stage is reached there can be no difficulty in making diagnosis. In the more localized forms in which there is no preceding eruption, the disease may be mistaken for sarcoma or carcinoma cutis. Against this diagnosis, however, there would be the absence of early implication of the lymphatic glands (although tumors in the groin may simulate them) and the comparative painlessness; and besides, as a rule, the course would be slower than in cancer and the internal organs would never be implicated.

With possibly two recorded exceptions, the disease has invariably terminated fatally, the extremes of duration being nine weeks (a case of Gaillard's) and fifteen years. The widespread cases, which commence as apparently simple inflammations, are much less malignant in their course than those which begin at once as tumors.

Pathology.—While the main facts as to the morbid anatomy of mycosis fungoides are generally agreed upon, much difference of opinion exists as to the interpretation to be placed upon these facts. Anatomically, the tumors consist of round cells supported by a scanty, delicate reticulum, which replace the normal tissue of the cutis. The new growth is somewhat scantily provided with vessels, and as it spreads it destroys the cutaneous capillaries. The boundary between the healthy and diseased tissues is ill defined. Ranvier and most French observers have classed it with lymphadenoma, but Sireday thought it was lymphosarcoma, and until recently all German authors have considered it to be a sarcoma. There is a growing tendency among observers at the present time to class the disease with the infectious granulomata. Various micro-organisms have been seen in the tissues by different observers and some have been cultivated, but none have as yet been demonstrated to have any pathogenic relation to the disease.

Treatment, so far as a cure is concerned, seems to be of little avail. Arsenic has been used hypodermically with apparent temporary benefit. Large doses of quinine are recommended. Resorcin subcutaneously has failed. The *x*-ray has of late been tried, but not with sufficient thoroughness to determine its value. Pyrogallic acid, aristol, iodoform, ichthyol have been used for the relief of local symptoms. It should, of course, be the physician's endeavor to make the patient as comfortable as possible by treating the various distressing symptoms as they arise. *Charles Townshend Dade.*

MYCOSIS INTESTINALIS. See *Anthrax*.

MYDRIATICS AND MYOTICS.—The opposing forces which maintain the iris in a state of equilibrium are controlled by two sets of nerves; the contracting muscle, the *sphincter pupillæ*, and the ciliary muscle being supplied by the third, while the dilating muscles are under the influence of the sympathetic nerve. The action of the third nerve has been very clearly demonstrated, but that of the sympathetic is not so evident, as the presence of radiating muscle fibres in the iris is a matter of dispute. Paralysis, or section of the third nerve, is followed by a relaxation of the sphincter muscle and dilatation of the pupil, and stimulation of the nerve produces contraction of the muscle and myosis. If the sympathetic nerve is stimulated there follows a dilatation of the pupil, and that the nerve exercises a positive dilating influence is shown by the greater degree of dilatation that takes place when a mydriatic is placed in an eye in which the third nerve has been paralyzed. This action of the sympathetic has generally been explained by the direct effect of the nerve upon the dilating muscles; but, since the presence of these latter has been called in question, a further explanation is necessary, and it has been suggested that the dilating nerve acts through the muscular tissue in the walls of the blood-vessels of the iris (see article on *Cocaine*).

Alterations in the size of the pupil may be due to ordinary physiological action, to some pathological change, or to the effect of certain drugs. Exposure to a strong light or to darkness, efforts at accommodation, the influence of fear or of shock, will produce an enlargement or a narrowing of the pupil, according as one or other set of muscles is reflexly irritated. So also diseases of the central nervous system, which interfere with the integrity of the third nerve, cause dilatation, as is seen in meningitis, hydrocephalus, brain tumors, etc., while any profound effect upon the basal ganglia or depression of the sympathetic will be followed by contraction of the pupil.

Mydriatics.—Mydriatic drugs produce their effect either by paralyzing the motor oculi or by stimulating the sympathetic nerve. Belladonna and its allies are examples of the first group, and cocaine belongs to the second.

In the first group are belladonna, hyoscyamus, stramonium, and duboisia, the alkaloids of which—atropine, hyoscyamine, daturine, and duboisine—are active mydriatics and are almost identical chemically. Many other plants, not employed therapeutically, are members of the order Solanaceæ and possess the same physiological action. Hyoscine and scopolamine are closely allied to atropine, yet differ from it to some extent and form another group.

Belladonna is the best-known mydriatic and has been longest employed. Whether administered internally or applied directly to the eye, one of its earliest and most marked symptoms is the dilatation of the pupil. This persists for several days, the length of time depending upon the dosage. In some cases of poisoning the pupil has remained under the influence of the drug for three or four weeks. When it is employed as a mydriatic, a solution of the alkaloid is applied directly to the eye in order to obtain a purely local action. Formerly the extract was painted around the eye or upon the temple, or an infusion of the leaves was applied as a poultice over the eye. The pupil is extremely sensitive to the effects of atropine. It will be influenced by gr. $\frac{1}{180000}$, and a solution of the strength of 1 to 80,000 will enlarge the pupil within an hour. Accommodation is not affected by solutions below a strength of from one-thirtieth to one-tenth per cent. Generally a one-per-cent. solution is selected, which, instilled into the eye, begins to act in fifteen minutes and fully dilates the pupil in half an hour, accommodation being lost in one hour. The paralysis lasts for three or four days and is accompanied by annoying disturbance of vision caused by the enlarged pupil and loss of accommodation. Minor disturbances may persist for several days. For convenience of use gelatin discs are prepared which contain gr. $\frac{1}{8000}$, and which are easily inserted beneath the lid. If paralysis of accommodation is required, discs containing gr. $\frac{1}{800}$ must be used. A solution of salicylate of atropine is to be preferred to the sulphate, as it forms an antiseptic solution which remains free from any fungoid growth such as forms in solutions of the sulphate.

