and usually local lymphangitis, which may occur anywhere, but is most common on the male genital organs (Fournier). It is said that ulcerative processes over such foci may simulate a recurrence of the primary chancre.

In connexion with the lymphatic system may be noted the enlargement of the spleen which has not infrequently been observed in secondary syphilis. In the congenital disease this is a common phenomenon, but in acquired syphilis precise data

are lacking as to the frequency of its occurrence. Post-mortem evidence is scanty, and the lesser degrees of enlargement of the spleen are apt to escape clinical observation. It is probable that some degree of splenic enlargement is a common thing in the secondary stage, and it has been observed early rather than late in this period.

Other Local Manifestations of Early Constitutional Syphilis. Although the blood-vessels may undoubtedly suffer in secondary syphilis their affections will most conveniently be considered together with those of the later stages.

We know very little of the pathology of most of the deeply-seated complications of this stage, for they rarely come under direct pathological observation. The locomotor system is very frequently affected—witness the common pains in the bones and joints—but the anatomical substratum of these pains is obscure. A true periostitis may indeed occur during the secondary stage, but incomparably less frequently than later. It is certain that the bone marrow is one of the seats of election of the syphilitic virus, for, with the spleen, lymphatic glands and testis, it is amongst the tissues giving the most constantly positive results on artificial inoculation; Neisser indeed considers the bone marrow the most constantly infective of all. The arthralgias of secondary syphilis are equally obscure, though serous exudation and reddening of the synovial membrane have been described.

The multiform nervous symptoms which have at times been observed in early constitutional syphilis assure us that the central nervous system is not exempt from attack at this stage, but we know next to nothing of the nature of the lesions produced, though we may infer that they are transitory.

The occasional occurrence of jaundice and of nephritis are indications of an almost equally vague nature. It is only when we come to the internal generative organs that the evidence becomes more precise. The influence of even early constitutional syphilis upon the reproductive function is a well-established clinical fact, and this in both sexes.

As regards the *male sex*, objective affections of the testicle are not common during the secondary stage of syphilis. An

epididymitis may occur quite early in this stage, while towards its close, as it merges into the tertiary stage, a diffuse, non-gummatous orchitis is not very rare, and has been classed by different writers now as a late secondary, now as an early tertiary manifestation. Later, gummatous orchitis is common. But though there may be no evidence of testicular affection, animal experiment is at one with clinical experience in indicating the testis as one of the seats of election of the syphilitic virus. It has already been mentioned that the testis forms perhaps the only exception to the rule that inoculation, to be successful, must be by cutaneous channels. In experiments with apes and monkeys the testis, according to Neisser, is second only to the bone marrow in the frequency with which it harbours the virus. The *Spirochaete pallida* has so far never been demonstrated in semen, but the infectivity of this secretion in man has on two occasions been demonstrated by Finger and Landsteiner; in one of these cases there was orchitis, in the other no evident testicular affection: Neisser on the contrary got negative results with human semen on seven occasions. The bearing of the above facts on the paternal inheritance of syphilis is obvious, and the clinical evidence for such inheritance from a syphilitic father, without known maternal infection, is very strong.

In the *female sex* interest centres upon what happens in pregnancy during the secondary stage of syphilis. It would be of interest to know whether the ovary shares the special susceptibility of the testis to the virus, but upon this point information is not as yet forthcoming. In the unimpregnated female the manifestations of secondary syphilis in the internal generative organs are of no special moment. Menstrual disturbance is not uncommon, as in other conditions associated with anaemia, but calls for no special remark. But when a syphilitic woman becomes pregnant, or a pregnant woman is infected with syphilis, phenomena of the greatest moment are apt to ensue. As Fournier has insisted, there is a reciprocal influence of the two conditions upon each other. Pregnancy exaggerates the local manifestations of secondary syphilis upon the genital organs: condylomata attain a magnitude rarely seen under other conditions. And

secondary syphilis exercises an even more malign influence upon the course of pregnancy. In general it may be said that, taking as an index what happens to the foetus, it is a more serious thing for a syphilitic woman to become pregnant than for a pregnant woman to become syphilitic.

The matter is an extremely complicated one, and many points are as yet far from clear. The following are the main possibilities :—

1. A syphilitic father may beget a syphilitic child, the mother remaining free from evident signs of the disease.
2. A healthy woman may become pregnant and be infected with syphilis at the same time.
3. An already syphilitic woman may become pregnant.
4. A pregnant woman may become infected with syphilis, early or late in the course of her pregnancy.

The questions of chief importance concern the transmission of the disease to the child and the viability of such a child. As regards the channel of foetal infection there are three possibilities :—

(*a*) The fertilized ovum may be already syphilitic, as the result of the presence of the virus in the ovum or spermatozoon. At least in the case of the spermatozoon, there is good ground for belief in the occurrence of this mode of transmission, though it is probably not the common channel of hereditary syphilis.

(*b*) The placenta remaining healthy, the foetus may be infected by transference of the parasite from the maternal blood. This again is probably an uncommon mode of infection, though it seems clear that in some cases of congenital syphilis there is no evidence of placental disease.

(*c*) The placenta itself may be the seat of syphilitic disease. This appears the commonest channel of foetal infection.

Placental Syphilis. The question therefore arises, what constitutes evidence of syphilitic affection of the placenta? The presence of so-called 'infarcts' and of the small necrotic yellowish bodies which have been described as miliary gummata,

but which seem rather to be aggregations of polynuclear leucocytes, is not now held to be irrefragable evidence of syphilis, common though these conditions are in the syphilitic placenta. Such appearances have been described even in the normal organ, and especially in the placenta of nephritis. It is hard to name any one criterion by which one can deem a placenta certainly syphilitic, apart from the occurrence of definite gumma, which is rare. One of the most constant features is an increase in the absolute weight of the placenta, and especially of its weight relatively to the foetus. The average normal placenta weighs some 600 grammes, and its weight should be to that of the foetus as 1 to 5½. In syphilis its absolute weight is habitually increased, while that of the foetus tends to be low from imperfect development, so that the relative weights are not uncommonly 1 to 3. The anatomical basis of this difference is held to be a hyperplasia of the chorionic villi, chiefly due to connective tissue increase about the blood-vessels in their axis, with or without secondary changes in the epithelium covering them. (See Plate XXXIII.) The effect of this is to narrow the maternal blood-spaces and so hinder the nutrition of the foetus : in the lesser degrees of such interference the weight of the foetus is diminished, while the higher degrees lead to its death. The affected region of the placenta may in part depend upon the channel of infection—maternal or foetal.

The viability of the foetus depends upon two factors—namely, the intensity of its infection, which alone may determine death, or the degree of interference with its nutrition secondarily due to placental disease, or more rarely to stenosis of the umbilical vessels from syphilitic affection of these.

I have entered into the matter here because it is during the secondary stage of syphilis that the influence upon the foetus is the most intense ; this influence seems to attain its maximum during the first year after infection, thenceforward gradually fading. Abundant evidence is forthcoming that a syphilitic mother may at first abort early, then later, then produce a living but syphilitic child, and finally healthy offspring.

If we consider the reasons for this special incidence of the

virus upon the reproductive functions of syphilitic parents, it is not unreasonable to trace it to the necessities imposed upon an obligate parasite for the continuance of its race. Such an organism has two main prospects of transference from an infected to a healthy body. One is by immediate implantation on the surface of the latter, and in syphilis this is secured in high measure by what one might call the 'determination' of the virus to cutaneous structures during the early secondary period, whereby the parasite comes to be present in large numbers in the secretions from the surface lesions. The other is by passage from parent to offspring, and the parasite of syphilis has succeeded in exploiting this method of transfer to a degree which has hardly a parallel amongst infective diseases. It has done so by developing a special proclivity for the reproductive tissues. It is interesting, in this connexion, to note the determination of the spirochaete of the African form of relapsing fever to the ovary of the tick which has sucked infected blood, whereby the parasite is transferred to the next generation of tick as a preparation for further human infection. Here, however, the matter is complicated by the alternation of hosts.

The Later Phenomena of Constitutional Syphilis. It is customary to regard the course of acquired syphilis as divisible into three stages, known respectively as primary, secondary, and tertiary. Such a division is convenient and corresponds roughly with known facts, but it rests on clinical data only, and pathology cannot recognize these stages as sharply defined. From the clinical point of view the *primary* stage is that in which the infection appears to be purely local; it comprises the period between the first objective manifestation of infection and the onset of constitutional symptoms. It has, however, been seen that the tardy bodily reactions against the progress of the infection render clinical evidence a very imperfect index of its true course. The primary stage is merely that in which it is apparently local. But even the clinical observer is baffled in attempting to draw a hard and fast line between the secondary and tertiary stages. In a general sort of way it may be said that the *secondary* stage is essentially one of exanthem and fever, and the *tertiary*

stage one of infective granuloma. As a matter of fact, the disease gradually loses the characters of a specific fever, while those of an infective granuloma become more and more apparent, but there are intermediate manifestations which cannot certainly be placed in one rather than in the other stage.

Nevertheless the later stages of constitutional syphilis present phenomena of very different type from those of the earlier stage. As the acuteness of the infective process gradually wears out, the bodily reactions against it undergo a profound change. From a pathological point of view the differences between the early, or secondary, phenomena of constitutional infection, and the later, or tertiary ones, may be grouped under several headings, as follows :—

(1) Whereas the earlier stages show a general bodily reaction in the way of febrile movement and changes in the blood, these phenomena gradually subside and in a few months may disappear.

(2) The earlier stages are characterized by a high degree of infectivity: the secretions from the local lesions contain an active virus in large amount. In the later stages this is not so. It was long believed that material from gummata was entirely devoid of infective properties, and it is certain that such material contains the virus in minimal quantity and of feeble vitality. Nevertheless successful inoculations upon apes have been recorded in at least eight cases by different observers, though more frequently the result has been negative. In the successful cases the material has been unsoftened granuloma from a gumma not yet ulcerated or necrotic. In one of Hoffmann's successful cases the disease was of twenty-four years' duration. The spirochaete has also been demonstrated in gumma by four or five investigators, though in small numbers. The supposed difference in infectivity between secondary and tertiary lesions is thus a quantitative and not an absolute difference. With the recession of the early acute lesions of the constitutional disease the virus is already much less abundant; in the later stages it is with difficulty demonstrable. But the change is a gradual one. What is true of the virulence of the local lesions

is true also of the liability to transmission by inheritance, which slowly fades with the progress of the case.

(3) Allusion has already been made to the contrast between the tendency to symmetry of lesion in the earlier stages of constitutional syphilis and the habitual asymmetry of the later lesions. It is not difficult to understand why the chance accumulations of the parasite, as it becomes more scanty, should lack the bilateral distribution seen when it is more abundantly distributed throughout the body.

(4) But perhaps more striking than any other contrast between the early and late manifestations of constitutional syphilis, is that which concerns their course and local gravity. Whereas the ordinary secondary lesions show little or no tendency to local tissue-death, but clear up leaving behind them no permanent trace of their presence, the gummatous and other lesions of the tertiary stage are characterized by a very striking liability to early necrosis and ulceration, and almost always leave permanent and often serious local disfigurement. The contrast is an odd one for this reason, that one would expect the lesion in which the virus is abundant to be a graver one than that in which it is scanty and difficult of demonstration. Yet the reverse is the case. If the reason cannot be sought in the relative abundance and virulence of the infective agent, it must perforce lie in some alteration in the nature of the tissue reaction against the virus—a view which has been long and ably maintained by Neisser. In every syphilitic new formation of tissue, early or late, the process begins with the development of a granulomatous tissue of much the same structure. A comparison of the microscopic sections from the three stages of the disease, figured in Plates XVIII to XXI, will show the essential similarity of the histological changes in their early phases, especially with regard to the accumulations of plasma cells. But whereas, in the early reactions of the normal and unspoiled tissues against the parasite, the granulation tissue passes on to fibrosis and induration, and never or hardly ever to necrosis and ulceration, there is seen in the secondary lesions a tendency to spontaneous absorption of the accumulated cells, without fibrosis.

Later still there is a gradually increasing frailty or perishableness of the reactive new formation, whereby at an early stage it undergoes softening and necrosis, with extensive local tissue-destruction. This is the essence of a gumma. The contrast between the early and the late lesions of constitutional syphilis depends, as Neisser has insisted, on a change in the tissues, and not on any change in the virus. The virus is reduced in quantity, but not in quality, for where simian inoculation with tertiary material is successful, the result is identical with that produced with material from the earliest stages.

The profound change in the nature of the tissue-reaction has further been shown by the experiments of Finger and Landsteiner, who inoculated human beings already in the tertiary stage with large amounts of syphilitic virus. In those cases in which positive effects were produced, the lesion induced did not resemble a primary chancre, but is claimed to have been of the nature of a tertiary lesion—a tubercular or ulcerative syphilide.

The differences between the earlier and later stages of constitutional syphilis are thus seen to be of an important kind, and the terms 'secondary' and 'tertiary' may be usefully retained if we bear in mind that these stages are not separated by any hard and fast line, but imply a gradual change in the characters of the bodily reactions against the virus. As in the case of the secondary manifestations of syphilis, I propose to mention here only the more general characters of the tertiary lesions. Their detailed characters are described elsewhere in this work.

In a general way, it may be said that the tertiary stage is essentially that of the graver lesions of syphilis—those which too often terminate life, or leave behind them irreparable consequences. It is not an absolutely inevitable stage in the evolution of the disease. There can be no doubt that really adequate treatment in the earlier stages prevents its occurrence in all but the most exceptional cases. It has been noted clinically that tertiary manifestations more often follow in cases which have run a benign course in the earlier stages than in those in which

the earlier symptoms have been severe, but it must be remembered that in the latter there is the more ground for prolonged early treatment. In practice the main condition which conduces to tertiary lesions is ineffectual early treatment. Nevertheless there appear to be exceptionally malignant types of the disease which are with difficulty kept in subjection by treatment, and it is also clear that the general bodily condition of the patient exercises an important influence on the occurrence of tertiary symptoms; bad hygienic conditions, alcoholism, any cause of ill health, local or general—all these are predisposing conditions. It is a question of the extinction of the virus in the body. Given good general health and adequate treatment this extinction is assured during the earlier constitutional stages and the patient is thenceforward safe. But in the absence of these conditions, the parasite is not actually destroyed: it is scotched but not killed, and the patient has 'latent' syphilis which, in spite of apparent good health, may at any time manifest itself by tertiary lesions.

