Transmutation of the food products in the alimentary canal is usually excluded from the discussion of "metabolism," or what the Germans include under the word "*Stoffwechsel*," which, strictly speaking, means exchange of material; although, as Schäfer says in his admirable article on metabolism: "There is no special reason . . . why this should be the case, for the digestive changes in the food must, like all other chemical changes occurring within the body, influence the general conditions of the economy." It is just this fact, that they do directly influence the transmutations which technically are more directly within the body, which makes it so essential to give prominence to the changes in the foodstuffs in the intestinal tract in the discussion of disturbances in metabolism. This is especially true in reference to the putrefactive changes in the proteid constituents of the food resulting from abnormal fermentation of these substances in consequence of defective formation of the enzymes necessary for a perfectly normal transmutation.

While the number of abnormal by-products formed as the result of defective digestion is very large, the one which deserves especial attention in connection with disturbances in metabolism is that substance which has received the name "indican" or "indoxyl potassium sulphate." This substance, by virtue of its combination with the inorganic element potash, obeys the law common to almost all inorganic substances and is readily absorbed as such from the alimentary canal and is eliminated under its own form from the system through the renal glands with the urine. When this occurs its presence is easily detected in the urine.* This substance has been singled out from all the rest because it is easily demonstrated and is therefore of practical utility in determining the slightest deviations from the normal state of the digestive system. It also indicates a disturbance in general metabolism. Indoxyl potassium sulphate, or indican, in the urine denotes primarily putrefactive fermentation of the proteid substances in the alimentary canal. With this putrefactive fermentation, instead of normal peptone only being absorbed, as occurs in a perfect state of the physiological economy, there are other and toxic products formed in the alimentary canal and absorbed with the peptone, saccharine elements, and fats. These toxic substances after absorption are discharged as such into the blood stream. Within the system they act with varying degrees of toxicity and interfere to a greater or less extent with an otherwise perfectly normal isomeric transmutation or oxidation reduction of the proteid molecules. When this occurs, depending upon the kind and amount of toxic substance absorbed or produced within the animal economy in consequence of the presence of these toxic bodies circulating in the blood, there will be produced various retrograde changes in the metabolism of the various organs and tissues of the body. So long as the deviations in the exchange of material in the bioplasm do not give rise to profound changes or only to such as are chemical in nature and do not produce changes recognizable by careful microscopic examination, the process may be classed as a functional disorder, so called, or as simply a disturbance in metabolism. Beyond this point we enter the realm of organized disease. This primary imperfect exchange of chemical substances in the bioplasm, unrecognizable except through changes in the composition of the urine, is unquestionably the beginning of many, if not all, of the more profound disturbances which sooner or later give rise to absolute and easily recognized structural changes in the various tissues and organs of the body. Some of these are so decided as to be readily detected by the unaided eye, while many will require the microscope for their demonstration. These minor disturbances in metabolism lower the nutritive tone of the bioplasm and of the fluids of the body, thus decreasing the resistance of the system against toxic or germ invasion. In this manner a suitable soil is developed in which the various micro-organisms can grow and produce the diseases with which their presence within the animal organism is associated.

Thus it is found that faulty transmutation of the proteid constituents of the food in the alimentary canal is very largely responsible for the disturbances carried on more strictly within the system. Furthermore, the defective transmutation of the foodstuffs in the alimentary tract must be corrected before the disturbances in the metabolism in the inherent structures of the body can be overcome. From a practical therapeutic standpoint, therefore, a discussion of both the extrinsic and intrinsic modifications in the exchange of material is absolutely necessary if a clear understanding of disturbance in metabolism is to be acquired.