Homatropine is replacing atropine when dilatation is required for the purpose of examination. The advantage is a more rapid and less prolonged action. The pupil begins to dilate in the course of a few minutes and accommodation fails in thirty or forty minutes. Its effect begins to subside in three or four hours, and the eyesight is quite recovered within twenty-four hours. The drug is also less irritating to the conjunctiva and is devoid of constitutional effects when used with ordinary care. For the purpose of simply dilating the pupil, a one-per-cent. solution is employed; when accommodation is to be paralyzed, a two-per-cent. solution is to be preferred. If mydriasis is required for a prolonged period, atropine is selected in preference to homatropine.

Hyoscyamine and *daturine* are rarely or never employed for their mydriatic action. Their action is the same as that of atropine, but they are less to be depended upon and offer no advantages.

Hyoscine exercises a much less marked influence upon the pupil, and is never used.

Duboisine.—This alkaloid has recently been extolled as possessing a more powerful action than atropine and as producing effects which are of shorter duration. As it is chemically identical with atropine, it will probably be found to have the same mydriatic action. The solution employed has a strength of one per cent., and produces dilatation within an hour.

Cocaine.—As a mydriatic cocaine differs from atropine and possesses many advantages. It is much less intense in its action, the pupil is not dilated to so great an extent, and a certain degree of reaction to light or other stimulus may be retained. Its effect is accomplished in half an hour and passes off in a few hours. There is little or no influence exerted on the power of accommodation. As before stated, it acts through the sympathetic nerves, either by stimulating the dilating muscle of the iris (if these exist) or by contracting the arteries of the iris.

When it is combined with atropine a very powerful mydriatic is obtained, as both a paralysis of the sphincter and a stimulation of the dilators are obtained. Koller uses a mixture of equal parts of a one-per-cent. solution of atropine sulphate and a five-per-cent. solution of cocaine hydrochlorate. This is applied every ten minutes until dilatation is secured, and if a prolonged action is required it is maintained by applying the solution three times a day. In inflammatory conditions much benefit is also obtained from the anæmia and blanching of the parts which the cocaine produces.

Mydriatics are employed to dilate the pupil for the purpose of an efficient intraocular examination and to facilitate cataract operations; also to remove the iris from the danger of adhesions in many inflammatory conditions. The dilatation of the pupil will also lessen the probability of prolapse of the iris in wounds of the eye.

For ophthalmic examinations and for simple dilatation of the pupil, homatropine and cocaine are now employed almost to the exclusion of atropine on account of their transient action. In examinations in which it is necessary to paralyze accommodation homatropine must be employed, as the action of cocaine upon the ciliary muscle is insufficient. In inflammatory states where a prolonged effect is required, atropine, with or without cocaine, is to be preferred. It is also indicated in all forms of iritis and in wounds or injuries accompanied by inflammatory action. When there is much ciliary spasm, it lessens the pain and photophobia by paralyzing the muscle.

The employment of mydriatics is not unaccompanied by dangers. For example, the alkaloid may be absorbed to such an extent as to cause severe constitutional disturbances, or some of the solution may pass into the nasopharynx and its local action be extended into the throat. Mydriatics may also, by continued use, prove so irritating as to produce a conjunctivitis. The most serious danger is the possibility of aggravating an incipient glaucoma—a result which has frequently followed their careless employment. This is due to the increased intraocular tension which accompanies the paralysis of the ciliary muscle, and, although cocaine is thought to have but little effect in increasing this tension, many cases are reported in which it has aggravated a glaucomatous condition of the eye. Certain signs of glaucoma, which readily distinguish it from iritis, are very marked and should never be overlooked. In iritis the iris is contracted and fixed, while in glaucoma it is dilated and also fixed; in iritis the eye is hypersensitive, in glaucoma it is almost insensitive. In glaucoma there are also the early symptoms of vomiting, with inflammation of the eye, and the prodromal disturbances of vision, with haziness of the cornea, color rings, etc.