As a rule the patient is in good general health during this latent stage, but from time to time a sudden and apparently spontaneous local growth of granulomatous new formation appears. This may occur but once, or may be repeated at irregular intervals. The granuloma may appear in any region of the body, though some tissues are more prone to it than others. The clinical phenomena are of the most varied description and cannot be considered here. As regards the date of outbreak, it can be said that tertiary lesions may appear at any date after infection from the first year onwards: in rare cases they may become manifest even while the secondary eruptions are still present. More usually there has been a period of quiescence and apparent health between the secondary and tertiary phenomena: the years of greatest incidence are the second and especially the third after infection. Fournier's figures, based on 4,400 cases of tertiary syphilis, show 188 cases during the first year after infection, 453 during the second, 471 during the third, and 388 during the fourth. The numbers fall in each succeeding year, at first rapidly, then more slowly, but the liability to tertiary

manifestations remains for even fifty years and longer. The body as a whole has long ceased to react against a virus which has become minimal in amount and lurks inactive in some remote region, but from time to time, owing to conditions of which we know little or nothing, there is a local awakening of the parasite to transitory activity and a corresponding local tissue-reaction. And in severe cases of tertiary syphilis—those especially in which there is extensive necrosis and ulceration—the general health may suffer to a marked degree, a severe cachexia supervening as a result of the local lesions.

As regards the site of tertiary lesions, Fournier has analysed his 4,400 cases and shows the skin to be considerably first as to frequency of attack. Next in frequency comes the central nervous system, followed by the bones. Visceral syphilis, though far more common than in the secondary stage, is yet infrequent as compared with tertiary syphilis of the foregoing tissues.

The lesions themselves are commonly of the nature of the perishable granulomata known as 'gummata', or are fibrotic in character; the two may be combined—a reactive fibrosis taking place around a gumma. Arterial disease also takes an important share in the lesions of tertiary syphilis. It may be gummatous or fibrotic in its essential character, but its importance rests in the serious consequences to which it may lead.

A *gumma* may be defined as a localised new formation of granulation tissue, occurring during the later stages of constitutional syphilis, vascular in its early phases, but tending to early tissue death and caseation, with softening and, if superficial, ulceration. In its early stages a gumma is a firm, semi-translucent, greyish or greyish-red mass of tissue varying in size from that of a pin's head to that of a walnut or larger. Later it becomes opaque, yellowish and caseous, with a liability to softening: it is frequently surrounded by a zone of fibrous tissue which, if the softened and necrotic tissue be absorbed or discharged, results in a dense fibrous scar.

A gumma is usually a localised new formation, but several such

may develop simultaneously or successively. The gravity of the result naturally depends upon the tissue or organ involved, and scarcely any part of the body is exempt. In addition to the formation of local gummata there is a diffuse type of perishable granulomatous infiltration, which may attack the skin, but is also apt to affect the fauces, pharynx, and larynx. Here the tissues seem to melt away, as it were by a process of rapidly spreading ulceration ; the loss of substance may be very great and the cicatricial contraction of the tissues concerned in repair may lead to serious deformities.

The *fibrosis* seen in tertiary syphilis is largely a matter of repair, though it cannot well be dissociated from the syphilitic element in the case. Any area of necrotic tissue—an infarct, for instance, or a tuberculous mass—acts as a mild irritant upon the tissues around, and excites a reactive fibrosis by which it becomes shut off. The natural cure of tubercle rests largely on such successful encapsulation of the infective foci. In the case of a gumma it is hard to say how much of the surrounding fibrosis and scarring is directly due to the syphilitic virus, and how much to the non-specific action of a focus of dead tissue. There are, however, good reasons for the belief that much of the fibrosis is directly excited by the virus of syphilis. The plasma cell, which forms so conspicuous and constant a feature in the earlier stages of all syphilitic lesions, is by many held to be a precursor of the fibroblast. In the later stages of syphilis it fails in its development into fibrous tissue, and, in the area mainly affected, shares in the general tissue-death, though towards the outskirts fibrous tissue is formed. But there are certain lesions of advanced syphilis which are intrinsically fibrotic from the first. In the congenital disease, the typical affection of the liver is a pericellular cirrhosis which is purely fibrous, and, as a rule, shows no localised gummata. The indurative lung affection known as ' white hepatization ', occasionally seen in new-born syphilitic infants, is also essentially a fibrosis. And in the acquired disease there are visceral affections such as interstitial myocarditis and orchitis, which are similarly fibrous changes. In the same category may be placed the sclerosing forms of osteitis which occur independently of gumma. Lastly, it may

be added that certain of the fibrotic changes in late syphilis are traceable to arterial disease.

Vascular Affections in Syphilis. Although this article deals with the general pathology of syphilis, the affections of the vascular system must be mentioned in some detail on account of the widespread consequences to which they lead. There can be no doubt that, even from the earliest stages, the virus of syphilis exerts a special influence upon the blood-vessels. In the primary sore small arterioles may at times be found with thickened walls and a lumen narrowed by endothelial proliferation—a true endarteritis. (See Plate XXVI.) The distribution of the secondary lesions tends to follow the course of the small blood-vessels (see Plate XXI), and microscopic examination reveals not only endothelial changes within the vessels, but also and more strikingly a perivascular infiltration in the form of accumulations of plasma cells around the vessels and in the lymphatics which accompany them.

The main incidence of vascular disease in syphilis is, however, in the later stages. The heart itself suffers in more ways than one, though cardiac syphilis is relatively uncommon. It may be the seat of gumma, of fibrous myocarditis, of fibrotic changes associated with disease of the coronary arteries, and, much more rarely, of pericarditis and endocarditis. Syphilitic affections of the veins, although known to occur, are of relatively small importance. But arterial disease in tertiary syphilis is very common, and of the gravest consequence. It may occur in any artery, but, of the large arteries, the aorta, the cerebral, the pulmonary and the subclavian, femoral, and popliteal are the most frequently affected. The changes found are not sharply defined from those seen in ordinary endarteritis and atheroma and they may easily be confounded with these. Nevertheless, syphilitic disease of the arteries has certain predominant features. Of these, the most striking is that of an obliterative endarteritis—i.e. of a thickening of the intima so marked as more or less to occlude the lumen of the vessel. (See Plates XXII and XXIII.) Not every obliterative endarteritis is syphilitic : a very similar change is sometimes seen in tubercle—e.g. in the middle cerebral arteries in tuberculous

meningitis—and indeed any chronic endarteritis may tend to obstruct the blood channel. But on the whole this feature is far more pronounced in arterial disease due to syphilis than in any other form of the affection, and the demonstration of obliterative arterial changes in or around a lesion, presumably syphilitic, offers strong confirmation of its truly syphilitic nature. The results of the obliterative process are necessarily serious, for not only is the blood supply by the affected vessel hindered in proportion to the degree of obstruction, but the vessel-walls themselves lose their contractility and become incapable of vasomotor response. Thus the nutrition of the parts supplied by the vessel may be impaired—even to the point of tissue-death. This may be brought about in a secondary fashion by the occurrence of thrombosis in the narrowed and diseased artery. Organs peculiarly prone to suffer from the effects of syphilitic arteritis are the brain and the heart; the cerebral and coronary arteries are amongst those commonly affected, and the organs in question are highly susceptible to interference with their blood supply.

Although obliterative changes are usually conspicuous in syphilitic arteritis, there are other features of the condition which are equally important. There is a tendency to a sort of callous induration of the arterial wall which in the smaller vessels is more diffuse, in the larger, and especially in the aorta, more patchy in its distribution. Much has been written as to the primary seat of this indurative change, and the following conclusions may be accepted. The primary and most characteristic changes in syphilitic arteritis are in the outer part of the tunica media and in the adventitia; the changes in the intima are secondary. In the middle and outer coats there appear accumulations of cells, chiefly around the vasa vasorum, which are themselves the seat of the syphilitic changes seen in affections of other tissues and organs. (See Plate XXIV.) Almost all the local manifestations of syphilis, it has been pointed out, begin in and about the blood-vessels, and arterial disease is no exception to the rule. The cell accumulations in the arterial wall rarely undergo necrotic change: small gummata in such situations are not indeed unknown, but gummatous arteritis is a rarity. The cell masses habitually pass on to fibrosis:

the adventitia becomes thickened and hard, and the boundary between it and the middle coat is obscured or lost. In the middle coat the muscular and elastic layers are here and there interrupted by fibrous foci : there is no new formation of elastic fibres, such as v. Hansemann has claimed to occur in ordinary arterio-sclerosis. The gaps in the elastic tissue are admirably seen in sections stained in orcein. (See Plate XXV.) These lesions necessarily impair the resisting powers of the arterial wall, and it is not improbable that the thickening of the intima is, at least in part, an effort at compensatory repair. Even so, the indurated and fibrotic arterial wall is far from possessing the strength and resilience of the normal vessel, and thus it comes about that syphilitic disease of the arteries, and notably of the aorta, is one of the most powerful causes disposing to aneurysm. It is also well established that syphilitic inflammation of the aorta tends especially to affect this vessel at its origin and to spread to the aortic valve. Hence it is that syphilis plays so important a part in the production of aortic valvular disease in young adults.

In all this there is nothing which absolutely distinguishes syphilitic arteritis from ordinary arterio-sclerosis. In the latter Thoma claims that the primary changes are in the middle coat, and that the thickening of the intima is secondary. Nevertheless we see in the subjects of syphilis arterial changes which, in non-syphilitics, occur at a much later age-period and which in certain respects are peculiar, e.g. in the commencement of the changes about the vasa vasorum, which themselves may show an arteritis, and in the tendency to indurative fibrosis, which has a much slighter tendency to fatty and calcareous degeneration than is seen in ordinary arterio-sclerosis and atheroma. It is probable that in any given case we see specific syphilitic changes intermingled with those common to all arterial degenerations. When once the integrity of the arterial wall is impaired, from whatever cause, the ordinary factors in defence are brought into play, but there can be no reasonable doubt that syphilis is an important cause of early arterial decay.

Even in congenital syphilis arterial changes are described,

especially in the aorta, which resemble those seen in the acquired disease. It is doubtful, however, whether they so often lead to serious consequences.

Arterial disease in syphilis presents certain differences from the ordinary tertiary manifestations; it is more conspicuously indurative, with little or no tendency to softening and breaking down; it does not seem influenced in its course by the administration of potassium iodide. Hence there are some who class it, not with the true tertiary lesions but with the so-called 'parasyphilitic' affections.

Parasyphilitic Affections. It has long been recognized that syphilis acts as a predisposing cause of other diseases. A study of the lists of predisposing causes given in textbooks of medicine will show how large a share is credited to syphilis in this respect in diseases of the most diverse kind. How much of this evil repute is deserved it is difficult to say, but there are certain diseases in which it is beyond cavil that syphilis plays a part of overwhelming importance. The two most striking examples are the chronic degenerative affections of the nervous system—tabes and general paralysis of the insane. These diseases are not in themselves manifestations of syphilis; they are in no wise controlled by anti-syphilitic remedies; it is agreed by cautious observers that, in a certain small proportion of cases, preceding syphilis can be excluded with an approach to certainty. But the percentage of tabetics and general paralytics who present either a history or evidence of syphilis is so great as to make it certain that syphilis has much to do with the causation of the disease, though it may not be the inevitable antecedent. To quote actual figures: W. Erb, whose authority will not be disputed, writes, in 1904, that of 1,100 cases of tabes under his observation, 90 per cent. had a history of past chancre or secondary syphilis, while in only 3 per cent. could syphilis apparently be excluded. Of non-tabetic males over twenty-five years of age, only 21·5 per cent. had suffered from syphilis. Only a small number of syphilitics become tabetic: probably syphilis alone does not suffice as a cause. Evidence of similar character might be quoted as regards general paralysis of the insane; it may occur in those who have

never suffered from syphilis, but the vast majority of its victims are syphilitics.

To express these facts the term 'parasyphilitic' has been applied to such affections, and it is a convenient one when used strictly in the sense above implied—i.e. to cover diseases not in themselves syphilitic, and occurring at times independently of syphilis, but in the great majority of cases affecting persons who have suffered from syphilis. It would appear that syphilis leaves behind it a tendency to certain changes, usually of a degenerative nature, which may become apparent long after all active signs of the disease have ceased. But it must be remembered that the subjects of parasyphilitic disease may still be in the stage of latent or indeed active syphilis. The term 'parasyphilitic' does not imply that the syphilis is necessarily a thing of the past: what has already been said as to the almost indefinite persistence of the virus negatives such a belief. And thus it comes about that such modern methods of research as the reaction of Wassermann, Neisser, and Bruck, presently to be mentioned, frequently reveal the presence either of syphilitic products or syphilitic antibodies in the cerebro-spinal fluid of tabes or general paralysis.

Accessory Infections in Syphilis. In the preceding sketch of the course of syphilis, I have confined myself to the phenomena due to that disease alone, uncomplicated by the invasion of foreign micro-organisms. But, as a fact, such secondary invasions are not infrequent, and they may greatly modify the character and course of syphilitic lesions. Two conditions favour such secondary infections. The lesions of syphilis are largely surface lesions, and many of them tend to ulceration, or at least to a denudation of surface epithelium, which assists the ingress of other micro-organisms. It need hardly be said that the skin, the buccal cavity, and other mucous surfaces are teeming with bacteria, many of which are potentially parasitic. There is thus ample opportunity for the occurrence of secondary infections. There is a second reason why they are apt to occur—namely, a lowered resistance against infection on the part of the body generally, where health is gravely impaired as the result of the syphilitic infection itself or owing to bad hygienic conditions. It has been pointed out that

as a rule the general health does not suffer much in syphilis. In an ordinary case the patient looks and feels in fair health, apart from his chancre, sore throat, or eruption: in correspondence with this maintenance of bodily health, his powers of resistance are not seriously impaired, and secondary infections are either absent or trivial and limited.

But in exceptional cases this is not so. The syphilitic infection may be of severe and malign type, and lead to serious ill-health and lowered resistance. Or the same effect may be traceable to previous illness, to malnutrition, or defective sanitary conditions, such as were at one time more common than at present. Under these circumstances secondary infections may assume a gravity out of all proportion to the syphilitic infection itself: widely spreading gangrenous and phagedaenic processes may supervene and may destroy life. The term 'malignant syphilis' has been used in such cases, but the question of the malignancy of syphilis is a complex one. As with other infective diseases, there doubtless exist 'strains' of the syphilitic virus which are more vigorous parasites than others, and capable of exciting more serious results in the body which they invade. Yet this factor probably plays an insignificant part in 'malignant' syphilis: the essential factor lies in the capacity for resistance presented by the body invaded.

This capacity for resistance may be racial or individual. In a country where syphilis has been endemic for centuries, what may be called a racial immunity becomes manifest: not only does the disease directly affect a certain percentage of the population, but, being eminently inheritable, it affects in lesser degree a large percentage of those who have not directly suffered from the primary disease. And thus in the course of centuries there comes about what has been called the 'syphilization' of the community, in the sense that almost every one has some ancestral taint, recent or remote, and, what is more important, a certain degree of inherited immunity. The truth of this might well escape remark were it not for the serious results which ensue when the disease is introduced into a country where it has not hitherto been present, and in which the racial immunity has not been developed. There is abundant historical evidence of the ravages

caused by syphilis in a virgin race, even though the introduced disease may have been of no intrinsic severity. Herein, then, lies one cause of the 'malignancy' of syphilis.

Individual lack of resistance depends chiefly on preceding ill-health or insanitary surroundings, and influences not only the course of the syphilitic infection, but also the occurrence of secondary microbic invasion. Cases of malignant syphilis in this country are mostly of this nature and are now rarely seen. The reasons for their rarity are manifold. Apart from the 'syphilization' of the community and the consequent increasing mildness of the disease, early and accurate diagnosis and treatment, and improved sanitation, have done much to lessen the severity of its incidence on the individual.