Looking into the system, it is necessary still further to consider the pancreas and the results of its defective secretion as an essential factor in the disturbance of metabolism. The experiments of von Mering and Minkowski* and others have conclusively shown that removal of the pancreas prevents a perfect exchange in the carbohydrates and proteids with the appearance of glucose in the urine. These results have been frequently confirmed. It has also been shown that the arrest in metabolism following this operation is entirely independent of any disturbance in the digestive function. Thus, it would appear that certain portions of the pancreatic gland, possibly the cells of the central acini or islands of Langerhans, instead of pouring their secretion into the ducts of the gland, discharge it through intercalary ducts into the blood-vessels or lymph channels from whence it enters the blood. In other words, certain cells of this gland take up from the blood proteid elements and isomerically or otherwise transform them for further use in effecting metabolism, in a manner somewhat similar to the formation of the enzymes that pass out through the main duct to reach the alimentary canal. In this instance, however, the secretion passes back into the system. That this internal secretion is essential for perfect metabolism appears to be conclusively established. Therefore, if the system is deprived of this particular isomeric form of proteid which has re-entered the blood, either by removal of the pancreas or by the introduction into the system of artificial chemical substances that destroy the special secretory power of the gland, the normal exchange in the food elements is interrupted and glucose appears in the urine. It is also possible that chemical substances are at times developed within the system that may arrest this particular function of the gland, thus causing the appearance of glucose in the urine. However it is brought about, the presence of glucose in the urine always indicates an abnormal exchange within the system. In this particular instance it is indicative of metabolic disturbance in the bioplasm in these special cells of the pancreas as well as of imperfect exchange in the carbohydrates and proteids. On the other hand, if it can be unquestionably established that such an internal secretion of the pancreas is always absolutely essential for perfect transmutation of the carbohydrates and proteids, and that only a suspension of or decrease in this special function causes arrest of exchange in the substances enumerated, then the etiology of diabetes will be greatly simplified, even though there are many diverse conditions that appear to give rise to the excretion of glucose in the urine. Thus far it has not been possible to arrest this form of metabolic disturbance by the administration of raw pancreas or by the use of extracts made from the gland, as can be done with some of the so-called internal glands—the thyroid, for example.

Owing to the great uncertainty in regard to the exact status of normal fat exchange, it is impossible to give any clear exposition of disturbances in its metabolism.

The secretions of the various so-called internal glands, for instance the thyroid, pituitary body, and suprarenals, must also be considered in the elucidation of disturbances of metabolism. It seems reasonably certain that

*See Jaffe's test, under *Urine*.

*Arch. f. exp. Path. u. Pharmakol., Bd. xxvi.; Minkowski, *ibid.*, Bd. xxxi., p. 85.

the bioplasm of the cells constituting these organs possesses the power of taking up from the circulation some of its proteid constituents. The proteid thus absorbed in passing through the cells of the various organs is isomerically or otherwise transformed and is then either discharged directly into the blood or it reaches this fluid by way of the lymphatic channels. On the other hand, the proteid taken up by the cells might be there changed by a process of oxidation reduction, thus causing the essential chemical element in the blood to establish perfect metabolism. It seems more probable, however, from the general absence of oxidation reduction products in the blood, that the change is one of isomeric transformation and of such a nature as to cause the proteid elements thus transformed to differ in their chemical activity, thus making them essential to the normal exchange constituting metabolism.

There are two theories advanced in explanation of the mode of action of these glands. One is that the newly formed substance is toxic in nature and gives rise to "autointoxication" of the system. The other theory is that the substance formed is not toxic, but is elaborated in a manner similar to that described in connection with the internal secretion of the pancreas; and, furthermore, that this newly formed substance is proteid in character but not necessarily a ferment, since it is concerned chiefly in metabolic exchange of proteids. This is shown by the fact that removal of the thyroid or its destruction by disease has a decided tendency to arrest the normal exchange between the blood plasma and the connective tissue, the disturbance being so great as to cause a peculiar hyperplasia of the connective tissue. The proteid molecules enter into the construction of the tissue and occupy, as it were, a larger volumetric space than normally is the case. This gives rise to a peculiar appearance of the tissue, so much so that the structures seem to be œdematous, but are not so in the strict sense in which that term is usually applied. Minor degrees of interruption in the secretion of the thyroid are unquestionably the cause of many of the lesser disturbances in metabolism in which the changes are not of sufficient magnitude to produce perceptible organic lesions accompanied by characteristic symptoms.

In like manner, the pituitary body produces a secretion which in a measure also seems essential for perfect metabolism, but in a way entirely different from what occurs when the thyroid secretion is interfered with. When the pituitary body is involved, the effect is noticed chiefly in connection with the bones of the extremities and face. In some cases there is also hypertrophy of the skin and mucous membranes, but without the gelatinoid consistency so characteristic of myxœdema. Minor changes of this character appearing before marked "acromegalia" occurs might be classed as disturbances in metabolism.