Myotics.—The action of myotics is quite the opposite to that of mydriatics, the contracting muscles being stimulated and the dilating muscles depressed. With the contraction of the sphincter pupillæ there is also a contraction of the ciliary muscle which lessens intraocular tension. The action of myotic drugs is not well understood. It is probable that they act upon both sets of muscles, but even in the case of physostigmine, the best known of these drugs, many authorities consider that its action as a stimulant of the motor oculi is the most important, while others claim that its influence is directed chiefly as a depressor of the sympathetic. Myotics are of less therapeutic value than are mydriatics, and were it not for the lessened intraocular tension that accompanies the narrowing of the pupil, they would very rarely be employed. They are recommended in cases of paralysis of the third nerve, but are rarely of any service, except in the paralysis following diphtheria. In glaucoma they are of undoubted value. The great tension is overcome and the eye is relieved, and in many instances their employment has apparently rendered an operation unnecessary. In wounds of the surface of the eye and in corneal ulcers the tendency to rupture of the coat is lessened by their use.

Physostigmine or *Eserine* is the drug always selected. Pilocarpine exercises the same effect, but it is mild and uncertain. A solution of the sulphate or salicylate of eserine is employed, of the strength of one-quarter grain to the ounce. This will begin to act in fifteen minutes, its full effect will be reached in an hour and will continue for two or three hours, and in twenty-four hours the myosis will have disappeared. In glaucoma myosis is more difficult to obtain, and a solution of two per cent. may be required. The condition of myosis is not so intense as is that of mydriasis, and if atropine has been applied to the eye eserine will have no effect until the action of the atropine has begun to pass off. On the other hand, atropine rapidly dilates a pupil under the influence of eserine. *Beaumont Small.*

MYDRIN is a colorless powder composed of ephedrine hydrochloride, 100 parts, and homatropine hydrochloride, 1 part. It is used in ten-per-cent. solution as an evanescent mydriatic. *W. A. Bastedo.*

MYELOMA.—Under the greatest variety of names there have been described in recent years cases of an affection of the bones which have in common certain features so distinctive as to justify their union under one name. Briefly stated, these cases show as a rule evidence of the presence of multiple new growths developing simultaneously in the most widely separated bones. Pain is often felt in these tumor-like masses, and from the destructive influence which they exert upon the bony structure fractures with dislocation and deformity soon appear as the result of the most trifling traumatism. A cachectic condition supervenes in the later stages and is associated with the occurrence of a peculiar urinary condition, — one in which the urine contains albumoses. Various paræsthesias and pareses may occur, and with the great increase in the deformities produced by the tumor masses the patient finally dies of exhaustion or succumbs to some intercurrent affection.

As early as 1847 a case of this sort was observed by Bence Jones[1] and Macintyre. Their attention was particularly attracted to the condition of the urine, in which a peculiar proteid could be demonstrated. The patient after a long and very painful illness died, and at the autopsy there were found red gelatinous masses replacing in large part the vertebræ, sternum, ribs, etc. They designated the condition "osteomalacia fragilis rubra."

Rustizky[2] first gave the name multiple myeloma to the condition in a paper published in 1873. He considered it a simple hypertrophy of the bone marrow, because, although the tumors were multiple, they were present only in the bones and did not give rise to metastases.

Since then a number of cases have been described under this name, while many others obviously of the same nature have been designated "osteomalacia," medullary pseudoleukæmia, sarcomatous osteitis, malignant osteomyelitis, lymphosarcoma, etc. Good summaries of the literature with descriptions of cases have recently been given by Hammer,[3] Winkler,[4] Wieland,[5] and Paltauf,[6] from which it appears that there is really a well-defined condition, easily distinguishable from the endotheliomata and sarcomata of bone, and for which the name myeloma is most fitting,—a condition which Virchow prophesied, although at that time no case had been published.

The disease may perhaps be made clear most easily by the description of a case which occurred recently at the

Johns Hopkins Hospital and which has been reported in its clinical and pathological aspects by Dr. Hamburger and myself. For the clinical description I quote from his paper in the *Johns Hopkins Hospital Bulletin* (vol. xii., 1901, p. 38).

The patient was a colored woman, fifty years of age, who entered the hospital complaining of "rheumatism" and a "sprained hip." Her personal and family history were unimportant, but for about a year she had had pain in the region of the right groin and hip. One night about six months ago, while picking up a bucket of coal, she experienced a remarkable sense of lengthening in the left arm, and next morning found that she could not raise it to her head because of pain and a feeling of weight. A week later the right arm became affected. She had pains in the shoulders, neck, and chest. About this time she noticed a swelling the size of a hen's egg on the back of her head. Pain and stiffness in the arms continued, so that after two months she could not feed herself. Six days before admission to the hospital, while walking, the right leg "gave way" without apparent cause. She fell to the ground and since then had not been able to stand or walk. She suffered great pain in the right hip.

She became much emaciated and very weak and anæmic. On admission to the hospital, any movement of the body was found to produce great pain. Over the occipital region there was a round, soft, fluctuating mass about 10 cm. in diameter, not adherent to the skin, not movable on the deeper tissues, not tender. A nodule, 3 to 4 cm. in diameter, was visible on either clavicle over its inner third, the one on the left being a little larger and evidently eroding the bone, for manipulation caused pain and crepitus. There was another tumor in the left supraspinous region, about 4 cm. in diameter, connected with the acromion process of the scapula. The right leg was rotated outward and abducted, the upper third of the thigh being markedly enlarged and deformed by the presence of a tumor about the size of a child's head, projecting from its postero-external aspect. It was firm and tender on pressure and any attempt to move the limb caused intense pain.