Amongst the common secondary infections in syphilis a few may be noted as of especial importance: (1) The occurrence of *gonorrhoea* and of *soft sore* as concomitants of the primary infection has already been mentioned. These, with their shorter incubation period, are at first the conspicuous feature: later, the manifestations of true syphilis gradually disentangle themselves from these preliminary complications; (2) *suppurative affections*, mostly of staphylococcal origin, may complicate the surface lesions of secondary syphilis, or of other stages. It is clear that syphilis, *per se*, is not a suppurative affection; any accumulation of true pus—i.e., of polymorphonuclear leucocytes—is almost certainly due to secondary infection by pyogenic cocci. Pustular syphilides are thus to be explained. In the throat, much of the severe inflammation of syphilitic angina is probably of streptococcal origin, if we may judge by what is known of sore throat in other diseases; (3) the occurrence of *phagedaena* and *gangrene* in syphilis, while certainly associated with adventitious infection, is largely determined by lowered resistance. The process is akin to that sometimes seen in other infective diseases, e.g. noma and cancrum oris in debilitated children as a sequel of measles. We do not certainly know the actual bacterial agent which produces these progressive gangrenes: probably it is the combined work of a number of species, amongst which anaërobic bacilli are to be included. But it is clear that putrefactive organisms never attack

healthy living tissues; a very greatly lowered resistance must occur before this is possible. Such depression of tissue vitality must be the essential condition of phagedaenic processes in syphilis; they are not confined to syphilis, and they are probably not the direct effect of the syphilitic virus; (4) lastly, it must be mentioned that *tubercle* is no uncommon complication of late syphilis. Many syphilitics die of pulmonary tuberculosis; much of what was at one time regarded as syphilis of the lung was probably in truth tubercle.

The General Pathology of Inherited Syphilis. The congenital form of the disease is the subject of a special section of this work, and I propose here to touch on a few general features only. The first striking difference between the congenital and acquired forms of syphilis lies in the absence of any known primary stage in the former. Whether the foetus be infected by way of the germinal elements or secondarily through the placenta, it would appear that the infection speedily becomes a general one without any evident local reaction at the portal of entry of the virus.

In the second place congenital syphilis commonly displays an intensity of infection almost without parallel in the acquired disease. The whole body is, as it were, saturated through and through with the virus. The spirochaete has been demonstrated in incredible numbers in the liver, spleen, and other organs: in acquired syphilis it is much more hard to find, and even in the primary sore it is less abundant than in the liver of the congenital affection. Even if this evidence be put on one side there remains another set of facts which cannot be gainsaid: by experimental inoculation of apes and monkeys it has been shown that the virus is abundantly present in congenital syphilis in the lungs, liver, kidney, ovary, and in the nasal secretion in 'snuffles'. Successful inoculations are the rule with such material, whereas in the acquired disease they are rarely if ever obtained. The abundance and diffuseness of the poison in inherited syphilis is further suggested by the severity and widely spread nature of its manifestations.

The explanation of the above features—viz. the absence of a primary stage and the severity of the infection—is probably to

be sought not so much in any peculiarity in the channel of infection as in the low degree of resistance presented during antenatal life, and especially during the early stages of development of the ovum.

Given an abundance and a wide diffusion of the virus, the manifestations of inherited syphilis, to be discussed in detail in another section of this work, are quite naturally explained. They differ in degree rather than in kind from those of the acquired disease, though differences must of necessity arise where the virus attacks developing instead of fully formed tissues. Thus, for instance, we find disturbances of dentition and lesions of the epiphyses of long bones, which are absent when the disease is acquired in adult life. It is, however, remarkable that anything approaching a general arrest of development is uncommon. The lesions of what corresponds to the tertiary stage are as a rule much more symmetrical than in acquired syphilis, and arterial disease is less conspicuous and less grave in its results. On the other hand diffuse fibrotic changes are common in the viscera, notably in the liver, lung, spleen, and pancreas.

But while the lesions of hereditary syphilis are commonly severe, and manifest either at birth or within a few weeks after that event, cases are by no means rare in which syphilitic manifestations are delayed for years, sometimes even to adult life. Just as the acquired disease may remain latent for half a lifetime after the initial manifestations, so in the inherited form, in which the early symptoms are concealed from observation, tertiary manifestations may appear for the first time in adult life, and this in cases where no suspicion of a syphilitic taint had existed. This is one of the reasons that makes it almost impossible absolutely to exclude syphilis as the cause of any given lesion in later life. It must be assumed in such cases that for some reason the initial infection was a slight one, and that it had remained latent: the term 'syphilis hereditaria tarda' is applied to such cases.

CHAPTER XIV

THE GENERAL HISTOLOGY OF SYPHILIS

Such vague terms as ' plastic inflammation ' or ' round-celled infiltration ' no longer suffice the histologist. Modern cytological studies have enabled us to discriminate with some minuteness between the various cells concerned in the inflammatory process, even though we are not in all cases able to be certain as to their origin and fate. These cells are in part derived from the blood, in part from the fixed tissues.

Of the haemal leucocytes, the *polymorphonuclears*, which take so active a share in acute inflammations, play little or no part in the bodily reactions against the virus of syphilis. Some stray intruders may be seen in this as in other granulomata, but their importance seems small. Even smaller is the part taken by the circulatory eosinophil and basophil cells : even when cells with these staining reactions are demonstrable in a syphiloma, it may be doubted whether they are truly of haemal origin. The only leucocyte playing a really important part in chronic inflammation and granuloma formation is the *lymphocyte*. Lymphocytes may form the bulk of the small round cells constituting the infiltration. Since it has been shown that lymphocytes are not destitute of the power of amoeboid movement, there is no great difficulty in accepting their haemal origin, though some pathologists (e.g. Ribbert) regard them as derived from local proliferation of minute foci of lymphoid tissue. It is not yet quite clear what becomes of the lymphocytes in granulation tissue ; by many they are regarded as the parents of the plasma cells.

The tendency of a granuloma, if it does not undergo premature decay, is to undergo transformation into connective tissue, with a permanent system of blood-vessels and lymphatic spaces. It is not surprising, therefore, to find the fixed tissue elements belonging to these categories taking a prominent part in granu-

lomatous formations. Proliferation of the local *connective tissue cells* and of the *endothelium* of the smaller blood-vessels and lymphatics is a constant feature.

There is one type of cell which plays so important a part in most granulomata, and in syphilis in particular, that it must be mentioned in some detail. It is the '*plasma cell*' of Unna. Since its recognition this cell has attained some notoriety in all doctrines concerning chronic inflammation. It is a cell considerably larger than the lymphocyte, with a granular protoplasm staining of a bright crimson colour by the method of staining introduced by Pappenheim (pyronin and methyl green, with differentiation in alcoholic resorcin) : it is thus readily recognized. Its nature and origin have been the subject of some dispute : by most authorities it is believed to originate from the lymphocyte ; others regard it as derived from the fixed connective-tissue cells. Pappenheim himself considers that the plasma cells and lymphocytes are not identical, though allied in their tissue genealogy. Both are derived ultimately from the connective tissues, but whereas the lymphocytes remain in the original round-cell stage, the plasma cells possess the power of transformation into spindle cells, and are identical with granulation cells. I can certainly affirm that in well-stained specimens of granulation tissue, it is possible to trace every gradation between the plasma cell and the fibroblast.

Only one other form of cell need be mentioned in this brief review of the elements in granuloma formation, namely the '*giant cell*'. In many granulomata, simple and infective, but most notably in tubercle, large multinucleate syncytia are seen, often of immense size, and containing at times hundreds of nuclei. In the case of tubercle there is much reason for regarding them as endothelial in origin, and this is very possibly true in other granulomata, though the subject is a contentious one. Giant cells are not uncommon in syphilomata.

Such is a short account of the more important cells which take part in chronic inflammatory processes generally. I have now to discuss the special characters of syphilitic granulomata, which present all the features of a chronic as opposed to an acute inflammatory reaction. In its earlier stages, at all events, the tissue

reaction is that which we associate with the idea of 'repair'. The local response to infection with the syphilitic virus is above all a proliferation of the fixed tissue-elements, or at least of cells capable of development into permanent tissue. This, however, is true of the reaction in any simple wound or tissue lesion. In what respects is the response to syphilitic infection peculiar? The answer is one which must be considered under several headings.

(1) A marked feature of syphilomata is their vascularity. Even to the naked eye a chancre is a red and manifestly vascular structure, easily bleeding if roughly handled. Ehrmann has demonstrated in the primary sore an abundant new formation of capillary blood-vessels as one of the earliest stages of the lesion; the richness of the chancre in capillaries is at all times plain on careful microscopic examination. This is, of course, even more true of simple granulation tissue, but it is a character in which the lesions of syphilis present a strong contrast to those of tubercle, in which no such new development of blood-vessels ever occurs. A tubercle has, in fact, no vessels of its own.

A gumma, in its earlier stages, also shows very numerous capillaries; in the later stages these have vanished in the central caseous mass, though the vascularity may still be manifest at its periphery.

(2) Apart, however, from any new formation of blood-vessels, syphilitic granulomata constantly exhibit changes in the pre-existing vessels of the affected area which are in many respects peculiar. It has been asserted, and with some truth, that almost every syphilitic manifestation begins in or about the blood-vessels. Both endo- and peri-vascular inflammation are seen. As regards the latter, it has been noted that even in the primary sore the columns of infiltration which spread from the main mass into the tissues around, tend to follow the blood-vessels, as well as the lymphatic trunks. Much of this, however, may be in truth a peri-vascular lymphangitis. In the cutaneous lesions of secondary syphilis the perivascular infiltrations in the cutis are perhaps the most striking histological feature. In gumma the perivascular changes are less conspicuous.

As regards the endovascular affection, in the small vessels it

is manifest chiefly as an endothelial hyperplasia, which may choke up the lumen. Thickened arterioles of minute size may at times be found in a primary chancre, their channels filled with rounded endothelial cells. (See Plate XXVI.) A similar condition prevails in the lesions of later syphilis. The larger blood-vessels are more especially affected in the tertiary stage, and this syphilitic endarteritis, which is much more than an endothelial hyperplasia, has already been described in sufficient detail.

(3) Syphilitic processes have also a close relation with the lymphatic vessels; peri- and endo-lymphangitis are commonly seen in syphilomata. But whereas the vascular changes are gravest and most pronounced in the later stages of the disease, the lymphatic changes are far more evident in the initial stages. The reason is that the lymphatic system constitutes the main portal of ingress of the syphilitic virus; when once constitutional infection is well established it is by the blood that the virus is disseminated. Thus it is that, in the primary sore, infiltration in and about the commencing lymphatic trunks is readily demonstrable; their channels are commonly blocked by endothelial proliferation and accumulations of leucocytes. A continuation of the process extends along the lymphatics to the bubo as already described.

(4) With regard to the individual types of cell taking part in the structure of syphilitic lesions, one stands out as pre-eminently characteristic. This is the plasma cell, found in abundance at all stages of the disease. In all the syphilomata which I have had the opportunity of examining in their early stages, provided that they have been appropriately hardened and stained, plasma cells have been abundant and conspicuous. To illustrate this I have caused coloured drawings to be prepared from sections of syphilitic products in the three main stages of the disease. (See Plates XVIII to XX.) One is from a primary chancre, one from a condyloma in the secondary period, while the third is from a young gumma of the skin. It will be seen that the histological features shown in the three drawings are so similar that it is difficult to discriminate between them.

Although an abundance of plasma cells is a striking and con-

stant feature of young syphilitic lesions, it is not pathognomonic. The plasma cell is seen, and often in numbers, in simple chronic inflammations, as indeed might be expected if it is a precursor of the fibroblast. There is, however, a wide difference in this respect between syphilis and tubercle. A miliary tubercle consists mainly of endothelial elements; the only plasma cells seen in connexion with it are a few scattered ones in the zone of reactive fibrosis at its extreme periphery, whereas in a miliary gumma they are thickly scattered through its whole substance. Nevertheless, there are forms of tubercle, especially in the skin, in which plasma cells are abundant: the trabeculae of cellular infiltration traversing the dermis in lupus may consist almost exclusively of these cells. This feature then, though habitual in syphilitic lesions, has no absolute diagnostic value.

A word may here be added as to the fate of the plasma cells in syphilis. Their natural destiny would appear to be transformation into fibroblasts and ultimately into fibrous tissue. In the indurative forms of syphilis this actually happens, but it is plainly not so in those lesions which clear up without permanent scarring. In the secondary eruptions, one may see under the microscope plasma cells in every stage of degeneration. In a gumma the plasma cells share in the central necrosis: only at the margin does fibrosis occur. Circumstances thus offer to the plasma cell three different fates. It may become organized into fixed tissue; it may undergo atrophy without any general tissue-destruction; it may share in a widespread tissue-death. And this is probably true of other tissue elements in syphilomata.

(5) The remaining tissue elements in the lesions of syphilis need detain us but a short time, as there is little about them distinctive of the disease.

The endothelium of the lymph spaces and vessels, and of the blood-vessels, undergoes great increase, but we do not find in syphilis that predominance of endothelial elements which is seen in a young tubercle. The latter essentially consists of a reticulum of so-called 'epithelioid' cells, of the endothelial nature of which there is not much question.

Nor do we find in syphilis that abundance of multinucleate

syncytia which is so characteristic of tubercle. Giant cells do, indeed, occur, as in all chronic inflammatory lesions, but they are usually few in number.

As regards leucocytic infiltrations, these are mainly due to accumulations of lymphocytes, which are commonly present in abundance amongst the plasma cells.

In the later stages of any syphiloma, primary, secondary, or tertiary, fibroblasts may be conspicuous, and are probably derived, at least in part, from plasma cells.

The general characters of syphilitic lesions may thus be summed up as those of 'plastic inflammation'—i.e. a reaction, mainly on the part of the fixed tissues, which produces a granulation tissue, or granuloma, which should, under ordinary circumstances, pass on to permanent new tissue. But, as a rule, little new tissue is actually formed, and several reasons have been advanced for this, no one of which is wholly satisfactory. Doubtless the syphilitic virus itself exerts some deleterious influence upon the cells concerned in tissue-formation, but this cannot explain the wholesale tissue-death seen in gumma. For the virus becomes progressively less abundant as the disease advances, whereas necrosis is chiefly marked in tertiary lesions. Vascular obstruction, again, must hinder nutritive processes, and so promote atrophy and tissue-death : of the direct causes which check the permanent organization of syphilitic infiltrations, this is probably the most effective. But behind all this is the change in the nature of the tissue-reactions as the disease progresses—the 'Gewebs-Umstimmung' of Neisser, whereby the new formation of tissue becomes more and more frail and perishable.

It will now be convenient to sum up the foregoing facts in a short account of the actual histological changes seen in the different stages of syphilis.