In a similar manner, the internal secretion of the suprarenal bodies is essential for perfect metabolism. Here the action seems to be more especially confined to exchanges taking place in the muscular tissue. This is noticeable particularly in the muscular tunics of the blood-vessels. Arrest or diminution in the secretion of the suprarenals will, therefore, cause imperfect exchange in the proteids passing from the blood plasma to the muscle structure, and vice versa. So long as the disturbance in the secretion of these bodies is moderate in character, only milder degrees of metabolic derangement result. On the other hand, if the secretion is more completely cut off, graver disturbances in the metabolism of the muscular tissue supervene. Under these circumstances there are developed great muscular weakness, pigmentary discoloration of the skin and mucous membranes, and organic changes such as are commonly found in the condition known as Addison's disease.

Primarily, disturbance in metabolism is the result of a more or less decided arrest of one or more of these various secretions, which are either extrinsic or intrinsic in nature, since they all appear to be essential for perfect exchange between the food and oxygen taken in and the excreta eliminated. These minor disturbances are the forerunners and causative factors in a very large measure of all the more pronounced organic changes. It is, therefore, often very difficult to draw a sharp line of demarcation between a simple disturbance in metabolism and a genuine pathological condition, especially as all lesions are the direct result of imperfect exchange between the food products and oxygen in the bioplasm of the organs and tissues of the body. The innumerable cases met with which present no well-defined symptoms upon which a positive diagnosis of a pathological state of the system can be based, yet in which a wide deviation from the normal standard exists, are good examples of simple disturbances in metabolism. Many of the vague and indefinite nervous conditions constitute another class illustrating disturbances in metabolism.

The chief evidences of disturbance in metabolism are found in the katabolic products excreted in the urine. First in importance among these katabolic bodies is indoxyl potassium sulphate, already referred to in connection with disturbances of digestion. This substance is easily detected in the urine, and indicates the normal or abnormal performance of the digestive transmutation of the proteids, the quantity determining in a general way the degree of digestive disturbance. A rise and fall in the amount of indican eliminated in the urine is evidence of increase or decrease of putrefactive fermentation of the proteids of the food in the intestine. Therefore careful daily estimation of the output of indican gives a comparatively exact idea of the state of the digestive system so far as the proteids are concerned. Its presence or absence is also, in a large measure, an index of the degree of intoxication of the system and of perfect and imperfect metabolism, because perfection in metabolism is chiefly dependent upon perfection of digestion.

Although uric acid is one of the normal constituents of the urine, its occurrence in excess of a certain amount is abnormal. When excreted in normal amount, it is combined chiefly with sodium or potassium as a urate. As a rule, uric acid is not found free in the urine. Imperfect metabolism and incomplete oxidation of the proteids give rise to free uric acid in the urine, and often in great quantities. This always indicates imperfect oxidation of the proteid constituents. Under these circumstances, estimation of the excess of uric acid and determination of the amount produced daily render it possible to detect the slightest imperfection of oxidation.

With more profound disturbances in the transmutation and oxidation reduction of the proteid elements, oxalic and lactic acids, glucose, and albumin appear in the urine. Excretion of oxalic acid with an excess of the phosphates usually indicates metabolic disturbances largely confined to the nervous tissue. Lactic acid is generally associated with those conditions commonly classed as rheumatic. Glucose is usually found in connection with diabetes. As rheumatism and diabetes belong in the domain of well-defined pathological conditions, they are beyond the limits of simple disturbances in metabolism. The same is, in a measure, true of albuminuria. The intermittent and transitory appearance of traces of albumin in the urine (cyclic albuminuria) may be regarded as evidence of simple disturbance in the exchange of the proteid materials. On the other hand, if albumin is persistent and present in considerable quantity, it must then be considered as indicative of a profound and often serious disturbance in metabolism.

As the starches, sugars, and fats are, in all probability, rapidly converted and oxidized directly into carbon dioxide and water, it is very difficult to trace their perfect or imperfect exchange and oxidation. The same is, in large measure, true in regard to their transit through the alimentary canal. If we accept the theory of glycogen formation from saccharine compounds, and that the glucose in the urine is the result of imperfect transformation of glycogen, then the presence of glucose in the urine indicates imperfect transformation of the starches and sugars. On the other hand, if we accept the more probable theory and one which is more in harmony with well-

known chemical laws—namely, that the glucose in the urine is the result of imperfect transmutation and oxidation reduction of proteid elements—there are no definite methods for practically determining from the composition of the urine whether the saccharine elements are perfectly or imperfectly exchanged. In a general way, if nutrition is well sustained and the urine practically normal, it is reasonable to suppose that all the ingredients of the food are perfectly transformed and that metabolism is normal. On the other hand, if the urine contains abnormal nitrogenous katabolic bodies and there is positive loss of flesh, this is conclusive evidence that the sugars and fats are imperfectly exchanged. Under similar circumstances, if there is rapid production of adipose tissue, it is reasonable to suppose that the sugars and fats are concerned in this disturbance in metabolism.

