

precipitate is thrown down by the citric acid, which is employed as a first step in the application of the test, and then a further precipitate falls on the addition of the ferrocyanide. Besides the other advantages which the ferrocyanic test possesses—these advantages being (1) that it will bear comparison with any other test for delicacy, (2) that it is not open to any fallacy, and therefore does not require a second test to be employed to check or corroborate it, (3) that it does not call for the use of a spirit lamp, and (4) that the agents are of a perfectly innocent nature in every way, and may be kept for use either in solution or in the form of pellet, which may be packed into a test-tube arrangement of about the size of a pencil case for carrying in the pocket,—besides these advantages, which are such that no other test can lay claim to, the ferrocyanic test affords suggestive information bearing upon the recognition of cyclic albuminuria.

## THE CLASSIFICATION OF NEOPLASMS.

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At a time like the present, when so many earnest seekers after truth are striving for better knowledge and understanding as to the nature of cancer and tumour formation, I propose to publish a short account of the results of my own labours in this direction.

In the course of organic evolution all parts are not equally developed, for while some are reduced and disappear others arise and become highly developed. In the majority of animals the most important morphological changes occur during embryonic life, as is the case with man, mammals, birds, and fishes. But in many amphibians, insects, &c., very remarkable changes of form occur long after completion of the foetal development. Of this the metamorphosis of the herbivorous tadpole into the carnivorous frog is one of the most striking examples. In man and mammals such changes are more restricted, but instances occur in the development of the teeth, thymus, breast, uterus, skeleton, and the changes at puberty. In short, many facts, both in normal and morbid development, indicate the possibility of tissues remaining unchanged for long periods, and then taking on new phases of growth and development by a kind of revival of the embryonic activity. With such changes the various pathological new formations must be associated. In the ordinary course of events, the proliferation and development of the cells of the unfolding organism proceeds in a regular and orderly manner, in accordance with the specific hereditary tendency of the whole. But the process, once started, does not cease on account of irregularity, or because it is taking a wrong direction. Hence, cells may arise at a place where they have no business, or at a time when they ought not to be produced, or to an extent that is at variance with the normal formation of the body. In the embryo, monstrosities and malformations are thus produced, and at a later period of development the various pathological new formations. These extremes graduate so insensibly into one another that it is impossible to separate them by any natural line of demarcation. Ever since the establishment of the cell theory, it has been recognised that the one common process underlying the evolution of all organic structures is development from cells. We are indebted to the sagacious Johannes Müller for insisting on the correspondence between the development from the embryo and the pathological neoplastic process. Virchow has pointed out that the structural elements of all neoplasms are derived by proliferation from pre-existing cells of the part whence they originate; and he has further shown that these pathological processes have their physiological prototypes. But hitherto no one has clearly indicated the physiological prototypes of cancer and tumour formation. This is the task to which I now propose to address myself.

In investigating the local changes in neoplasms, it is impossible not to be struck by the fact that at every turn the phenomena met with have their counterparts in the normal evolution. This is especially true of the elementary histological processes. Pathological and physiological cells

are alike in their morphological and vital properties. Cell and nuclear division conform entirely to the physiological type, even as to the details of karyokinesis. In both cases the tendency of the newly formed cells to revert to the parental type is perfectly obvious, and it is especially so when the cells become developed into tissues, whether normal or pathological. Hence it happens that throughout the whole range of pathological neoplasms no structures of new and specific type are to be found; but we meet everywhere with structures which resemble the physiological tissues, both genetically and histologically. In the ordinary course of development the process of cell multiplication goes on until the proper amount of structure for the needs of the organism has been produced; then it ceases within certain limits. During this process most of the original undifferentiated protoplasmic cells are metamorphosed into special structures, only a few remaining lowly organised and capable of further growth and development. In the healthy organism these cells subsequently concern themselves only in the maintenance and repair of the established structures. In this quiescent state they continue throughout the whole life of the individual, unless aroused by abnormal conditions. In all this there is evidence of definite law regulating the development of the tissues and organs in relation to each other and to the organism as a whole.