The Primary Sore. Around the first manifestations of the initial lesion the epidermis shows an overgrowth of its inter-papillary processes, which extend deeply into the dermis. The lymph spaces, which in the epidermis lie between the individual cells, are distended, and cavities of some size may arise by dropsical disintegration of epithelial cells : such cavities are often seen

occupied by leucocytes. Finally, when the chancre is well established, the epidermis may be removed by ulceration over the central area. Meanwhile, changes of greater complexity have been going on in the subjacent dermis, and it must be remembered that the virus has been introduced at the outset into an excoriation, so that the dermis is early affected. At the actual point of entry of the virus into the dermis, Ehrmann claims that the earliest recognizable changes are an abundant new formation of capillaries, and a dense infiltration with mononuclear leucocytes. From this centre the process invades the healthy tissues; the infiltration spreads amongst the clefts in the fibrous tissue, following especially the lymphatics and blood-vessels, and being everywhere accompanied or even preceded by a new formation of capillaries. There is thus a central area where the density of infiltration is greatest, surrounded by a zone of lesser, but still dense, infiltration, from which, again, columns of infiltration radiate into the normal tissues around. The infiltration consists essentially of plasma cells and lymphocytes, but is complicated by multiplication of the fixed connective tissue cells, and by endothelial proliferation on the part of the small blood-vessels and lymphatics in the form of an inflammation of the internal and external coats of these vessels. (See Plates XVIII and XXVI.) Giant cells are rarely seen in the infiltrate, but basophil cells may occur. The general impression given by a section from a primary sore is that of a dense granulation-tissue, but in the ultimate result the amount of tissue-destruction is slight, and there is little cicatricial scarring. A marked scar on the penis suggests the former existence of a soft-sore rather than of a true chancre.

Lymphangitis and Bubo. It has been already remarked that the lymphatic system constitutes the main channel of entry of the syphilitic virus. In correspondence with this, marked changes are found in the lymphatic trunks emerging from the chancre and in the regional lymphatic glands. The lymphatic trunks show a peri- and endo-lymphangitis, which is often nodular and irregular in its distribution. Frequently the lymphatics are actually blocked by endothelial proliferation and accumulations of leucocytes, and hence arise the local swellings known as ‘bubonuli’.

In such infarcted lymphatics may be found, in addition to endothelial cells and lymphocytes, fibrinous clots and groups of plasma cells. Ordinary syphilitic changes have also been described in the blood-vessels accompanying the lymphatics. It has been suggested, with some reason, that these obstructive changes in the lymphatics represent an attempt to bar the ingress of the parasite. If so, the attempt cannot be said to meet with the success which deserves, for constitutional infection is practically always the it sequel.

The histological changes in the primary bubo present nothing very distinctive. There is seen an indurative condition such as may be met with in chronic glandular irritation of other kinds. The enlarged lymphatic gland shows a manifest overgrowth of its stroma: there is a sclerosis of the connective-tissue framework so that the adenoid tissue is traversed by thick trabeculae of fibrous tissue. The endothelial elements of the framework show a marked hyperplasia; large rounded endothelial cells are a conspicuous feature, and may present more than one nucleus; even giant cells may occur. (See Plate XXVII.) In correspondence with this overgrowth of the stroma, the normal packing of the tissue with lymphocytes becomes relatively more sparse. Collections of cells are seen, however, in the lymph-paths and sinuses, and the blood-vessels and lymphatic channels frequently show obliterative changes. Fibroblasts and young connective tissue also develop around the glands. In all this there is nothing that can be regarded as actually distinctive of syphilis.

The Histology of Secondary Syphilis. Much attention has been paid to the histological changes seen in the various cutaneous syphilides. While the more fugitive eruptions, such as roseola, are chiefly due to capillary dilatation, most syphilides show a circumscribed exudation of cells in the papillae of the cutis, with changes of various kinds in the overlying epidermis. I can here allude to two general features only in these eruptions, but these are of such constancy that it is usually possible to determine the syphilitic nature of a skin eruption upon histological evidence. The first feature is the relation of the infiltration to the blood-vessels. It is essentially a patchy infiltration, lying immediately round the

vessels, which it may surround like a mantle, or accompany at one side only. Secondary syphilides seem, indeed, governed in their distribution by the branching of vascular stems (Ehrmann). I have endeavoured to illustrate this feature of secondary syphilides in the coloured drawing (Plate XXI) which has been prepared from a section of typical syphilitic psoriasis. I owe this specimen, and many other sections of syphilitic skin affections, to the kindness of Mr. J. E. R. Macdonagh, to whom I am glad to acknowledge my debt.

The second constant feature of cutaneous syphilides lies in the abundance of plasma cells in the infiltration. Plasma cells are a common enough feature of chronic skin inflammations apart from syphilis : they are in no way diagnostic. But given a skin eruption in which a perivascular distribution of accumulations of plasma cells and lymphocytes is demonstrable, a strong case is made out for syphilis.

In addition to these characteristic changes in the dermis, there is commonly a marked proliferation of the epidermis, and especially of its interpapillary processes. In moist situations the thickened epidermis is swollen by imbibition of fluid, and may become a conspicuous feature, as in mucous tubercles. On the dry surface of the ordinary skin, the proliferated epithelium separates in scales. Ulceration and suppuration in secondary syphilides usually imply the action of adventitious infecting agents, mostly of staphylococci.

The skin lesions of secondary syphilis tend to clear up, leaving no permanent traces of their presence. During the recession of such lesions, the plasma cells may be seen undergoing atrophic changes. But although the syphilide may vanish to outward view, the microscope reveals for a long while the traces of its former presence. Hjelmman, in particular, has studied these residua, and finds remains of the infiltration persisting for at least a month after the apparent disappearance of the exanthem. Thus, perhaps, may be explained local relapses and the later occurrence of tertiary at the site of old secondary lesions. The pigmentation which at times persists is not altogether peculiar to syphilitic eruptions ; Ehrmann associates it with the presence

of special connective tissue cells which he terms 'melanoblasts'.

Not rarely, infiltrations occur about the hair follicles and other cutaneous adnexa; thus arise the so-called 'syphilides pilaires', while the well-known syphilitic alopecia appears to result from a deep folliculitis with subsequent atrophy of the hair-bulb.

Our knowledge of the histology of secondary syphilitic manifestations, other than those of the skin, is exceedingly imperfect. Reference has already been made to what is known of their general character; they probably correspond in a general way to the affections of the skin—i.e., they are mainly characterized by perivascular infiltrations in which plasma cells play an important part.

The Histology of Tertiary Syphilis. It is customary to regard the formation of gummata and the process of fibrosis, which are the essential lesions of tertiary syphilis, as two distinct changes. This is not strictly the case. Both are new formations of connective tissue, and at their outset are similar; but whereas in fibrosis permanent fibrous tissue is formed, in gumma the cells tend to early necrosis and death; in the one case the reaction achieves its goal, in the other it fails. If this be so, it is no matter for surprise that the two processes are often seen in company—i.e. that failure occurs in one part of an affected area and success elsewhere. In most gummata there is a zone of successful repair at the margin.

Very young gummata are not easily obtained for examination except in infants dying soon after birth, but they may at times be excised from the skin in acquired syphilis; the specimen from which Plates XX and XXIX have been drawn was obtained in the latter way. There is really little to distinguish a gumma in this early stage from the tissue seen in a chancre or secondary syphilide. It is a local infiltration of the tissues with cells which are for the most part plasma-cells or lymphocytes. It is a highly vascular granuloma, with abundant new-formed capillaries, and though it is not always easy to demonstrate its commencement in relation to pre-existing vessels, there is reason for believing that

this relation exists. It is claimed that the earliest changes are seen in the adventitia of arteries and veins; in the liver of congenital syphilis, where these very early stages have chiefly been studied, the process seems to begin as a 'peri-pylephlebitis'—i.e. an infiltration in the adventitia of branches of the vena portae. When the gumma is more fully developed, this early relationship to vessels is obscured, but now the arterioles, and to some extent the veins also, begin to exhibit the thickening of the intima which has been already alluded to as characteristic of syphilis, and which may usually be found, often to an extreme degree, in these vessels as they traverse the gumma or the tissue in its vicinity. (See Plates XX and XXVIII.) Groups of giant cells are not rarely met with in young gummata. (See Plate XXIX.) But at the time when a gumma comes under histological investigation it has commonly undergone extensive degenerative changes. In certain cases these are of a mucoid nature: there occur forms of gumma, most often in connexion with the bones, which are relatively poor in cellular elements and are gelatinous in character from mucoid transformation of their tissue. Much more frequently the degeneration is a caseous one. Either in the early round-cell stage, or later when fibrillation of the matrix has taken place, the tissues undergo necrosis and the cell outlines vanish. There is now seen in the central part of the mass a granular or obscurely fibrillar material, staining well with acid dyes such as eosin, but in which nuclear staining with basic dyes is absent, save in the broken-down chromatin-residua which alone remain, or in a few secondarily intruding leucocytes. (See Plate XXVIII.) The capillaries and other tissue-elements share in the general cell-death. Fat granules and other products of degeneration are present. Always, however, at the periphery of the mass a living capsule remains, cellular and vascular in the less advanced, dense and fibrotic in the more advanced forms; the area of central necrosis merges gradually into this.

The necrotic portion of a gumma may finally undergo liquefaction and, if superficial, be discharged. Usually it is gradually absorbed, so that only the fibrotic area at its edge remains. The cicatricial contraction of this leads to puckering and scarring,

whereby, in an organ such as the liver, a high degree of deformity may be produced. In this case the reactive fibrosis alone remains to tell the tale of former tissue destruction.

In other cases the necrotic changes are absent, and fibrosis forms the fundamental and sole lesion of tertiary syphilis. (See Plates XXX, XXXI, and XXXII.) This is perhaps commoner in the congenital than in the acquired form of the disease, but even in the latter it is by no means rare; indeed, in the heart and vascular system it forms the usual type of tertiary lesion. There are those who regard these purely fibrotic lesions, not only in the vessels but in the testis and other organs, as parasyphilitic in nature. Atrophy of the functional tissue elements is a common secondary consequence of fibrotic changes in the stroma.

Parasyphilitic Lesions. The histology of these need not detain us long. In tabes and general paralysis, which must be regarded as the types of such affections, the essential change is a degenerative one in certain definite regions of the nervous system. The degeneration primarily affects the nerve elements themselves, and is ultimately associated with a diffuse fibrosis due to overgrowth of the supporting connective-tissue stroma.

A word may be added here as to the occurrence of lardaceous disease in syphilis. It is notorious that this condition is habitually associated with chronic suppuration, and in many cases of tertiary syphilis lardaceous changes may be thus explained. But it is a well-established fact that, in syphilis, lardaceous disease may be set up without the occurrence of true suppuration. I know of no other condition, except syphilis, in which lardaceous disease occurs apart from suppurative affections. The experimental production of lardaceous change by Krawkow and others has enlarged our knowledge concerning it, but we are still far from understanding how the condition is produced. Syphilis is clearly an important cause of lardaceous disease: why it is so is uncertain.

CHAPTER XV

THE PROBLEMS OF IMMUNITY IN SYPHILIS

THERE is perhaps no infective disease in which the problems of immunity are so difficult of solution as in syphilis. In the past, reliance has necessarily been placed on clinical evidence only and although certain definite facts have thus been established, we have remained largely in the dark as to their real inwardness. Even inoculation experiments upon human beings have failed to settle these problems, for syphilis has always confronted us with a difficulty almost peculiar to itself—namely, its tendency to remain indefinitely latent in the body, still uncured. It has been impossible, on merely clinical evidence and even by human inoculation experiments, to decide whether cure was real or apparent, or whether apparent immunity did not truly represent, in many cases, the latent disease. But with accession of knowledge as to the causal agent, with the means of animal experiment which the discoveries of Metchnikoff and Roux have rendered possible, and with the application to syphilis of Bordet and Gengou's reaction by Wasserman, Neisser, and Bruck, paths of investigation have been opened up by which a solution of these problems may reasonably be anticipated. They are not yet solved, but they are defined, and in process of solution. I propose here to consider shortly what the problems are, and how far they have yet been cleared up.

Natural Immunity. Syphilis has always been regarded as an exclusively human disease. It is not known to occur naturally in any other animal species: innumerable attempts have been made to produce it in lower mammals, but never with unequivocal success till Metchnikoff and Roux inoculated the chimpanzee. The limits of inoculability are now fairly defined: below the monkeys there seems but one animal in which the syphilitic virus can take root and produce recognizable effect; this is the

rabbit, in which Hänsell's corneal inoculations, confirmed by several later observers, seem to have produced a specific keratitis and iritis truly due to the *Spirochaete pallida*. This, however, is merely an exceptional and isolated pathological observation; it is interesting that the rabbit, when inoculated in the cornea, may serve as a temporary host for the virus, but the fact has no bearing whatever on the origin and epidemiology of syphilis. The susceptibility of simians is of greater practical importance, because in them the induced disease has a much closer analogy with human syphilis, and is provoked with much greater readiness and certainty, so that inoculation of monkeys, and especially of anthropoid apes, constitutes a practically effective test as to the presence of the syphilitic virus. But even amongst simians the response to syphilitic inoculation bears a definite relation to the presumable genealogical affinity to man of the species inoculated. Many of the lower simians are immune. In the genera Macacus, Cynocephalus, and Cercopithecus only a primary lesion can be induced: true secondary phenomena do not occur, or are slight and doubtful, though by experimental means it is demonstrable that generalization of the virus actually takes place. Only in the anthropoid apes, and above all in the chimpanzee, is the primary sore followed by true secondary lesions, comparable with those seen in man. And even in the chimpanzee tertiary lesions are so far unrecorded, though this may be due to the fact that these apes do not live long enough in captivity to afford a fair test.

The inference from these facts is sufficiently clear. It is that syphilis is essentially a human disease, as has always been believed. It must have originated in the human species, and still has this limitation, under natural conditions. That it can be transmitted to the ape, in lesser degree to certain monkeys, and even in a manner to the rabbit, proves only that the chemical and physical conditions offered by the tissues of such animals, in proportion to their affinity with man, permit of the more or less limited growth of a parasite which is still essentially a human parasite. Lower mammals present in the main a natural immunity: their tissues are adverse to the development of the parasite—so adverse that no local reaction against it is needful.

Acquired Immunity. Allusion has already been made to the mitigation, in regard to severity of symptoms, which seems to occur in countries where syphilis has long prevailed. This cannot be due to any inherent weakening of the virus itself, for, introduced into a new country, the ravages of the disease may become at once of great severity. It must be traced, as has been already suggested, to a change in the resistance of the population as a whole—a partial racial immunity, as it were, which has arisen where some degree of inherited taint prevails, with greater or less remoteness, in almost every family.

But the question which here chiefly concerns us is the immunity acquired by the individual as the result of an attack of syphilis. It is a well-known fact that a person who has suffered from syphilis is little liable to contract it a second time, but it must not be inferred from this that a true immunity is necessarily present. For syphilis is peculiar amongst infective diseases in the long years during which it may remain latent, and in the majority of cases the patient is apparently immune only because he is still syphilitic. This, as Neisser has justly urged, is not true immunity : the most that can be said of such a case is that the skin is relatively insusceptible to the access of new virus.