With this understanding of the conditions deserving of classification as simple disturbances in metabolism, they must be regarded as largely responsible for most of the graver states of the system, which must be combated as definite diseased conditions. These minor disturbances in metabolism must be recognized and corrected early in their development in order to prevent more serious disturbances. If recognized in their incipiency these trivial disturbances in metabolism can, in many instances, be arrested in their progress by close attention to the diet, to digestion, and to hygienic surroundings. Diet and digestion, however, are the chief elements to be considered if even the milder forms of disturbance in metabolism are to be successfully dealt with.

William Henry Porter.

REFERENCES.

[1] König: Chemie d. menschl. Nahrungs- u. Genussmittel, Berlin, 1882, 2te Auf.
[2] Rubner: Zeitsch. f. Biol., xv., S. 115; xvi., S. 119; xix., S. 45; xxx., S. 73.
[3] Atwater: U. S. Department Agriculture Bulletin, No. 109, Washington, 1892.

METACHLORAL.—This body is polymeric with chloral (not chloral hydrate), having the formula $C_6H_3Cl_9O_3$. It is formed from chloral by the action of concentrated sulphuric acid, and is a solid body distinguishable from chloral hydrate by being insoluble in water. It appears to have an influence over animal physiology akin to that of chloral hydrate, but it is not an official medicine.

Edward Curtis.

METACRESOL-ANYTOL (see *Anytin*) is a forty-per-cent. solution of metacresol in anytin. Löffler called attention to its powerful bactericidal qualities, and Schwab showed that a two-per-cent. solution (metasol) is indifferent to instruments and does not lose its antiseptic power in the presence of albuminoids. Seybolds noted no ill effect on animals from eight minims per kilogram of body weight. Koelzer painted erysipelatous areas and the neighboring healthy skin with a 7.5-per-cent. aqueous solution with excellent results. Used in full strength the preparation is capable of setting up dermatitis.

Metasol is a trade name for one- and two-per-cent. solutions of metacresol anytol. *W. A. Bastedo.*

METACRESOL CINNAMIC ESTER is a mixture of metacresol and cinnamic acid heated and acted upon by phosphorus oxychloride. It is insoluble in water, but soluble in alcohol, ether, and chloroform. It has been proposed as a local application in laryngeal tuberculosis, and as an inhalant for both laryngeal and pulmonary tuberculosis. *W. A. Bastedo.*

METAPLASIA.—The direct transformation of one tissue into another without the formation of an intermediate embryonal tissue is known as metaplasia. Such a change can occur only in tissues closely related to one another genetically, as are the different forms of connective tissue. Under certain conditions any one of these may become changed into another; thus, fibrous connective tissue may become adipose or myxomatous tissue, cartilage may be changed into bone, lymphadenoid tissue into fat tissue, etc. In the majority of these changes the intercellular basement substance is chiefly affected; thus, in the transformation of connective tissue into cartilage, the basement substance loses its fibrillæ and becomes homogeneous; by a further change into a denser hyaline substance it may assume an osteoid character, and this through the deposit of lime salts may become bone-like. Likewise, in the change of fibrous tissue into myxomatous tissue the basement substance undergoes a mucoid change. On the other hand, in the transformation into fat tissue the change is brought about by the connective-tissue cells themselves taking up the fat; so also in the change into myxomatous tissue the cells become stellate; in the case of cartilaginous or bony metaplasia they assume the characteristic appearance of either cartilage or bone cells.

That epithelial metaplasia occurs is still a matter of some doubt; the change of tall columnar cells into squamous cells, which apparently takes place under certain pathological conditions, while theoretically explainable as a true metaplasia, is probably in the majority of cases brought about through the agency of intermediate stages of cell forms which are essentially embryonal cells. In the upper respiratory tract such changes may take their origin from the small islands of squamous cells found there normally, these increasing in size under certain pathological conditions. In other cases the apparent epithelial metaplasia may be explained by the presence of fœtal inclusions of undifferentiated tissue or by a transplantation of neighboring squamous epithelium.