Physical examination was otherwise negative. There was no glandular enlargement and examination of the blood showed only a diminution in the number of red corpuscles with a corresponding diminution in the percentage of hæmoglobin. The urine was turbid, light yellow, and usually alkaline; from 600 to 800 c.c. were voided daily, of a specific gravity varying from 1.012 to 1.030. Heller's reaction was positive. When the urine was acidified and heated to a temperature of 56° C., a heavy white precipitate appeared. It redissolved in part on boiling and returned on cooling. The nitric-acid precipitate disappeared on boiling, to reappear on cooling. The mixture assumed a darker color and particles of the precipitate adhering to the tube became pink. The biuret reaction was marked. The proteid content measured by the Esbach albuminometer varied from 0.3 to 0.6 per cent.

This case illustrates well the symptoms which have been spoken of as fairly constant, viz., the emaciation and anæmia, the simultaneous occurrence, over the bones, of soft, almost fluctuant masses, and the erosion of these bones with fracture and deformity associated with great pain. Particularly well, however, is the albumosuria illustrated. Acute transitory or slight albumosuria has been observed in many acute febrile diseases, and similarly slight peptonuria has been described in the greatest variety of conditions. The work of Kühne and Chittenden renders it probable that all of these are instances of albumosuria, the proteid substance found in the urine being very closely related to, but not exactly identical with, the products of partial digestion described by those authors. These cases, however, are without difficulty distinguished from those in which the quantity of albumoses is large and its occurrence persistent throughout a long time. It has been found (Hamburger) that in the great majority of cases of definite albumosuria multiple myelomata have been found at autopsy, although as yet the evidence is not sufficient to prove that in all cases of myeloma albumosuria is found.

The origin and exact nature of this proteid substance are as yet quite obscure, but when it is present in considerable quantities it is easily recognized by the reactions described above, and especially by its property of redissolving at boiling temperature in acidified solution, from which it was precipitated by a temperature of 56° C.

The pathological anatomy of the multiple myeloma may be made clear by a further reference to the case above mentioned.[7] The patient died after a stay of some months in the hospital, and at the autopsy multiple tumor masses were found involving various bones. The right leg was shorter than the left by about 3 cm., and in the trochanteric region, where there was a large tumor mass, there was excessive mobility of the femur. The organs in general showed only the evidences of senile atrophy and in the lungs a few old tuberculous scars. On removal of the sternum it was found to contain, at the points of insertion of the second and third costal cartilages, a tumor mass, which, being very soft, allowed free movement of the two parts of the sternum upon each other. The left clavicle was much enlarged at its sternal end, the bone being apparently distended by the tumor mass within, for the cortical portion was very thin and could be compressed by the fingers. On sawing through the bone lengthwise the cancellous bone was found to be much rarefied and the cortical portion very much thinned; the marrow was almost entirely replaced by the tumor mass, which extended quite to the acromial end.

The right clavicle showed evidences of a healed fracture, the portions having united in a somewhat abnormal position, so that a slight angular deformity existed. The marrow of this bone also showed tumor masses, which did not, however, cause any extensive erosion of the bone.

From the spinous process of the left scapula there arose a soft tumor mass which on section was found to have eroded and replaced a considerable portion of the bony process. None of the cortex or cancellous bone tissue was to be discovered in this one. The ribs were not involved. Unfortunately, the vertebral column was not sawn through, but there were no evident tumor masses visible from without. The right ilium was completely eroded through in its median portion by a large soft mass, which had destroyed the whole thickness of the bone and which projected both ways—inward into the pelvis under the iliacus muscle, and outward under the muscles covering the outer surface of the ilium. The hip-joint on this side showed no abnormality, but in the intertrochantèric region a large tumor mass sprang from the marrow of the femur. At the upper end of the shaft of the femur there was a fracture, the shaft being displaced upward. On sawing through the bone at this point the intertrochanteric region was found to be extensively involved in the new growth, which extended into the adjacent tissues. The cancellous bone was almost entirely destroyed and the cortex much atrophied and roughened internally. For a distance of about 5 cm. the cavity of the shaft of the femur was invaded, the yellow marrow being pushed ahead and fairly sharply limited from the dark purple new growth. The bone marrow was atrophic and œdematous, grayish-pink and moist in appearance, and sunken below the level of the cut surface of the invading tumor. The left femur showed no evidence of tumor formation.

Removal of the large mass at the vertex of the skull revealed a large aperture in the skull, the edges of which were very ragged, as if gnawed away, with here and there loose spicules of bone lying in the soft tumor mass which evidently sprang from the marrow cavity. This tumor mass spread itself between the cranium and the dura for a short distance, and, completely filling the aperture in the skull, projected outward to form the large soft mass felt under the scalp.

No other tumor nodules were to be found so far as it was possible to examine the bones.