The very careful investigations of Finger and Landsteiner have shown that the insensitiveness of the skin to re-inoculation, in syphilitic subjects, is not so complete as has been supposed. The ' immunity ' is not absolute, though it is far-reaching. They find that re-inoculation is successful in proportion to its proximity, in point of time, to the primary inoculation. If general infection is not yet complete, a typical chancre can be produced, but from the time when constitutional symptoms appear it becomes progressively more difficult to succeed. During the secondary period the result has some resemblance to a secondary papule, while in the tertiary stage ulcerative or tubercular syphilides are produced, resembling tertiary lesions. And to produce any effect at all in these later stages, large amounts of the virus must be introduced.

It is probable that many so-called second attacks of syphilis are of the nature indicated by the experiments of Finger and

Landsteiner—i.e. re-exposure to infection has led to a local effect which is not a true primary sore but a manifestation corresponding in character with the stage of the disease at which the patient has arrived. Again, ulcerative processes over foci of syphilitic lymphangitis on the penis, may in rare cases simulate a recrudescence of the primary sore.

There is nevertheless evidence that true second attacks of syphilis may at times occur. By a true second attack should be meant the occurrence, twice in a patient's life, of a primary sore followed by secondary symptoms, and if this definition be accepted, the phenomenon must be admitted to be of extreme rarity. As Neisser points out, it means not only that the patient has been completely cured of his first attack, but that his tissues have so returned to the normal as to react to the syphilitic virus like those of an intact person, and, it may be added further, that he has lost any immunity which may have been conferred by his first attack.

It will be apparent, from the above considerations, that it is a matter of extreme difficulty to decide on the degree of true immunity conveyed by an attack of syphilis. True immunity can only be present when the disease no longer exists, and we have no body of evidence to show to what extent such immunity is present in cured syphilitics. It is probable that an attack does leave some degree of immunity; but the rare occurrence of second attacks proves that it is not always perfect; and there is a strong presumption that much of what passes for immunity depends on still latent syphilis. This is one of the problems which still await final solution.

Other problems are presented by inherited syphilis. It is a well-established fact, formulated in *Baumes'* or *Colles's Law*, that where a mother, herself apparently free from syphilis, bears a child syphilitic by inheritance from the father—a not infrequent occurrence—she is immune and cannot be infected by her child, although such a child may readily infect another person, such as a wet-nurse. Another well-known fact formulated in *Profeta's Law* is that, where a non-syphilitic child is borne by a syphilitic mother, the child exhibits a similar immunity. These laws are

the reciprocal expressions of a single fact, that, though the disease has itself to all appearance failed to be transmitted in one or the other direction through the placental circulation, an apparent immunity has been so transmitted.

That the facts are as just stated is not a matter which can be disputed, but we do not yet understand the nature of the immunity which is presented by the two cases cited; indeed it is not certain whether it is a true immunity or a latent infection. Something has traversed the placental circulation, from mother to foetus, or foetus to mother, as the case may be. This 'something' may be the syphilitic virus itself, in which case the immunity is apparent only, and what is really present is a latent infection. Or it may be, not the actual virus, but toxins or other chemical substances (antigens) derived from the virus, and capable of exciting the formation of antibodies in the uninfected individual; if so, the phenomenon is of the nature of an active immunity. A third possibility is that antibodies are formed only in the tissues of the infected subject, but are transmitted through the placenta to the uninfected subject: if so, there is a true immunity, but it is of the passive variety. It is not yet settled which of these three conjectures represents the truth, nor are we certain how lasting is the apparent immunity stated by the laws of Colles and Profeta; it is probably transitory.

Such are some of the chief problems concerning immunity in syphilis. In the past there has been no means of solving them in the only way in which a lasting solution is possible, namely, by actual experiment. But now more than one way has been opened out by which we may hope for definite answers to all such questions in the near future. The distinctions between a latent and a cured syphilis, or between a latent syphilis and a true immunity, may in time be finally settled by inoculation experiments upon apes—a costly method, it is true, but not too costly in view of the importance of the issue. There is, however, another method of investigation, too recently introduced for us yet to judge of its full possibilities, but promising information of such extraordinary value that it must be explained in some detail. I refer to the reaction of Wassermann, Neisser, and Bruck.

Serum-diagnosis. The reaction in question is based on a principle first published by Bordet and Gengou in 1901. It is well known that the serum of an animal which has been immunized with the red blood corpuscles of another species acquires the power of haemolysing these corpuscles. It is established that the haemolysing agent is of dual nature. The acquisition of the haemolytic power depends on the development of an 'immune-body' or 'amboceptor', which is thermo-stable (i.e. can resist a temperature of 55° C.). The other active agent in the haemolysis is a thermo-labile 'complement', or ferment-like substance, normally present in the serum, but destroyed at the above temperature. If the serum of the immunized animal be heated for half an hour to 55° C., its haemolysing power is lost, because the natural complement is destroyed, though the immune body is untouched: such a heated serum is said to be 'inactivated', but it can be 'activated' again by the addition of the serum of a normal animal, since this contains the natural complement. The serum of the normal animal alone, in spite of its complement, cannot cause haemolysis because no immune body is present: the complement can produce its effects only through the intermediation of the immune body. If we have simultaneously present (1) the red corpuscles of a given animal, (2) the inactivated serum of another species of animal which has been immunized against the corpuscles of the first animal and (3) fresh complement in the form of the normal unheated serum, we have what is called a 'complete haemolytic system'.

What is true of haemolysis is true also of bacteriolysis, in which also immune-body and complement are concerned: similar facts seem, indeed, to hold good for most reactions between 'antigens' and 'antibodies'. (The term 'antigens' is applied to those substances, be they bacteria or their products or other foreign cells or material, which evoke the formation of antibodies.)

Bordet and Gengou showed that, in an otherwise complete haemolytic system, haemolysis was prevented if the complement had first been incubated in the presence of cholera vibrios together with cholera-immune serum. The explanation was that the bacteria and the antibody, by their interaction, abstracted the

complement and so rendered the haemolytic system incomplete. Later they extended this to other microbes and their antibodies, e.g. plague, and the phenomenon is now a well recognized one going by the name of *deviation of the complement.* Wassermann has extended the scope of the reaction, proving that it can occur with the crude infective material in cases where the microbe cannot be cultivated in the pure state. The paper in which Wassermann, Neisser, and Bruck first published their observations on complement deviation in syphilis, and established the possibility of serum diagnosis in this disease, appeared in 1906. The method has since been employed by other observers, and no doubt can now be entertained as to its practicability and value.

The details as to the method employed are as follows: The haemolytic system which Wassermann and his colleagues used was composed of (1) the red corpuscles of the sheep, washed and suspended in normal saline solution; (2) inactivated serum from a rabbit highly immunized against sheep's corpuscles; (3) fresh guinea-pig's serum as complement. In any experiment the activity of this admixture must be tested as a control. The syphilitic antigen consists of an extract of any virulent syphilitic material obtainable: this may be primary chancre, or condylomata, or, best of all, fresh viscera from a case of congenital syphilis, preferably liver, since in this the virus is most abundant. The extract is made, so far as possible with aseptic precautions, in normal saline solution containing 0·5% carbolic acid, four parts of the fluid being used for one part of the tissue. The tissue is first ground in a mortar, then shaken with the fluid for twenty-four hours, and finally centrifuged. The resulting clear extract contains the antigen (4). The syphilitic antibodies (5) consist of known antisyphilitic substances, such as the inactivated serum of monkeys previously immunized by large doses of syphilitic material. If now a mixture be made of syphilitic antigen and antibody (4 and 5) with (3) fresh guinea-pig's serum, and incubated at body temperature for three quarters of an hour, and if then the corpuscles and haemolytic serum (1 and 2) be added, and the whole be further incubated for two hours, no haemolysis is found to occur. The interaction between the

syphilitic antigen and antibody has used up the complement and the haemolytic system is rendered incomplete.

Such is the reaction with known syphilitic antigen and antibody, and it is plain that the method can be used as a test to determine the presence of either of these in unknown material. If, for example, one has, under (4), known and certain syphilitic antigen, and the unknown material be used as (5), the reaction can determine whether or not antibody is present in this material. Conversely if, under (5), one has known antibody the test becomes one as to the presence or absence of antigen in the unknown material used as (4). A positive reaction (i.e. inhibition of haemolysis) answers either question in the affirmative, while if haemolysis proceeds unchecked it may be concluded that no antibody (or antigen, as the case may be) is present in the material tested. More than this, by employing a standard antigen in various dilutions, it seems possible to determine not only the presence, but even the approximate amount, of antibody in any given serum or extract.

The principle of the reaction will be apparent from the above short account, but it must be added that the fallacies which may beset it are numerous, and require a variety of control tests to exclude them. Normal serum should be employed as a control to the suspected serum, and normal tissue extract as a control to the extracts of syphilitic tissue. The titre of the haemolytic amboceptor must be known, and the dose should be double that capable of causing complete haemolysis of the volume of corpuscles employed.

Neisser states that he and his colleagues have always been able to demonstrate antigen in material certainly syphilitic, and never in material which was certainly non-syphilitic (e.g. the tissues of normal apes). They have tested 262 cases of human syphilis, manifest or latent, and have obtained evidence of the presence of either antigen or antibody in 65·5 % of the cases (70 % in manifest, 58 % in latent syphilis). A positive reaction thus comes to be of diagnostic value in a doubtful case : a positive antigen-reaction implies the existence of active virus in the body : a positive antibody-reaction means a past infection which may still be latent or may have been replaced by an immunity. A negative reaction allows of no certain conclusion.

For purposes of practical diagnosis, more attention has been paid to the reaction for antibody than that for antigen. The blood is the only material which can conveniently be examined in clinical practice, and even in cases of evident syphilis antigen may be totally undemonstrable therein, just as, again and again, it may be found lacking in infective properties. Antibody, on the other hand, is more constantly to be found in the blood.

On the strength of some 1,000 cases in which the serum reaction has been tested, Wassermann considers that fairly consistent results have been obtained. The reaction is invariably absent in non-syphilitic persons, and it is positive in about 85 % of syphilitics. The percentage of syphilitics giving the reaction varies with the stage of the disease: no result may be obtained in the first six or eight weeks, and the secondary stage is that in which a positive result is most constant, though the percentage is nearly as high in the tertiary stage. Treatment, too, probably exercises an influence on the reaction.

The highest value of the reaction is not, however, in manifest syphilis but in obscure cases—those in which syphilis has never been diagnosed or treated. In parasyphilitic affections the reaction is often positive. In the cerebro-spinal fluid of general paralysis of the insane Wassermann and Plaut obtained a positive result in 78 % of forty-one specimens examined. The blood also commonly gives a positive reaction in this disease, and also in tabes dorsalis, but in the latter the cerebro-spinal fluid is, for some unexplained reason, more often negative.

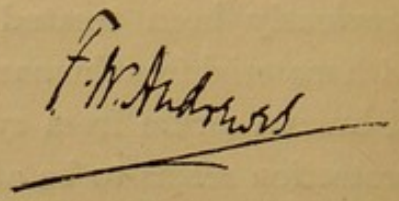
The reaction may very possibly be of value as an indication for treatment. It is probable that in cases of old syphilis the amount of antibody present affords an index of latency or cure. Experience is not yet sufficiently abundant to determine how far the reaction will prove of utility in this respect.

It will be seen, from what has been said, that this reaction of Wassermann, Neisser, and Bruck promises to be of singular value in the solution of immunity-problems in syphilis, since it affords information of a kind which can be obtained in scarcely any other way. We may, indeed, await the settling of these doubtful questions in the near future with some confidence.

Artificial Immunity. By this is here to be understood a true immunity, such as can be produced against various bacterial infections, not a therapeutical prophylaxis with local ointments. Numerous attempts have been made to immunize human beings and apes, but so far with little or no success. Amongst the means which have been tried are injections with the serum of animals naturally immune against syphilis, of animals which had previously been treated with mercury, of animals syphilized with material from human cases of the disease, and lastly injections of human serum from syphilitics in all stages. No satisfactory protection seems to be afforded by any of these procedures, and the outlook for serum therapy in syphilis is at present far from encouraging.

There remains, however, a somewhat more hopeful possibility, to wit, the employment of an attenuated virus as a vaccine. Just as the virus of small-pox, modified by bovine transmission, can be employed with safety as a prophylactic against that disease, so it may prove possible to attenuate the virus of the great pox, by passage through a relatively insusceptible animal, to a point at which it may be used without risk for human inoculation, while still conferring an immunity against the virulent disease. The facts as to the results of animal inoculation which have been set forth in this article point to some of the lower monkeys as the most likely agents for such an attenuation of the virus, and Metchnikoff has already brought forward some evidence, not indeed conclusive, but pointing in this direction. One of the attendants upon his monkeys developed two small ulcers in succession upon the lower lip. These soon healed, but material from one of them produced syphilis when inoculated upon a Macacus. The man was not treated for syphilis, yet he developed no further sign of the disease, and Metchnikoff regards the case as one in which a weakened virus, derived in some accidental manner from a monkey, produced a localised and trivial human lesion only. Metchnikoff further inoculated an old man of 79 years, who voluntarily offered himself for the experiment, with a virus which had been passed five times through monkeys. Papules resulted, which slowly disappeared, and no

further phenomena of syphilis occurred during the succeeding twelve months. A chimpanzee and a Macacus, inoculated at the same time with the same virus, developed typical primary syphilis. These observations are highly suggestive, though too few to establish any far-reaching conclusion. Nevertheless, along some such path the most hopeful prospect of inducing a true immunity against syphilis would seem to lie.



BIBLIOGRAPHY

The bibliography of Syphilis is enormous: the following short list of authorities contains only those works which I have chiefly had occasion to consult in the preparation of the foregoing article. I must, in particular, acknowledge my debt to Herxheimer's laborious review of the subject in the eleventh volume of Lubarsch and Ostertag's 'Ergebnisse', to Neisser's masterly address at the Berne Congress of the German Dermatological Society, and to Fournier's well-known treatise.

1. Ehrmann, Centralbl. f. Bakt., (Orig.), vol. xliv, p. 223.
2. Erb, Berl. klin. Wochenschr., 1904, Nos. 1 to 4.
3. Finger and Landsteiner, Sitzungsberichte d. Akad. d. Wissensch., Wien, 1905, p. 497, and 1906, p. 179. Verhandl. d. deutsch. dermatolog. Gesellschaft, 1906, p. 25.
4. Fournier, Traité de la Syphilis, Paris, 1906.
5. Herxheimer, G., Lubarsch and Ostertag's Ergebnisse, 1906, vol. xi, Part I, p. 1.
6. Hoffmann, Deutsch med. Wochenschr., 1906, No. 13.
7. Metchnikoff and Roux, Ann. Inst. Pasteur, 1903, 1904, &c.
8. Müller, F., Charité Annalen, vol. xiv, p. 259.
9. Neisser, Verhandl. d. deutsch. dermatolog. Gesellsch., 1906, p. 1.
10. Neisser and Baermann, Deutsch med. Wochenschr., 1904, pp. 1369 and 1432; 1905, p. 748; 1906, pp. 1, 49, 97,
11. Ravaut, Annales de Dermatologie, 1904, p. 1057.
12. Schaudinn and Hoffmann, Arbeiten aus d. Kaiserl. Gesundheitsamte, vol. xxii, p. 527.
13. Volk, R., 'Placentar-Syphilis,' Lubarsch and Ostertag's Ergebnisse, 1902, vol. viii, Part I, p. 509.
14. Wassermann, A. Neisser and Bruck, Deutsch med. Wochenschr., 1906, p. 745.