Though each of the constituent cells of the higher organisms is to a large extent dependent upon others, yet at the same time each manifests a certain independence or autonomy. If we wish to grasp the significance of the special changes underlying pathological new formations, we must never lose sight of this important factor—the *autonomy of the cells*. There are good reasons for believing that every component cell of the multicellular aggregates has the inherent power, under favourable conditions, of developing itself into the form of the parental organism; we may say, then, that each cell is potentially the whole organism. That the degree of development actually attained by each cell usually falls far short of this is due to the restraining and modifying influence exerted by the whole organism upon its protoplasm, which is thus compelled to perform comparatively subordinate modified functions. In proportion as the cells become thus specialised, they suffer more or less complete loss of their primitive reproductive power. But certain cells never attain a high degree of development; they remain in a lowly organised condition. As long as such cells are subject to the normal restraining influence of the organism, they develop in accordance with the specific hereditary tendency of the whole. But when this influence is weakened or withdrawn their potential reproductive powers may become actual. In the ordinary course of the life of the higher organisms the only cells thus set free are the reproductive cells. But *any* cells abnormally emancipated may then grow and multiply more or less independently, regardless of the requirements of the adjoining tissues, and of the organism as a whole. Collections of lowly organised cells thus arise, which, not being required for the building up of the parental structure, become superfluous, and are no longer retained directly under its controlling influence. In their development such cells soon assume an *individuality* of their own; there is manifest tendency to the formation of a new aggregate rather than to enlargement of the old one. This is the essential idea of a neoplasm, which in *ultimate analysis* may be regarded as the product of an abortive attempt of certain cells to reproduce a new individual by agamogenesis. There is, then, a certain amount of truth in the remarkable saying of Paracelsus, that “in such a disease a man is himself and another; he has two bodies at one time, enclosed the one in the other, and yet he is one man.” In this way, then, the various pathological new formations originate by reversion of cells, which are usually engaged in maintaining the normal structure of the body, to an embryonic state of activity. The morbid products, though themselves redundant, generally represent a reduction or *minus* of the corresponding healthy structures whence they originate, differing from them only in degree. In all of these cases, as in the new formations of embryonic life, the subordination of the local processes to the specific hereditary tendency of the whole appears to be lost or diminished, so that unspecialised cells then manifest their potential reproductive qualities by taking on semi-independent growth and development. In short, there is departure from the definite order, limitations, regular stages, and fixed periods of the normal evolution.

Since the structures composing morbid growths form by a process analogous to that by which the normal tissues and organs evolve, the next step in our investigation must be to work out their evolution in association with that of the corresponding tissues and organs.

Every higher animal originates from a single cell—the cytula or fertilised germ—by continually repeated cell-multiplication. A solid spheroid of similar protoplasmic cells—the morula—is at first produced. Within the morula fluid collects, and the cells become spread out upon its surface in the form of a single limiting layer—the *blastoderm*. The cells of the blastoderm differentiate into two layers, one of which becomes more or less completely enclosed within the other. The outer layer is the *epiblast*, the primitive integument; the inner layer is the *hypoblast*, which forms the primitive digestive organ. Between these two layers a third, the *mesoblast*, usually appears. It probably originates from the primary layers by differentiation. All embryologists are now agreed that each blastodermic layer originates only a certain series of tissues. For the present purpose it will suffice to state that the *epiblast* gives rise to the epidermis and its derivatives—nails, hairs, and the various integumentary glands, including the mammary glands. The lining membranes of the mouth (stomodæum) and anus (proctodæum), with their glandular derivatives, are also of epiblastic origin. The dermis, however, is derived from the mesoblast. The line of junction between epiblast and mesoblast corresponds therefore, in the adult, with that between dermis and epidermis. The *hypoblast* is the source of the whole epithelial lining of the digestive canal with its derivatives, including that of the air-passages, lungs, bladder, liver, pancreas, and the glands of the alimentary tract. The primitive origin of the pleuro-peritoneal epithelium and of the genital cells is probably hypoblastic. The *mesoblast* gives origin to the connective tissue series of all parts of the body, including cartilage, bone, and bloodvessels. It distinguishes only two germinal layers—the *archiblast* and the *parablast*. The former he regards as originating from the cells of the ovum, the latter from the white yolk. As to the correctness of this theory I must leave embryologists to determine. However, I shall not hesitate on this account to avail myself of the classification of His, because, independently of theory, it is perfectly natural and very convenient. The *archiblast* originates all the products usually ascribed to the epiblast and hypoblast: in short, all the structures of the body, except the connective tissue series and the bloodvessels, which develop from the *parablast*.