These growths presented everywhere the same appearance. Everywhere they evidently sprang from the marrow of the bone, from which they were not by any means sharply demarcated. Only where the tumor seemed to invade the yellow marrow of the shaft of the femur was the outline sharp, but even there the microscopical examination showed evidences of the presence of tumor elements far past this outline. Where the red marrow of the short bones formed the point of origin, the outline was not nearly so sharp. The well-defined tumor masses were perhaps somewhat firmer than such a mass of bone marrow would be. They varied somewhat in consistency, however. In general they were soft; some of the larger ones were almost diffluent, and they flattened out when they were cut and laid out on a pan. Others were less soft, and in some parts the gelatinous pulpy consistency gave way to a fair degree of firmness. In color there was also considerable variation. The greater part of the masses was of a deep red color, perhaps even darker than that of the normal red bone marrow, but showing everywhere a grayish tint. Usually lines and streaks of gray were to be seen throughout this deep red, and in nearly all the masses definite nodules of firmer consistency and of grayish-white color were found. At some points there was a slight yellow opacity.

Microscopically, the various authors have emphasized the regularity in form and size of the cells, and Wieland has adduced this as a distinction from the myelocytes. Nearly all writers have thought the tumor cells to be derived from some cell or other of the bone marrow. Wright alone considers them to be plasma cells or closely related cells at least, to explain which he states that plasma cells are present in the bone marrow. The results of attempts to determine the histogenesis of the cells in this case will appear from the following description of the microscopical appearances:

The tumor masses present in sections a remarkably homogeneous appearance. There is, as described in practically all of the other cases, a delicate stroma with rather wide meshes in which lie innumerable rather large round cells. These are not in intimate connection with one another, but lie singly and loose; sometimes, where their number is very great, they are somewhat compressed into a polygonal form, but in general they are quite regularly rounded; they vary slightly and may be elongated or pear-shaped or even notched. The nucleus is large, round, and vesicular, sometimes lying eccentrically. The protoplasm presents a rather ragged granular appearance. Blood-vessels exist throughout the tumor and are indeed rather numerous. The smaller ones lie in very intimate contact with the tumor cells, their walls being merely a single layer of endothelium. Connected with these and the coarser strands of the stroma are exceedingly fine filaments of connective tissue which run in between the cells. Everywhere, scattered quite without order through the tumor mass and among the tumor cells, are numerous red blood corpuscles, which are quite well preserved. These evidently give the dark red color to the tumor masses, being absent or present in only very small quantity in the translucent grayish-white nodules described above.

More careful examination of the characteristic cells of the tumor shows them to be distinctly of one type, although certain variations in size occur. They measure from 13 to 21 μ in diameter, and thus approach very closely the myelocytes, while they exceed considerably the plasma cells in size. The nucleus is provided with a definite nucleolus, which shows especial avidity for certain aniline dyes. In smears from the tumor the nuclear structure is shown clearly. The nuclei appear large and flattened out, and in the general pale blue stain there appear irregular spaces which do not stain or take only the tint of the cell protoplasm. In this respect they resemble closely the myelocytes as described by H. F. Muller. The protoplasm is rather ragged and granular-looking, but the granules are not sharply outlined and with specific stains they take on no different coloration from the rest of the protoplasm. These are, therefore, not specific granulations. In sections as well as on smears stained with the polychrome methylene blue of Unna or the alkaline methylene blue, the protoplasm takes on only the palest greenish-gray coloration; there is nothing of the specific staining described by Unna and others for the plasma cells. With polychrome methylene blue and eosin the protoplasm stains with eosin.

The relation of these cells to the other normal cells from which they might possibly arise is therefore about as follows: In size they greatly exceed the plasma cells, but agree fairly well with the myelocytes and non-granular cells resembling myelocytes found in the bone marrow. With polychrome methylene blue, etc., they do not show the reaction typical of the plasma cells; on the other hand, their protoplasm, although in its raggedness it does resemble the "granoplasma" described by Unna for the plasma cells, shows none of the specific granulations characteristic of the myelocytes. The presence of a nucleolus must be admitted for all these various types of cells, so that it is of no help in determining such relations. The cells of the myeloma and the myelocytes and non-granular cells of the bone marrow have in common, however, the peculiar lacunar structure of the nucleus, as seen in dried smears, which H. F. Müller[8] describes as follows: "With adequate magnification one sees in the myelocytes a remarkable nuclear structure; one finds often nuclei in which definite clear fields are visible. These may be in part nuclear substance, but in many such nuclei these fields seem to represent the cell substance which stretches itself into pre-existent holes or pores in the nucleus." And then again: "There is a large round or oval nucleus limited by a thin chromatin wall which shows frequently more or less numerous larger and smaller clear areas, which are often plainly seen to be definite apertures in the nucleus through which the cell substance extends into the interior of the nuclear body."

This structure seems so peculiar that its occurrence in these various cells at least indicates their close relation to one another. The descriptions and figures of plasma cells in the papers of Unna,[9] Jadassohn,[10] Marschalko,[11] Justi,[12] Krompecher,[13] and Councilman[14] give no hint of such a structure in the nuclei of these cells.