Plate XVIII.

Section of the granulomatous tissue in a recent, but fully developed, primary chancre of the labium majus. Stained with pyronin and methyl green to show the abundance of Unna's 'plasma cells', which are distinguished by the crimson granulations in their protoplasm. × 500.

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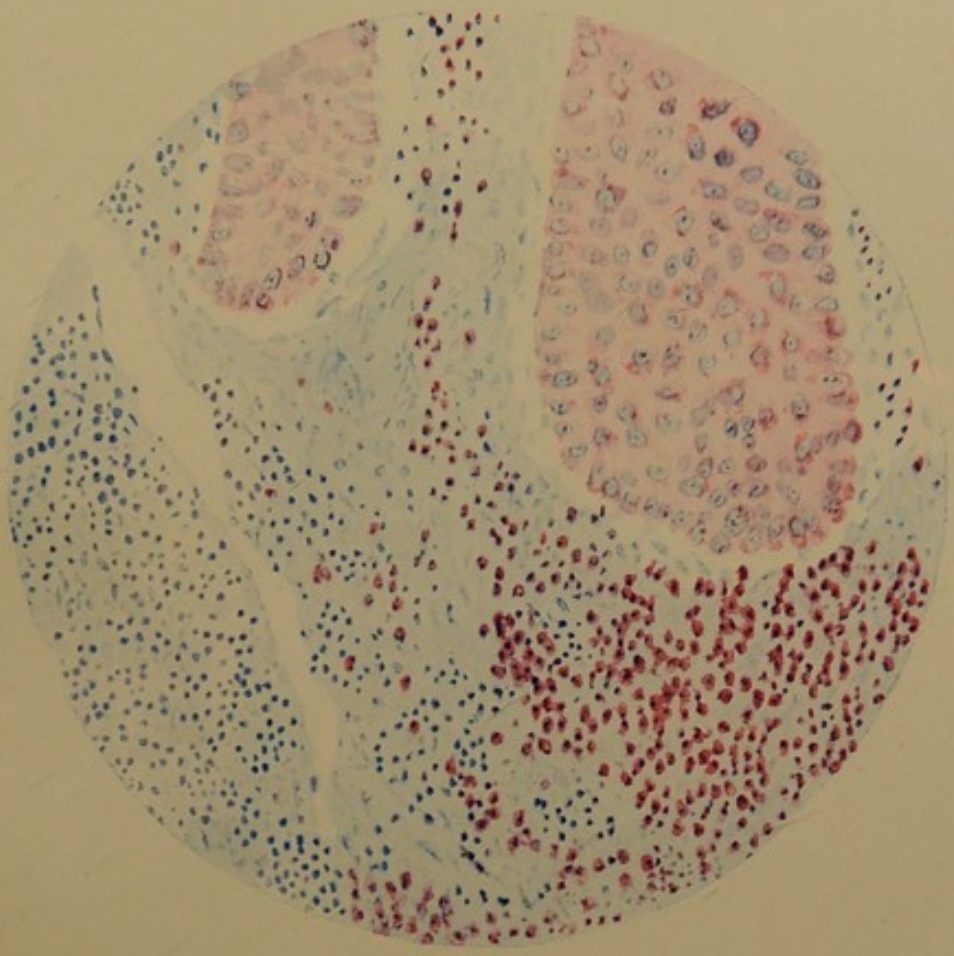

Plate XIX.

Section of a syphilitic condyloma, stained by Pappenheim's method to show the dense infiltration of the cutis with plasma cells, the protoplasm of which is stained crimson. Two interpapillary processes of the epidermis are seen. × 200.

(*From a preparation by Mr. J. E. R. Macdonagh.*)

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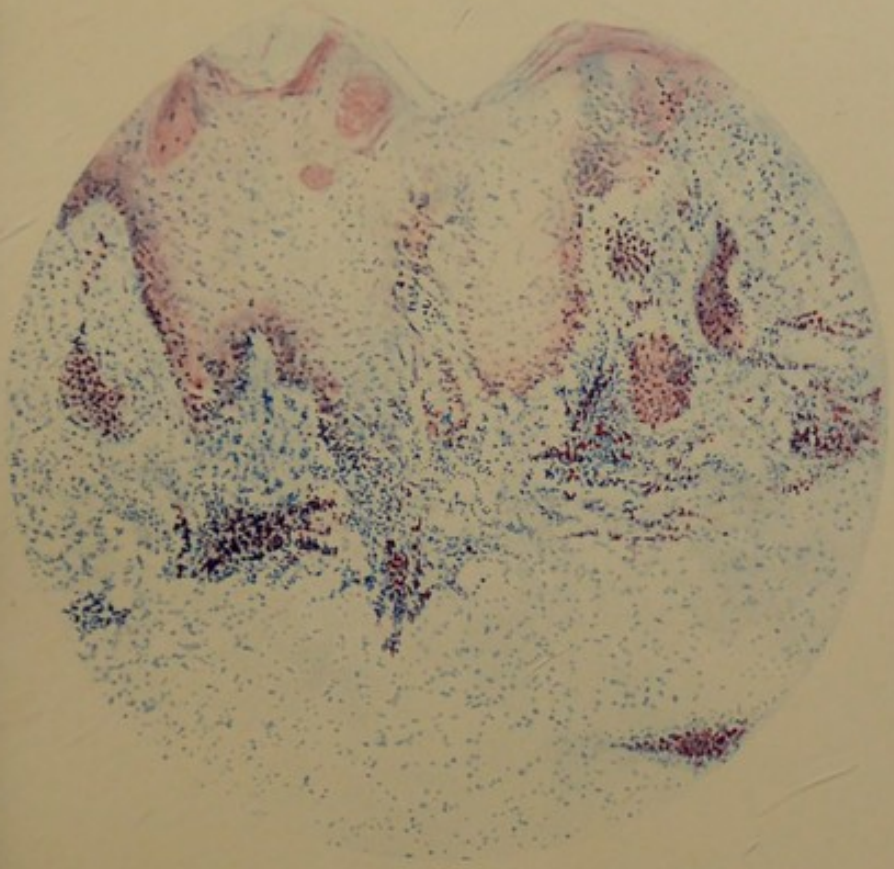

Plate XX.

From a section through a small recent gumma of the skin, stained by Pappenheim's method to show the numerous plasma cells. The plasma cells are here seen grouped round a small blood-vessel. × 500.

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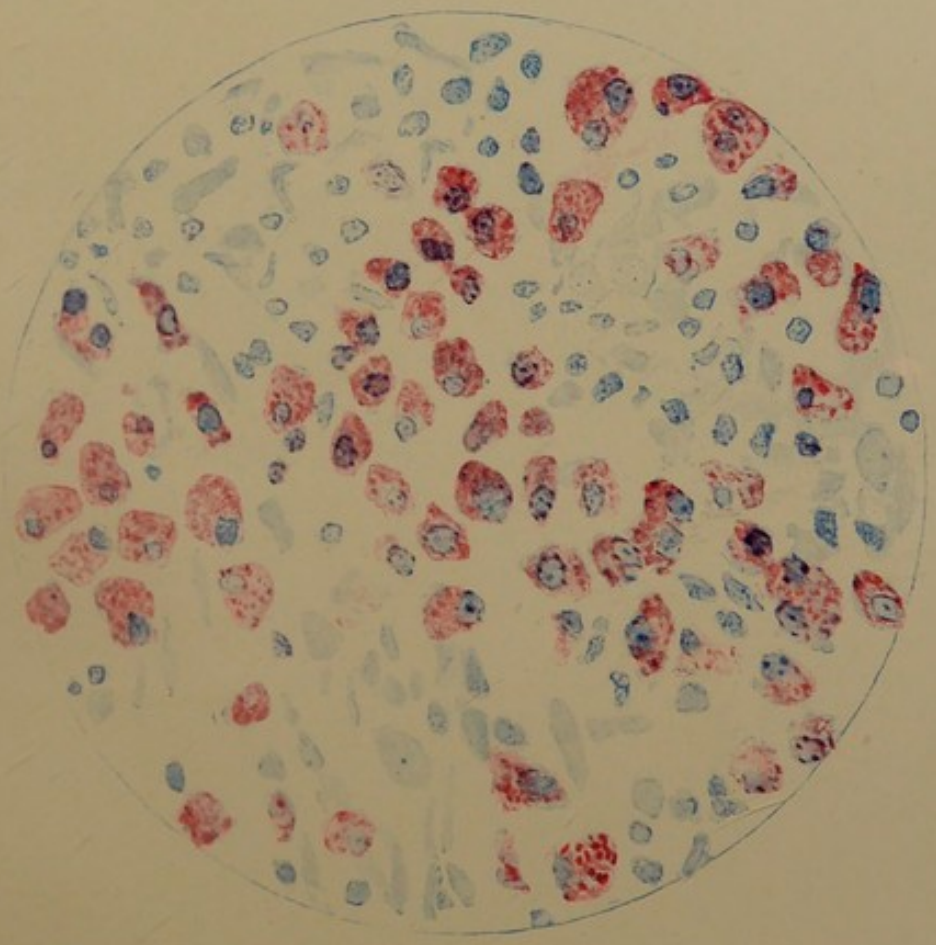

Plate XXI.

Section through a squamous secondary syphilide (syphilitic psoriasis), stained by Pappenheim's method. The figure is designed to give an impressionist view of the distribution of the plasma cells. They occur in patches in the dermis because they are grouped round the blood-vessels, but these vessels are scarcely indicated in the figure. × 100.

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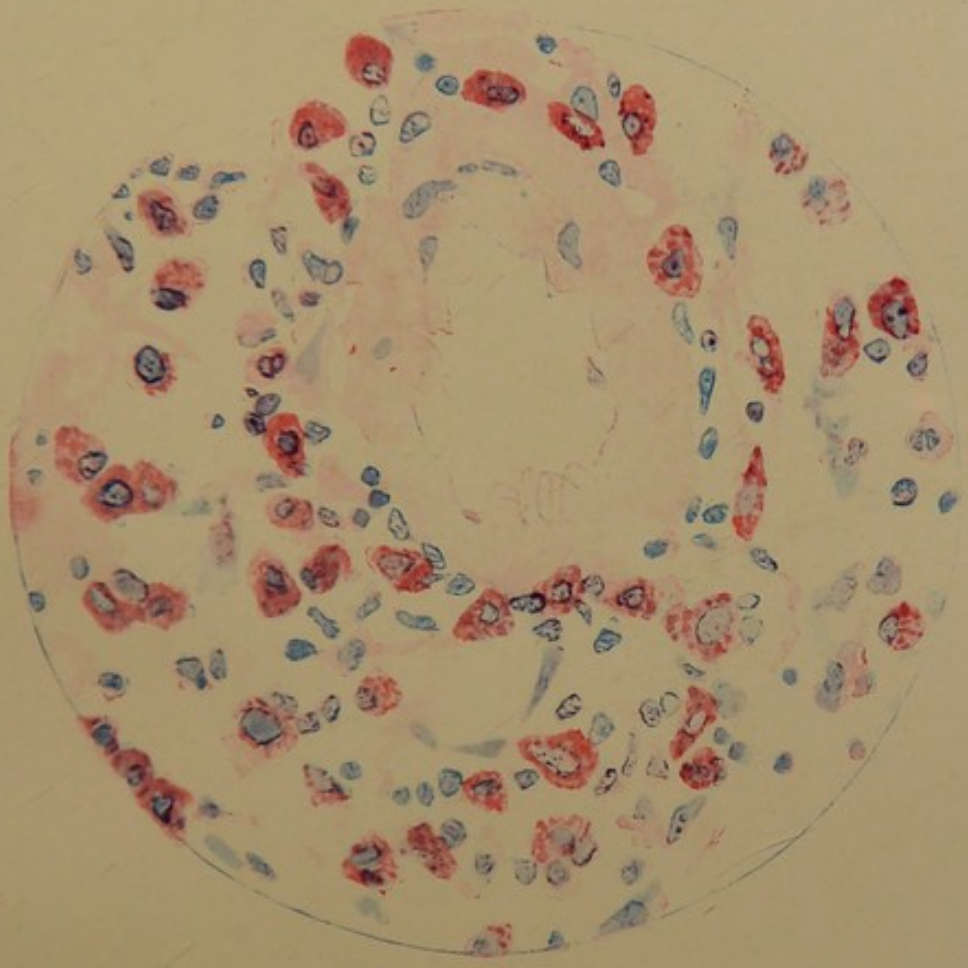
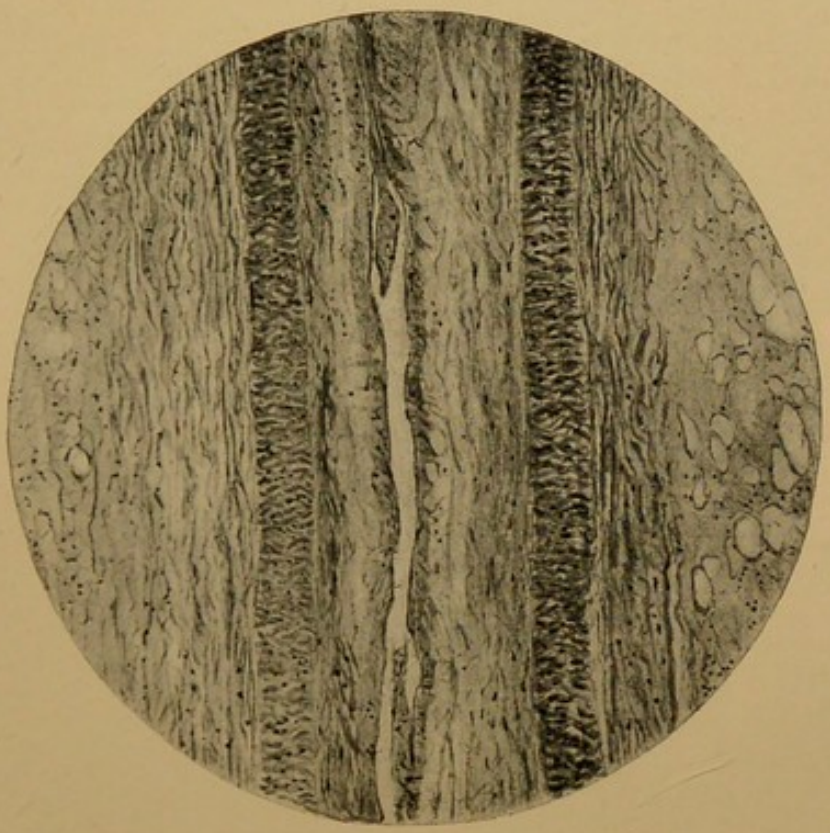
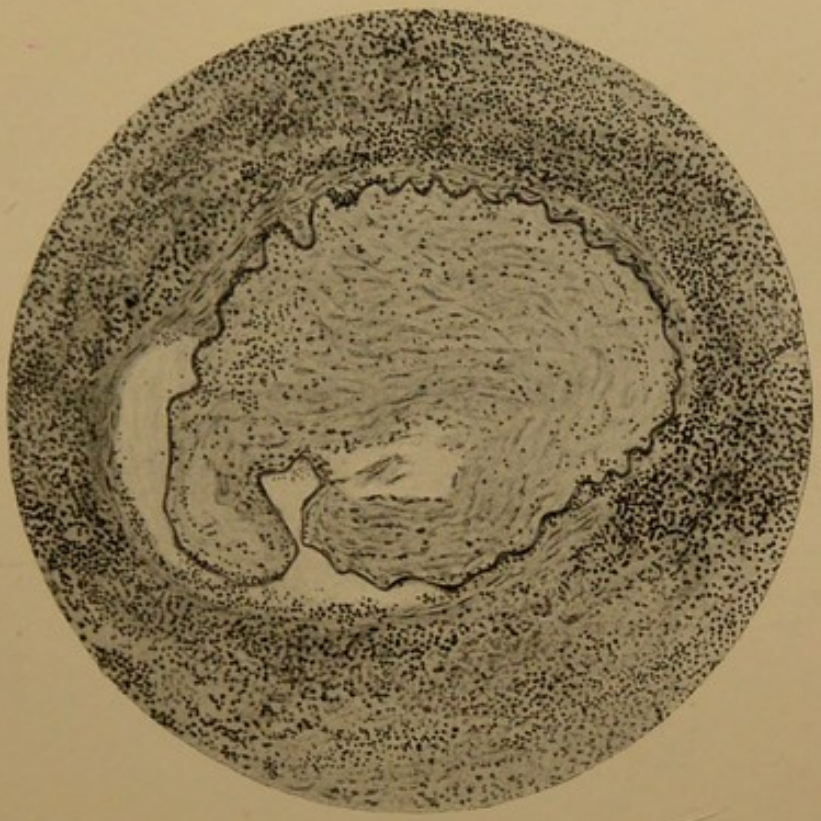