Metaplasia of connective tissue into epithelium or of epithelium into connective tissue can never occur—a change of type is not possible: *omnis cellula e cellula ejusdem generis.* The older conception of metaplasia, now and then revived, that epithelium may arise from connective tissue, lymphocytes from connective-tissue cells, tissue cells of every kind from leucocytes, etc., receives scanty support at the present day. The accepted idea of metaplasia is that of a variation in cell forms due to changed conditions,—not a change of type. The cell types of the body may be regarded as being of as fixed a nature as the species of the animal and vegetable worlds; variation occurs to a slight extent and only between closely related forms.

As examples of physiological metaplasia may be mentioned the formation of adipose and myxomatous tissues from fibrous tissue, the development of fatty marrow from lymphoid, or in old age the change of the former into a gelatinous or mucoid marrow, the old-age atrophy of lymphadenoid structures into fat and connective tissue, etc.

Pathological metaplasia is for the greater part of a retrogressive nature, as in the transformation of fibrous tissue, bone, and cartilage into myxomatous tissue. The process is also closely associated with progressive changes, inasmuch as it is a constant occurrence in certain forms of tumors. It is very difficult to draw a definite line of separation between the degenerative and the progressive features of the process; in many cases metaplasia may be regarded as standing between degeneration and growth. In so far as the metaplasia itself is concerned there is no new formation of cells, only a change of those already formed. In quickly growing tumors, however, metaplasia may occur so rapidly as to assume the character of a direct new formation. Moreover, developmental changes often follow as well as precede the metaplasia. On the other hand, the tissue resulting from the metaplasia is practically always of a lower type and not infrequently of a perishable nature as shown by its tendency to necrosis. The degree and rapidity of both progressive and degenerative processes depends largely upon the vascular supply; an abundant supply of blood favoring the former, a poor one the latter process.

The occurrence of pathological metaplasias may be explained by the assumption that the cells of closely related tissues possess common potentialities which, under normal conditions of growth, are latent or subordinated to their specific qualities. Under such pathological conditions as

inflammation, disturbance of function, changed nutrition, etc., these latent qualities assert themselves even to such an extent as to result in the changing of the character of the tissue. The potentialities of the germ layers are distributed during the development of the body in an unequal degree among the cells arising from these layers, so that, with the exception of cells genetically widely separated, not only special but also like potentialities are represented in these cells in varying degree. The more closely related are the cells genetically, the greater the degree of common potentialities. Metaplasia in fœtal tissues should therefore be much more possible than in later life, since in the former the individual cell forms are less differentiated and possess more qualities in common. This point is of great importance with reference to the origin of tumors. From indifferent cell material in the form of fœtal "inclusions," "rests," etc., a great variety of tissues might arise in later life. The mixed sarcomas of the kidney, some of the teratoid growths, the formation of cartilage and bone in connective tissues, etc., may be explained in this way.

The most common form of metaplasia is the transformation of fibrous connective tissue into adipose tissue. This is brought about by the taking-up of large amounts of fat into the connective-tissue cells, the latter becoming changed into the large round cells characteristic of adipose tissue. Fatty metaplasia is one of the most common physiological processes; it occurs pathologically in connective tissues which ordinarily do not contain fat, in cases of fatty infiltration. As a result of atrophy or of changed conditions of nutrition the fat tissue may be changed back into fibrous tissue. Not infrequently after disappearance of the fat there is a formation of myxomatous tissue, a mucoid substance being formed in the intercellular substance. On the other hand, mucous tissue may become changed to fatty, the stellate cells taking up fat and becoming changed into round fat cells. Lymphadenoid tissue is also closely related to fatty, and there are evidences of frequent physiological variation between these two forms of tissue. In atrophic lymph glands and in the change of lymphoid to fatty marrow there is first a removal of the lymphoid cells and a change of the reticular cells to fat cells. In the development of lymphadenoid tissue from connective and adipose tissues the fat is removed from the cells in the case of the latter, the connective-tissue fibrillæ become loosely arranged, a portion of the cells becoming changed into reticular cells, while at the same time there is an infiltration of round cells in the reticular meshes.

Myxomatous metaplasia occurs physiologically in the adult body in the bursæ, synovial membranes, and tendon sheaths; pathologically in inflammatory conditions of these structures, and particularly in the connective tissue of certain neoplasms. Fibrous and adipose tissues, bone, and cartilage may become changed into myxomatous tissue; in the case of fibrous tissue the fibrillæ disappear, the basement substance undergoes a partial liquefaction with the formation of mucin, while the spindle cells become changed into stellate or irregularly branched cells.