The myeloma cells are apparently separated from the myelocytes by the absence of the characteristic neutrophile granulations. An examination of a bone-marrow smear, and more especially of a smear from actively proliferating bone marrow, will convince one of the great variations in the abundance of the granules which occur in these cells. In a recent paper on the relation of the myelocytes to leucocytosis, Rubinstein[15] describes the transitions which take place in the development of myelocytes from smaller cells whose protoplasm is quite free from granules. These young myelocytes reach quite the size of the adult myelocytes before the granules appear, which they do gradually a few at a time. The resemblance then between these non-granular myelocytes, as they may perhaps be called, and the myeloma cells is most striking, and suggests most strongly the origin of the myeloma from these characteristic cells of the bone marrow in one or other stage of their development.

Further evidence of this close relation is given in the abundant presence of the tumor cells in the marrow adjacent to the tumor masses, where they take on exactly the arrangement of the myelocytes among the fat cells and are intermingled with the occasional eosinophile cells. Indeed, if, in a large section, we pass gradually from the relatively normal marrow toward the tumor, we find a gradual and insensible transition, the myelocytes being replaced entirely in time by the tumor cells, which become more and more densely arranged, forming finally definite nodules. Among the trabeculæ of the cancellous bone this consolidation of the cells which have the position and form of myelocytes into solid strands in direct continuity with the tumor mass is very convincing evidence of the direct relation between the tumor and bone-marrow cells.

Various alterations in the appearance of the tumor cells, such as fragmentation and partial division of the

nucleus, occur. Indeed, one sometimes finds large cells containing numerous nuclei and a vacuolated protoplasm in which irregular or rounded cellular inclusions are present. These are perhaps best interpreted as evidences of degeneration.

The tumor mass as described above contains in the interstices between the cells very numerous red blood corpuscles in a very well-preserved condition. There is very little evidence of any breaking down of the red corpuscles,—hardly any deposit of hæmatoidin in the tissues, which would certainly be present if the presence of the blood were due to actual hemorrhage. Red corpuscles are found scattered in considerable numbers among the myelocytes and other cells in the normal bone marrow, however, and it seems probable that the condition here is analogous. The walls of the blood-vessels in the tumor are nevertheless of extreme thinness and extravasations might readily occur. So also tumor cells are quite frequently found inside these blood-vessels lying among the red corpuscles, although an examination of the circulating blood a few days before the death of the woman showed only one or two doubtful myelocyte-like cells among a great number of leucocytes, the varieties of which were those of the blood in practically normal relations.

From this description, then, it is seen that in this condition we have multiple new growths from the bone marrow, not very sharply delimited from the marrow and showing very gradual transitions into it. The cells have the form and general characters of the bone-marrow cells, lacking the specific granules of the myelocytes, but possessing the peculiar nuclear structure found in the myelocytes and their formative antecedents. They differ in essential particulars from the plasma cells, and in view of these facts and of the fact that they largely replace the myelocytes in the marrow in the neighborhood of the tumor, there being no sharp boundary between the myeloma-like marrow and the myelocyte marrow, we may consider them directly related to these cells and probably derived from the large non-granular forerunners of the myelocytes.

The exact relations of this condition to others with which we are familiar are difficult to determine. On the one hand, there are none of the anatomical features of the ordinary forms of chronic inflammation, while on the other hand the process differs from that which characterizes the majority of tumors in its simultaneous origin in many bones and in its mode of growth, which while destructive is not of such a nature as to give rise to metastases. We are quite ignorant of any etiological factors, but on the whole the condition seems most analogous to those forms of lymphosarcoma which, arising often simultaneously from many lymphoid structures, invade and destroy the adjacent tissues.

William G. MacCallum.

[1] Bence Jones: Phil. Trans. Roy. Soc., 1848, Part i., p. 55.
[2] Deutsch. Zeitschr. f. Chir., 1873, Bd. iii., S. 162.
[3] Virchow's Archiv, 1894, cxxxvii., p. 280.
[4] Virchow's Archiv, 1900, clxi., p. 252.
[5] Primäre multiple Sarcome der Knochen. Inaug.-Diss., Basel, 1893.
[6] Ergebnisse der allgemeinen Pathologie u. pathologischen Anatomie. Herausgegeben von Lubarsch u. Ostertag, 1896, iii., 1, p. 676.
[7] W. G. MacCallum: Case of Multiple Myeloma. Journal of Experimental Medicine, vol. vi., No. 1, 1901.
[8] Deutsches Archiv f. klin. Med., 1891, xlviii., p. 57.
[9] Monatshefte f. prakt. Dermatologie, 1891, xii., p. 296.
[10] Berliner klin. Wochenschrift, 1893, xxx., p. 222.
[11] Archiv f. Dermatologie u. Syphilis, 1895, xxx., p. 3.
[12] Virchow's Archiv, 1897, cl., H. 197.
[13] Ziegler's Beiträge z. path. Anat., 1898, xxiv., p. 163.
[14] Journal of Experimental Medicine, 1898, iii., p. 401.
[15] Zeitsch. f. klin. Med., 1901, xlii., p. 161.