In the whole course of its subsequent development a derivative of one germ layer never develops a structure originally derived from another. Hence after the differentiation of the blastodermic layers, no wholly embryonic cells are ever formed—that is to say, no cells are formed, like those of the morula, from which any structure might finally develop. Cells subsequently arising can only develop certain tissues—viz., those that are normally derived from the layer whence they originate. Hence derivatives of the archiblast always remain within this type, and never originate parablastic structures. In the development of pathological new formations the same law is observed. There are among neoplasms no transitions from one type of tissue to another. The law of the specific nature of the tissues is everywhere obeyed.

Since the origin and development of pathological new formations follows a course homologous to that of the tissues in which they originate, we may classify these growths, like the normal tissues in association with which they develop, according as they originate from cell derivatives of the one or the other of the germinal layers; that is to say, they are either of *archiblastic* or *parablastic* origin. Further, since all organic structures are primarily derived from cells by a process of differentiation, it follows that a really scientific classification should be founded on the *degree of development* attained by the cells in their upward progress to form tissues and organs. In accordance with this I divide each of the foregoing classes of neoplasms into two sub-classes, the *lowly* and the *highly organised*. This classification has the great advantage of indicating clearly the *genetic relationship* between the normal and the pathological processes.

All *archiblastic* neoplasms are built up after the type of epithelial tissue. They consist of newly formed epithelial cells of epiblastic or hypoblastic origin; and this is their essential characteristic. These cells are derived by excessive proliferation from the normal cells of the part whence they

originate, and the tendency to reproduce the parental type is always manifest. Hyperplasia, and not inflammation, is the starting point of every pathological neoplasm. Inasmuch as many archiblastic neoplasms in the course of their development mimic glands of the body, they have been called organoid. Some parablastic elements are usually associated with archiblastic neoplasms, but these elements never form the essential part of the tumour. Most archiblastic neoplasms never attain a high degree of development; they exhibit, as it were, only the initial stage of the evolutionary process which they mimic. The result is a confused and indefinite mass of structure, consisting of proliferous epithelial cells in-growing into the adjacent tissues. Such are the *epitheliomata*, which is the term I use for all malignant epithelial neoplasms. As there are several varieties of normal epithelial tissue, so there are several corresponding varieties of epitheliomata, the differences depending upon the nature of the constituent cells, which may be either squamous, cylindrical, or glandular. What I call glandular epitheliomata are usually named carcinomata. In other instances the newly formed cells undergo well-marked developmental changes, the result being new formations *closely resembling* the homologous parental structures. Such are the *adenomata*, the neoplastic cysts, and the *papillomata*, which are all of them non-malignant.

The *parablastic* neoplasms may be treated in a similar way. All the members of this class are of mesoblastic origin, and they are modelled after the type of the embryonic or adult connective tissues, in association with which they originate. In many cases only a low grade of organisation is attained; the new formations consist of structures homologous with corresponding embryonic stages of development, or but little removed from them. Such are the *sarcomata* and *myxomata*, which resemble immature connective tissue and are more or less malignant. In other instances the evolution of the morbid structure is much more complete; then we get fibromata, lipomata, chondromata, osteomata, &c., which differ but little from the normal parental fibrous, fatty, cartilaginous, and osseous tumours, and are non-malignant. My classification, then, may be briefly stated as follows:—

I. Archiblastic neoplasms.	1. Lowly organised—	{ Squamous. Cylindrical. Glandular.
	Epithelioma.	
II. Parablastic neoplasms.	2. Highly organised—	{ Round-celled. Spindle-celled. Myeloid.
	Papilloma.	
	Adenoma.	
	Cystoma (neoplastic).	
	1. Lowly organised—	
	Sarcoma.	
	Myxoma.	
	2. Highly organised—	
	Fibroma.	
	Lipoma.	
	Chondroma.	
	Osteoma.	