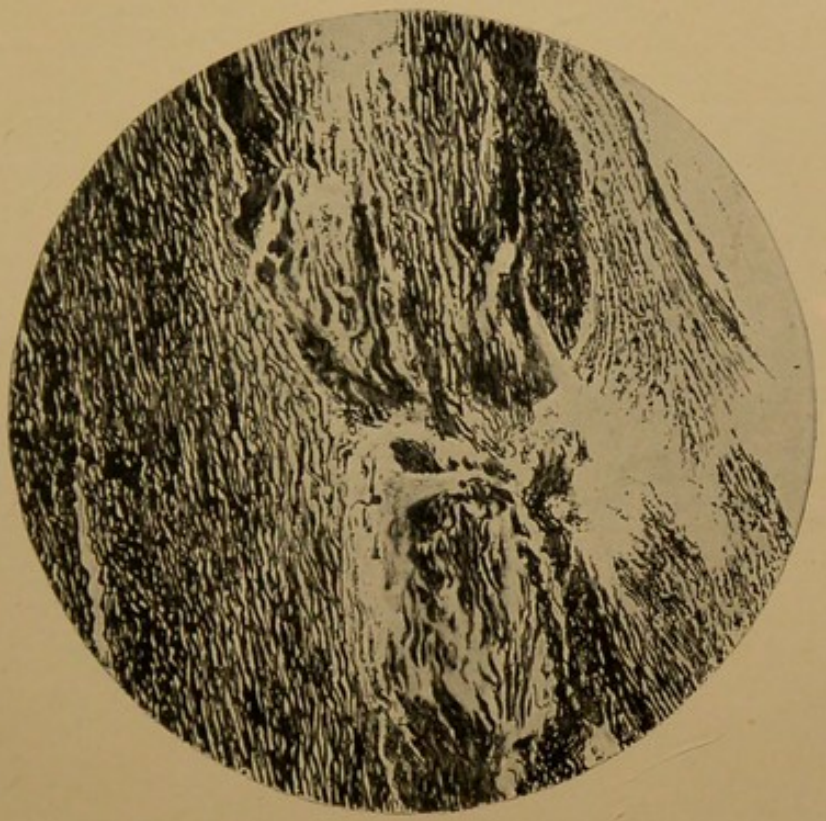
Longitudinal section of a small branch of one of the Coronary Arteries lying in the visceral pericardium over a gumma of the heart wall. It shows an obliterative endarteritis which has reduced the lumen of the vessel to a narrow chink. × 150.



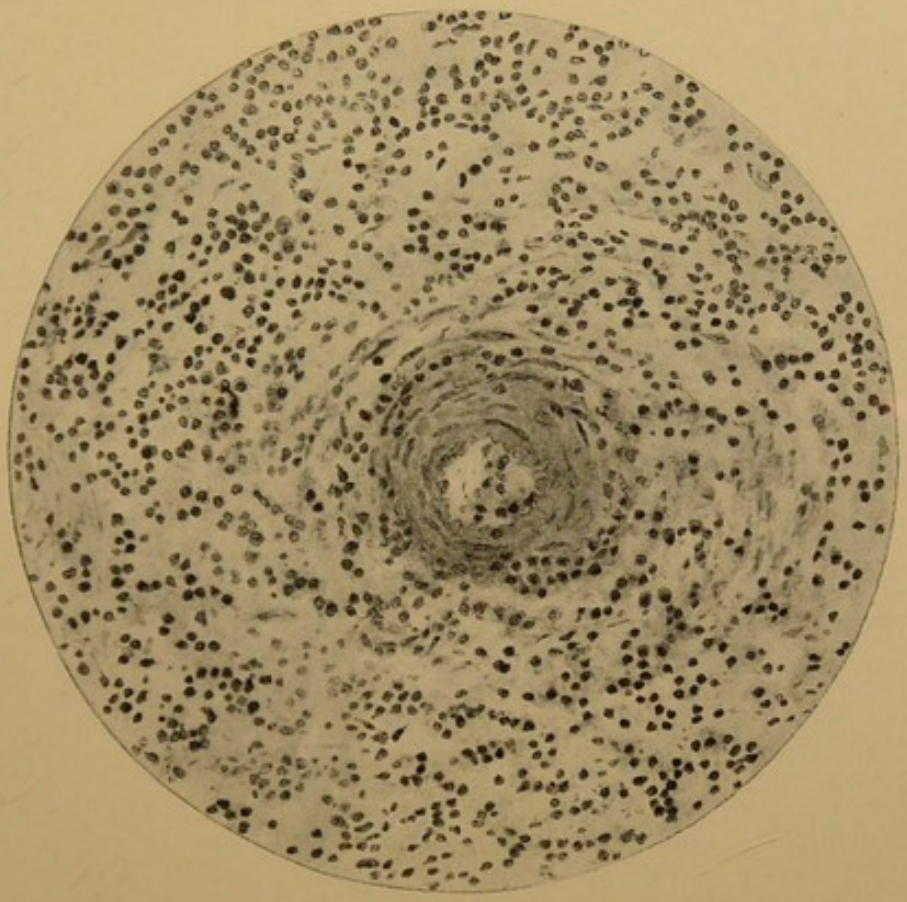
Transverse section of a small cerebral artery, included in a gumma of the brain. The lumen is almost occluded by an obliterative endarteritis. The internal elastic lamina has in one place become detached from the rest of the tunica media. × 150.

From a preparation lent by Dr. J. H. Drysdale.

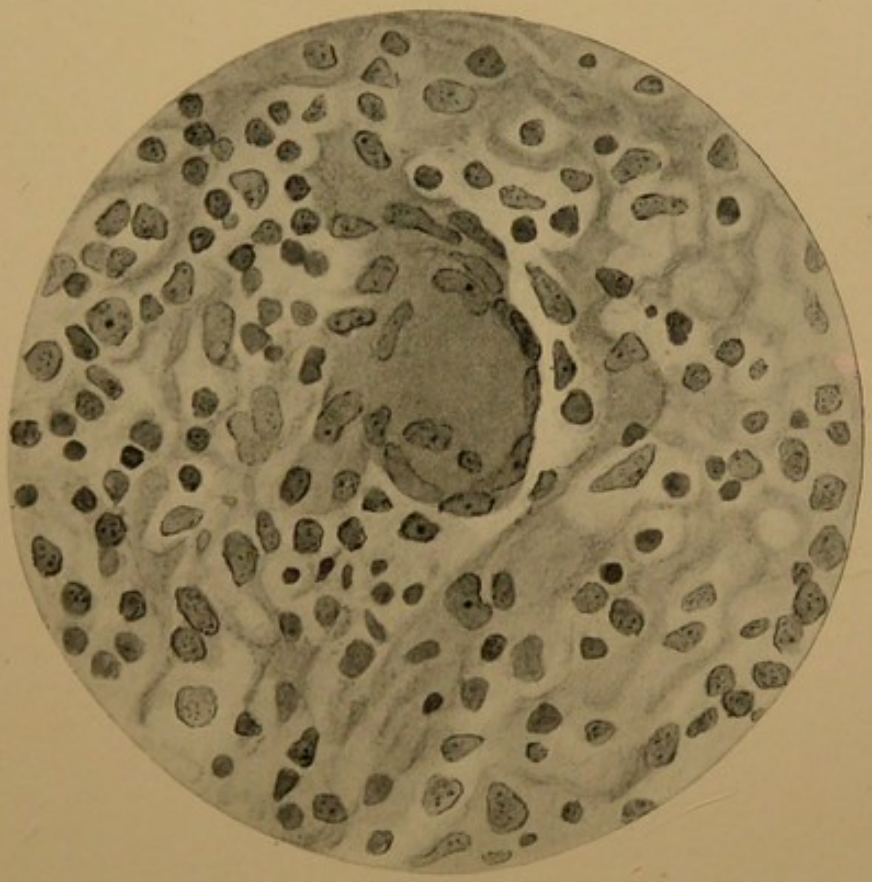
Section taken through the tunica adventitia of an aorta. The subject was a young man known to be syphilitic, and the cause of death was acute valvular disease; there was extensive implication of all three coats of the aorta. The section shows local areas of inflammatory infiltration in connexion with vessels and nerves in the adventitia and outer layers of the media. The large area of infiltration lies in the adventitia, and is in connexion with one of the vasa-vasorum, which itself shows typical syphilitic endarteritis. The following plate, showing the gaps in the elastic tissue of the media, is from the same aorta. × 100.



Section through the middle coat of the aorta of a young man who died of aortic valvular disease due to syphilis. The preparation is stained with orcein, and the elastic tissue is alone visible. The gaps and irregularities in the elastic network indicate the breaking up of the middle coat by syphilitic infiltrations. × 100.

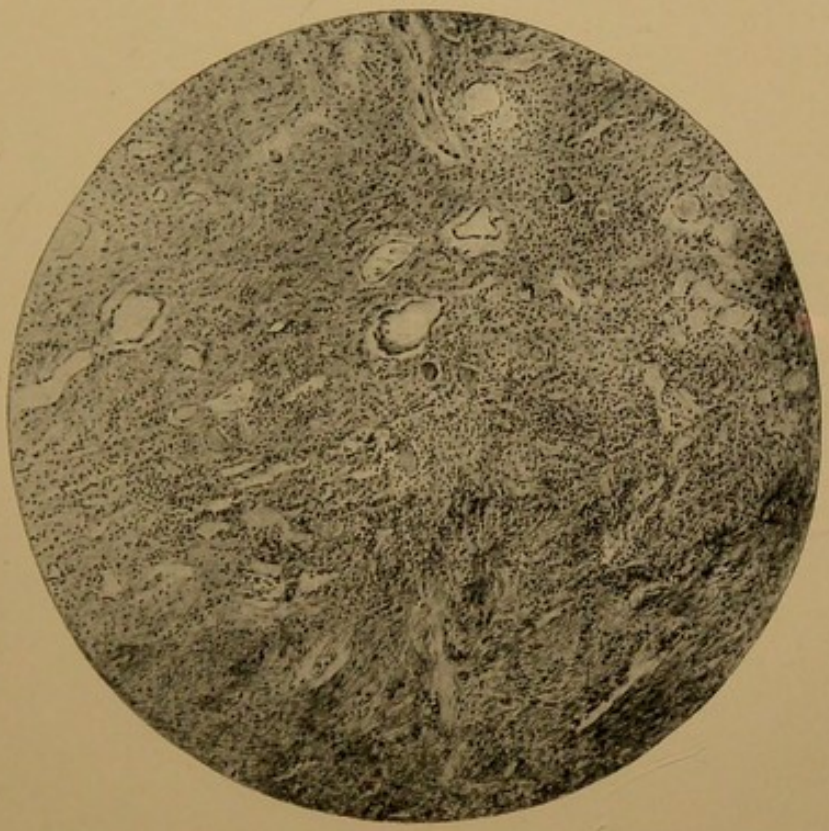


From a section through a primary chancre of the labium majus, to show the arterial changes which may be present even at this stage. An arteriole is seen cut across transversely; its walls are thickened, and the lumen is occupied by proliferated endothelial cells. The remainder of the section shows the granulomatous tissue forming the bulk of the chancre. ×400.

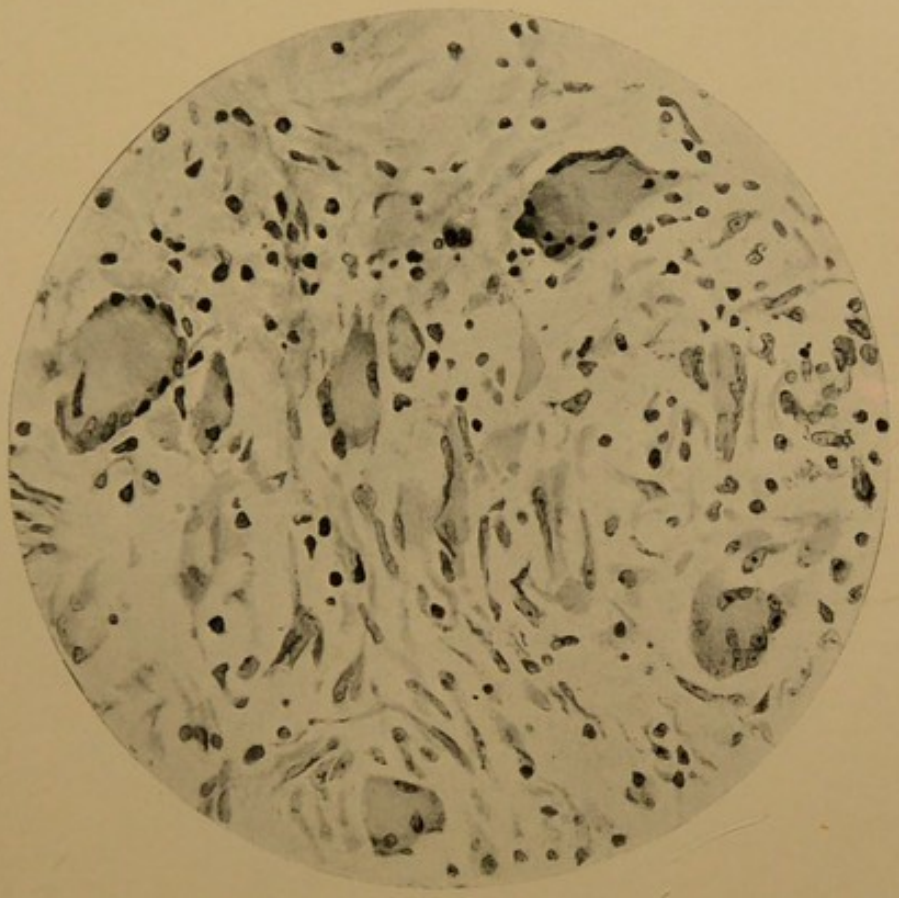


From a section of an indolent bubo of the epitrochlear lymphatic gland, consequent on primary syphilitic infection of the index-finger. The gland, which was as large as a chestnut, was excised about the time of the appearance of the secondary eruption. It shows overgrowth of the stroma and marked endothelial proliferation, with a well-marked giant cell in the centre of the field. ×500.