MYOMA.—The myoma is a tumor composed chiefly of muscle tissue, therefore of mesoblastic origin, and belonging in the connective-tissue group. According to the type of muscle tissue of which myomata are composed, they are divided into leiomyoma (Zenker) or myoma lævicellulare (Virchow), containing smooth muscle fibres, and rhabdomyoma or myoma striocellulare, containing striated muscle fibres.

In general, the term myoma, without further distinction, is used for leiomyoma.

Leiomyoma.—Of the two varieties, the tumor composed of smooth muscular fibres is by far the most frequent and of the most importance clinically.

Histology.—The physiological type of the tissue, the smooth muscular fibre, is widely distributed over the body, and is best seen in the intestinal canal and in the uterus. The smooth muscular fibres are long, fusiform cells, which are connected by a small amount of cement substance. The nucleus is a long rod-shaped body situated in the middle of the cell. The tumor is composed for the most part of such muscular fibre cells, which are arranged in bundles, closely packed together, frequently interlacing, and separated from one another by a small amount of connective tissue which carries the blood-vessels. On section of the tumor these bundles are cut at various angles, and when the nuclei are brightly stained the section often appears peculiar. When a bundle of fibes is cut exactly across, the section of the muscular fibres, with the brightly stained nuclei in the centre, may be mistaken for round cells with a central nucleus, or, still more readily, for a section of a nerve. The nuclei may be mistaken for connective-tissue nuclei and the tumor for a fibroma. In the myoma the nuclei are longer, narrower, and more refractive than connective-tissue nuclei, and in the fibroma the arrangement of the fibres in bands is never so characteristic as in the myoma. In cross-section of the fibres the muscle substance around the nucleus is seen to be denser, more homogeneous, and more refractive than the protoplasm of other cells. When fresh unstained sections are examined the tumor may be mistaken for a sarcoma, in which the cells are often arranged in bundles in the same way, but a careful study of the nuclei will reveal its true character. Th separate cells which compose the tumor may be isolated by macerating small portions in a twenty-per-cent. nitric-acid solution or in a thirty-per-cent. solution of caustic potash. This dissolves the cement substance between the muscular fibres, and they can then readily be teased apart. There is often a considerable difference in size between the tumor cells and the cells of the analogous physiological tissue. The cells may be very much larger or very much smaller than these. Sometimes cells as large as the muscle cells in the rapidly growing pregnant uterus are found. There is always with the muscular tissue a variable amount of connective tissue which is principally found between the larger muscle bundles. From this, smaller septa are given off which run between the smaller bundles of cells. White (*Johns Hopkins Hospital Bulletin*, xi., 114, 1900) has demonstrated that this connective tissue is of the white fibrous and reticular types, and that each muscle cell is surrounded by a connective-tissue capsule. He could demonstrate no elastic fibres. In this connective tissue run the blood-vessels. In some cases the connective tissue is so abundant that it forms a considerable part of the tumor, and in others there is scarcely any present, except around the larger vessels. The amount seems to vary with the age of the growth, being always less in small tumors of recent formation. When there is much connective tissue present the tumor is generally firm and fibrous, but in some places it may have more the character of loose areolar tissue and contain numerous lymphoid cells. In some of the very large myomata of the uterus the development of connective tissue is so great that the tumor appears to be principally composed of this, and it is only after considerable search that the muscular tissue is found. To this form the term *fibro-myoma* is given. In almost every tumor some places will be found where neither muscular tissue nor connective tissue can be made out. There are larger or smaller areas of firm, highly refractive, homogeneous tissue, in which a few rod-shaped nuclei are scattered. Such areas are most abundant in the larger tumors, and represent a hyaline transformation of the tissue. As a rule the myomas have a very poor vascular supply, but cases are sometimes seen in which the blood supply is so abundant that the tumor almost resembles a cavernous tissue. This variety of tumor will be considered more fully in speaking of myoma of the uterus.

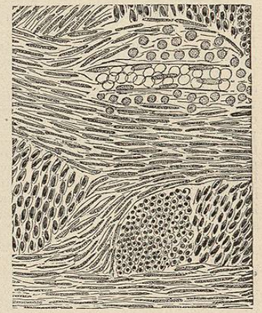

Fig. 3466.—Section of a very Small Myoma of the Uterus, Hardened in Müller's Fluid and Stained with Hæmatoxylin. Bands of muscular fibres are seen cut in various directions. (×175.) (After W. T. Councilman.)

Gross Appearance.—Macroscopically the myoma resembles most the hard fibroma or one of the sarcomas. It is always sharply circumscribed, and generally surrounded by a firm capsule of connective tissue. On section of the tumor it can always be easily separated from the tissue surrounding it. The cut surface has a whitish or yellowish color and glistens. It is not homogeneous, but marked by fissures and lines which represent the spaces between the muscular bundles, and which often have a concentric or spiral direction. Whiter and darker patches are sometimes seen on the surface; these generally depend on degenerative processes in the tumor.