Just as there are intermediate gradations between the various orders, genera, species, &c., into which naturalists have arranged the animal world at large, so between the classes, sub-classes, &c., of pathological neoplasms, transitional forms exist. All such arrangements are, in fact, merely subjective conceptions, chiefly of use as indicating, amidst many varying degrees of modification, the common bond underlying them all—propinquity of descent.

As I have previously indicated, many neoplasms are malignant—that is to say, they have the power of reproducing themselves, either locally after removal, or in distant parts; while others have no such infective properties. Need we assume any specific difference between the two kinds of neoplasms to account for this? Certainly not. Between the malignant and the non-malignant growths so many transitional forms exist that it is impossible to sever the chain otherwise than by arbitrary methods, contrary to the nature of things. Upon what, then, does this difference depend? It must be borne in mind that before any neoplastic action can arise in a part, the normal restraining influence exerted by the whole organism upon its cells, in accordance with the specific hereditary tendency of the whole, must be weakened, modified, or withdrawn. Moreover, it has been found that the product of the evolution of cells thus abnormally emancipated varies according as the emancipation is complete or more or less incomplete. As I have previously mentioned, the natural tendency of cells thus completely

emancipated is to form new individuals by agamogenesis. But in the higher animals this never happens, because the emancipation is always more or less incomplete; hence in them only new parts, new tissues, and neoplasms are formed. Here the nature of the product seems to depend upon the grade of organisation attained by the neoplastic cells. It is well known that in the formation of highly organised structures the cells of the part suffer loss or impairment of their proliferous (reproductive) power, owing to their protoplasm being used up and converted into special tissues. Most non-malignant neoplasms are of this nature; their histological character closely resembles that of the corresponding normal tissue, whence they originate. Such neoplasms lack infective properties because they are highly organised. On the other hand, all lowly organised neoplasms are more or less malignant, and the most malignant are the most lowly organised. Hence it may be concluded that the degree of malignancy of a given neoplasm is chiefly dependent upon its grade of organisation. To this cause, and not to any essential difference in nature of the morbid process, I attribute the different behaviour of these two kinds of neoplasms.

Viewing the matter in this light, I can see no probability of there being any truth in the theory that neoplasms are the outcome of general blood disease, dependent upon the presence of micro-organisms like tubercle and syphilis. I think De Morgan came nearer the truth than anyone else when, in the memorable debate on cancer at the Pathological Society in 1874, he said, "I can see no analogy between new growth, whether as innocent as lipoma or as malignant as cancer, and the products of true general or blood disease in respect to their genesis and destination. From the first a tumour is a living, self-dependent formation, capable of continual growth by virtue of its own power of using the nutritive materials supplied to it. Nothing like this is seen in any of the blood diseases."

## THE TREATMENT OF ACUTE RHEUMATISM, WITH SPECIAL REFERENCE TO THE USE OF THE SALICYLATES,<sup>1</sup>

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THIS paper is based upon 2200 cases of acute sthenic rheumatism occurring in both sexes under thirty-six years of age. Of these cases, 850 were taken from the clinical records of Guy's Hospital before the introduction of salicylates; the remaining cases were all treated with salicylates, the remedy being in almost every instance salicylate of soda; the dose uniform—twenty grains, every one, two, or more hours. Through the great courtesy of the staff of St. Bartholomew's Hospital, 515 of these cases have been drawn from the clinical reports of that hospital; the remaining cases, without exception, are from Guy's.

The introduction of the salicylates has completely revolutionised the treatment of acute rheumatism, and the time appears now ripe to inquire into the advantages of this specific treatment, and it appears right to ask if with these advantages there may not, at least in some cases, be corresponding disadvantages which a more complete and exact knowledge of the action of the drug may prevent or mitigate. An analysis of this large number of cases was conducted principally for the purpose of estimating the comparative results in the case of patients treated specifically, and on general principles, (1) with regard to the suffering due to the joint effusion, (2) the length of illness, (3) the percentage of cases affected with cardiac complications, (4) the mortality, and (5) the dangerous symptoms which many observers state follow the use of salicylates.