From a specimen lent by Dr. F. Parkes Weber.

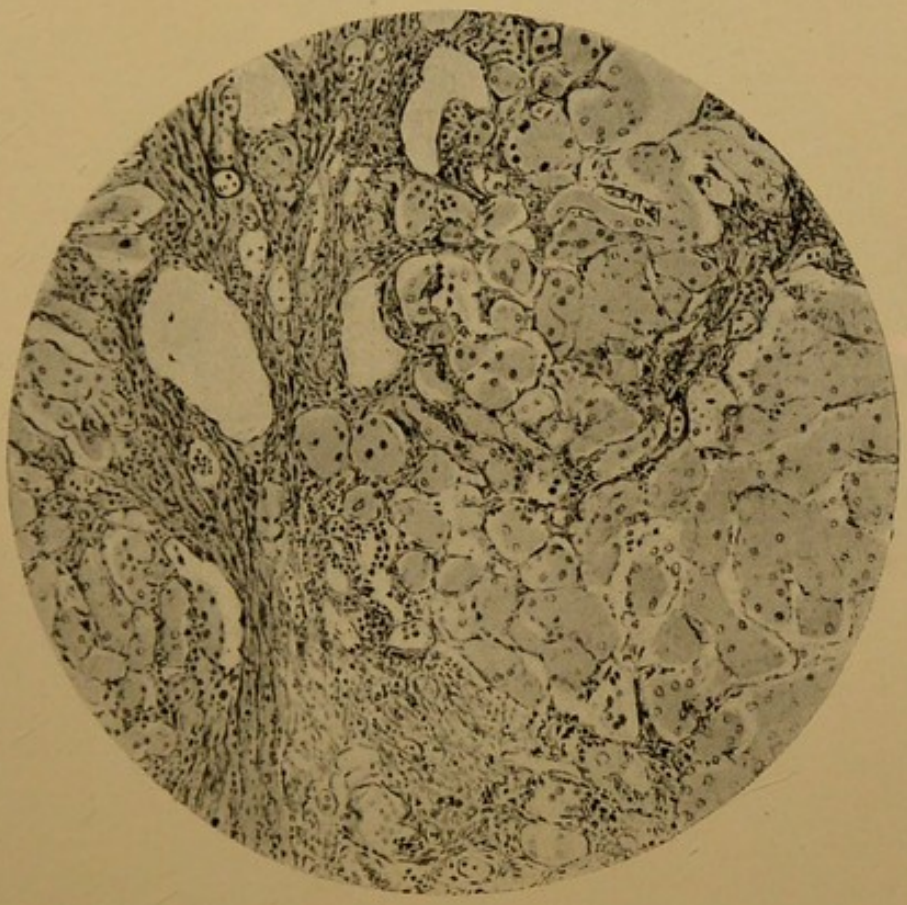


From a section through the edge of a gumma of the brain. At the lower side the tissue is caseous and fibrillated, but the greater part of the figure shows a cellular granulomatous tissue in which numerous blood-vessels are present. × 100.

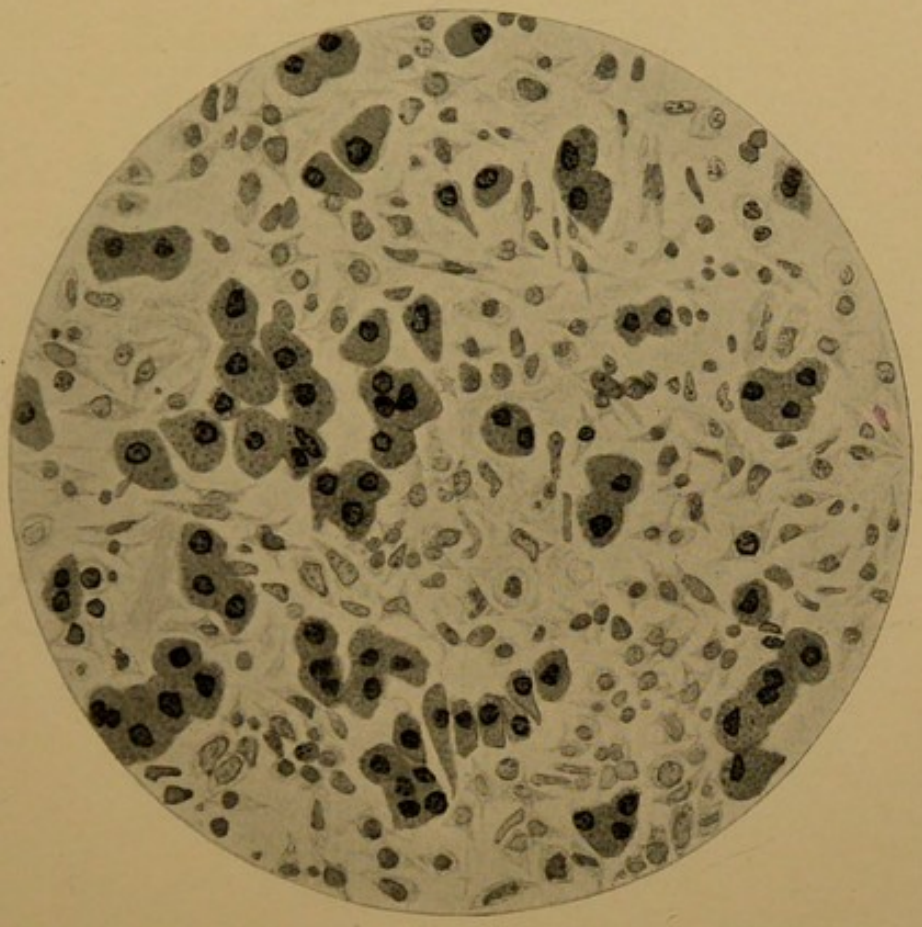


Giant cells from the margin of a young gumma of the skin. Four or five large multinucleate syncytia are seen in the figure, with plasma cells, fibroblasts, and endothelium. The specimen was stained with polychrome methylene blue. × 500.

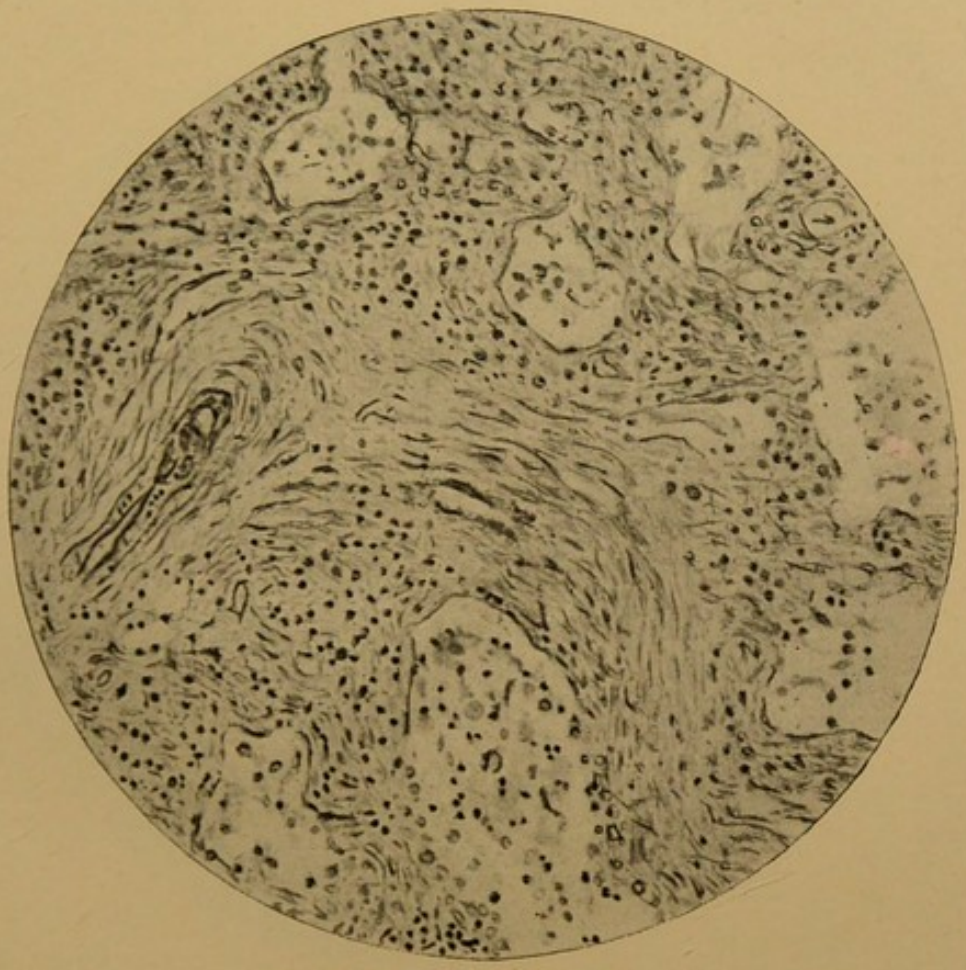
From a preparation by Mr. J. E. R. McDonagh.



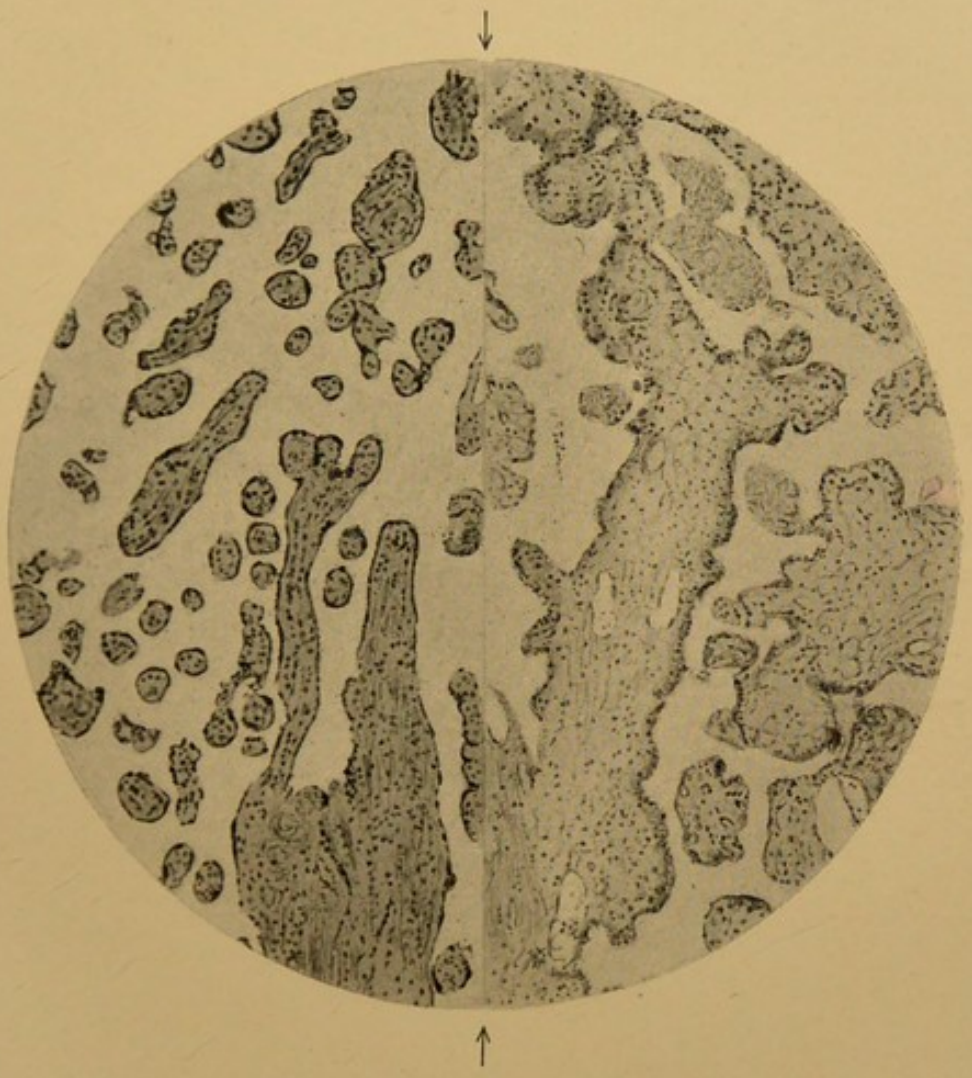
Syphilitic cirrhosis of the liver. Apart from the grosser fibrous bands, the lower cells are separated from one another by fine strands of newly-formed connective tissue. Various stages of atrophy are seen in the liver cells. × 150.



Section through the liver of a syphilitic infant which did not long survive birth. No gummata were present in the liver, but a uniform pericellular cirrhosis was everywhere found. The changes seen in the figure are characteristic, but somewhat extreme. The liver cells are separated into small groups of two and three by an abundant development of young and very cellular fibrous tissue. × 400.



Syphilitic pneumonia. Section through the lung of a still-born syphilitic infant. The lung was airless and in the condition known as 'white hepatization'. The alveolar walls are greatly thickened by young fibrous tissue, while the cavities of the alveoli are occupied by cast-off epithelium, with a few leucocytes. A broad band of fibrous tissue crosses the section; the artery, which is seen in longitudinal section, shows this to be a perivascular fibrosis. × 200.



Showing the contrast between a syphilitic and a normal placenta. The left-hand half of the figure is drawn from a normal placenta at term. The right-hand half is drawn to the same scale from a section of the enlarged and heavy placenta of a syphilitic pregnancy which went on to term. The villi of the affected placenta are seen to be greatly thickened, chiefly by a mucoid transformation of their ground substance. × 100.

From preparations kindly lent by Dr. H. Williamson.