Origin.—The tumor always develops from non-striated muscular tissue. Unlike the rhabdomyoma, it never develops in any locality where this tissue is not found; it is never heterologous. Although its origin from smooth fibres has long been generally accepted, it is interesting to note that Kölliker and his followers believed its origin to be from the connective tissue. The exact histogenesis, however, is not always clear. Keifer (*La Presse médicale*, 1899, No. 10, p. 49) has demonstrated by injection methods small islands of non-vascular tissue in the uterus, which increase peripherally by the addition of smooth muscle fibres. In the centres of these masses was frequently seen an arrangement of cells suggesting obliterated vessels. From these masses about obliterated vascular trunks he believes myomata take their origin. Cohen (Virchow's *Archiv*, 1899, clviii., 524), in a study of the histogenesis of myomata of the uterus and stomach, concludes that in many cases it is impossible to determine the origin. He examined by serial section small tumors, and in many but not in all he found a central blood-vessel without an adventitia, whose muscular coat could not be differentiated from the newly formed muscular fibres.

In myomata of the skin the origin of the new growth is supposed to be the muscular coat of the blood-vessels and the erector muscles of the hair shaft (Jadassohn).

Nature.—The leiomyoma is a benign tumor, distinctly encapsulated and of slow growth. Although not in itself a dangerous tumor, it may, mechanically, cause serious complications; thus submucous myomata of the uterus may become eroded and be the source of a serious hemorrhage. Pedunculated tumors may be forced into the cervix uteri, causing a spurious labor; or if of large size they may perhaps produce prolapse of the uterus. Similar tumors beneath the peritoneum may exert pressure on the rectum or bladder, or by their weight bring about displacement of the uterus and other pelvic organs. They may form adhesions to other organs and thus induce strangulation; or they may themselves, if pedunculated, become strangulated and form free masses in the peritoneal cavity. Myomata of the digestive tract may cause occlusion or serious results may follow the traction superinduced by their mere weight.

Etiology.—Little is known in regard to the etiology of the myomata. In the uterus they are found most frequently after middle life and are much more frequent in blacks than in whites. On the other hand, the analogous tumor of the prostate in man is much more common in the white race than in the black. It cannot be shown that irritation exerts any influence. Some uterine tumors containing glandular acini suggest a congenital origin, the result of misplaced uterine fragments, thus supporting Cohnheim's theory.

Seats.—The more common situations are the uterus, gastro-intestinal tract, and prostate; the less common are the bladder, skin, nipple, and walls of blood-vessels.

Uterus.—The most frequent place of the formation of the tumor is the uterus. Every variety of the tumor is found, and it can be studied best here. The new growth may spring from any part of the uterine wall, but usually from the portion above the cervix; and it may vary in size from a microscopic nodule to a mass or masses weighing over a hundred pounds and entirely filling the abdominal cavity. The chief mass of these tumors is composed of muscle fibres, which are generally much larger than those of the normal uterus. The increase in size affects principally the width of the cell and the nucleus. Cells are often seen which are wider than the diameter of a red blood corpuscle. The muscle fibres are arranged in bundles, which are surrounded by wide capillary vessels. The walls of these vessels consist of a single layer of endothelial cells with large nuclei, supported by a thin layer of connective tissue. Both between the muscle bundles, and between these and the connective tissue of the vessels, are small spaces which contain white corpuscles and are surrounded by a fine tissue in which here and there nuclei are enclosed. In this way a cavernous structure is formed, which is not present in the normal uterus. Klebs supposed that these spaces represent lymphatic cavities, in which the whole tissue, muscular fibres, and blood-vessels are suspended by the small bands of connective tissue. Larger blood-vessels, with thick walls and a wide adventitia, are but seldom found, and then in the broad partitions between the larger bundles of muscular fibres.

The tumors may increase in size by the joining together of the neighboring growths, but this mode of increase is rare. Generally it appears that the same process of new formation, in consequence of which the smallest and most simple myoma was formed, repeats itself. Every single vessel, with the muscular and connective tissue belonging to it, proliferates again and forms a second generation of nodules, which are situated in the original tumor. These different centres of growth can, as a rule, be easily made out, and sometimes the arrangement is such that the tumor appears to be composed of triangular masses, the apices of which point to the centre and the base is along the periphery of the tumors. In other cases, the formation of secondary nodules takes place only in certain parts of the tumor, and in this way very irregular, uneven masses arise. This peculiar process of growth leads to the displacement of the tumor, which originally is enclosed in the walls of the uterus. If the growth takes place most rapidly in the part of the tumor nearest the mucous or the serous membrane, that part escapes from the muscular tissue and projects into the uterine cavity or on the surface of the organ, and finally the whole tumor becomes separated from the uterine walls. In this way the submucous and subserous varieties of the tumors arise, which are either connected with the uterus by a narrow pedicle or have a wider attachment. This attachment often contains dilated venous vessels in the loose connective tissue. The tumors which remain within the muscular coat are termed interstitial or intramural. When the connective tissue is much developed the tumor is denser and harder, and on section the lines and fissures are not so evident. The lymph spaces and blood-vessels become narrower and partly obliterated. The smooth muscular fibres remain preserved, but the single fibre cells can no longer be recognized, and in place of them small, long, rod-shaped nuclei are found embedded in a substance which appears more or less fibrillar (fibromyoma). The