In the case of bone or cartilage there is a liquefaction of the basement substance with mucin formation, the bone or cartilage cells becoming changed to stellate or anastomosing branched forms.

Cartilaginous and osseous metaplasias occur in the connective tissue of the large arteries and of the cardiac valves, in the subcutaneous and intermuscular connective tissue, also in newly formed connective tissue in the eyeball, and in the stroma of both the mature connective-tissue tumors and sarcoma, more rarely in that of carcinoma. The basement substance loses its fibrillar character and becomes homogeneous in the change into hyaline cartilage, the connective-tissue cells assuming the appearance of cartilage cells. Fibrous cartilage may be formed by the development of fibrillæ of collagenous material in the hyaline matrix. With the deposit of lime salts in the hyaline intercellular substance and the change of the cartilage cells into bone cells, bone may be formed directly from the cartilage. Bone may also be formed directly from fibrous tissue by the change of the fibrillar intercellular substance into an osteoid substance which later becomes calcified; the connective-tissue cells lying in the spaces appear as bone cells. Cartilage may become changed into fibrous tissue, but there is no evidence that fully formed bone undergoes such a metaplasia.

A metaplasia of unstriped muscle into striped as well as the reverse process has been claimed by many observers to occur under various pathological conditions, particularly in the case of the mixed sarcomas of the kidney. It is very probable, however, that these neoplasms are due to congenital inclusions of the myotome, and are not to be regarded as examples of true metaplasia of adult tissues.

Except in the case of tumors, myxomatous, cartilaginous, and osseous metaplasias must be regarded as of fairly rare occurrence. They are found very often in the mixed connective-tissue tumors and in certain forms of sarcoma, particularly those arising from periosteal or intermuscular connective tissue. Both myxomatous and cartilaginous metaplasias are very common in the mixed endothelial tumors arising from the salivary and lachrymal glands, less common in those of the mammary gland and testicle. It should be remembered, however, that the presence of bone and cartilage in these growths may be explained also on the ground of inclusions of fœtal tissue. The ossification of the costal, tracheal, and laryngeal cartilages is of such frequent occurrence as to fall within normal limits and is hardly to be regarded as a pathological metaplasia except under extraordinary conditions. The change occurs more rarely in the bronchial cartilages.

The metaplasia of lymphoid out of fatty marrow occurs in leukæmia and the various forms of anæmia. Very rarely marrow-like tissue is found in the spleen and lymph glands. Whether this is to be regarded as metaplasia or as metastasis is not settled. Metaplasia of adipose tissue into lymphoid occurs also after removal of regional lymph glands, splenectomy, etc. Such metaplasia is to be regarded as regenerative or compensatory in nature.

The so-called metaplasia of epithelium is limited to the transformation of columnar into squamous epithelium or the reverse process. In inflammatory processes of the upper respiratory tract (ulceration, ozæna, etc.), in the urethra following chronic gonorrhœa, in the endometrium (chronic endometritis, inversion, ichthyosis uteri, uterine polypi projecting into the vagina or beyond the vulva, etc.), in chronic inflammations of urinary and gall-bladders, kidney pelvis and oviduct, and in chronic inflammation of ear polypi arising in the middle ear and perforating the tympanum, transitional or columnar epithelium may be replaced by squamous. In all these cases the chronic inflammatory process leads to frequent desquamation or necrosis of the epithelium, this being followed by regeneration, the newly formed epithelium being of the squamous type. On the other hand, the transitional epithelium of the bladder may be changed to columnar in the case of bladder papillomata.

As a result of such epithelial metaplasia new growths of the nature of epidermal or squamous-celled carcinoma (cancroid) may arise in regions normally covered by transitional, columnar, or ciliated epithelium. The cases reported of cancroid of bladder, kidney pelvis, endometrium, and gall-bladder have been explained in this way, but the possibility must also be considered that these arise from congenital misplacement of squamous cells or from ingrowths or transplantations from neighboring squamous epithelium (in the case of the endometrium, from the epithelium of the cervix). Columnar-celled or adeno-carcinoma may arise from the columnar cells of bladder papillomata. *Aldred Scott Warthin.*

METASTASIS.—The transportation of substances from one part of the body to another, the transportation of disease-producing agents, the production in one part of the body of a local disease from a primary focus of similar disease in some other part not immediately adjacent,