With regard to the pain due to joint effusion, there cannot be any doubt that patients treated with salicylates in many cases experience a marked and rapid diminution or total cessation of pain, and parallel with this loss of pain there is frequently an equally rapid fall of temperature. Tables were prepared showing that in the case of 728 patients treated with salicylates, 582 lost their pains within seven days.

Making full allowance for the heavy list of relapses—namely, 137,—these figures dwarf those derived from patients treated on general principles, for here we find that, among 612, 140 only lost their pain in a similar period of time. Complete relief from pain within three days was noted in 300 patients treated at St. Bartholomew's out of a total of 515. Forty per cent. of these relapsed, the word "relapse" not being made use of unless there had been decided return of joint pain accompanied by a temperature above 100°, the condition lasting longer than twenty-four hours. In many cases it was noted that the illness following on a relapse was of more intense character, being marked with higher temperature than noted at the initial seizure, and, again, in most cases was complicated with cardiac mischief. Pain and stiffness of joints appeared more general after the fever had subsided, among patients treated specifically, than among those treated on general principles.

Although all observers do not exactly agree as to the relative frequency with which acute rheumatism is complicated with cardiac lesions, the various estimates closely coincide, and may be said to indicate from 50 to 60 per cent. of patients as likely to have cardiac complications. With this estimate the figures quoted will be found to agree. It has been impossible to differentiate between different forms of cardiac disease. Among 850 patients treated on general principles, 500 were noted as having cardiac mischief. Examining the salicylate cases in series as they were collected, of 328 cases from Guy's 190 were affected. In a second series from Guy's, of 360 cases 241 had cardiac complication; and, again, in 515 cases from St. Bartholomew's 316 were affected. A study of these figures purposely reported in series shows how extremely difficult it is to form an exact numerical estimate of the comparative frequency with which the heart is affected in acute rheumatism. Taking any one of these series by itself, a different conclusion would be arrived at from that obtained by considering the cases in aggregate. If the total number of cases be taken, we find that among the salicylate series slightly over 60 per cent. were affected, whereas in the case of patients treated without salicylate slightly under 60 per cent. were affected. Practically these percentages agree, and enforce the impression gained from studying a large number of cases that the salicylates have no effect whatever in either reducing, preventing, or limiting the intensity of cardiac inflammation occurring during the course of acute rheumatism.

From the records of St. Bartholomew's ninety-five cases were taken, showing the commencement of cardiac disease after the patient was admitted into hospital, where, on admission, the heart having been carefully examined, no trace of disease had been found, and where the patient at the time of the inflammatory attack was thoroughly under the influence of salicylates. Estimating the value of the specific remedy in cases of primary rheumatism, it was found that of 516 patients treated without salicylates 290 were affected with cardiac complication; of 736 cases of primary rheumatism treated with salicylates 402 had cardiac complication; the proportion between the two groups being almost identical.

Tables were constructed to show the effect of treatment as influenced by the length of illness before admission; i.e., before the patient was placed under treatment, specific or otherwise, 1089 cases were so tabulated, 507 being treated without salicylates and 582 with that drug. The study of these cases showed little or no difference between the two groups.

Attention was drawn to the dangerous symptoms observed following the use of the drug, and Dr. Broadbent's remarks, when president of the Clinical Society, were quoted, showing the necessity of making some such inquiry. The author stated, from his own study of the matter, dangerous symptoms occurred in many cases where the temperature had fallen to normal, and the pains had completely subsided. In these cases furious delirium ushered in hyperpyrexia, with fatal results. In order to make the inquiry more complete, advantage had been taken of all published cases in THE LANCET since the year 1864. In twelve years, 1864-75 there are 19 fatal cases mentioned; in 16 of these death was attributed to hyperpyrexia. These cases all occurred prior to the introduction of salicylates. In ten years and six months—1876 to June, 1886—24 fatal cases are reported as occurring among patients treated by salicylates; in 20 of these cases the fatal result was attributed to hyperpyrexia. These published cases were not referred to for the purpose of estimating the comparative mortality, but rather with the view of drawing attention to the fact—which has been

<sup>1</sup> Abstract of paper read before the Medical Society of London, Feb. 13th, 1888.