if we count roughly, from fifteen to twenty-five years of age, occupies ten years, and the more gradual rise, from twenty-five to forty-five, occupies twenty years. In the hen, the rise is from 15 to 135, and the decline from 135 to 1. In woman, the decline is from about 1.02 to 1, and the rise again to about 1.02. There can be little doubt that a similar rise and fall, or fall and rise, are to be found in the history of the fertility of other living things. The curve of this climax and anti-climax is not a part of a circle. Dr. Routh, in a valuable paper on "Procreative Power," published in the *London Journal of Medicine* for 1850, describes this curve, representing what he calls the inclination of procreative power, and thinks the circle is perhaps the nearest that could be selected; but the circle cannot be made to represent the figures on which he relies. He makes the age of greatest fecundity in woman twenty-six, and the climax and anti-climax may be partially indicated by the following figures, which he gives: At fifteen years of age, the figure is 22; at twenty, it is 32; at twenty-six, it is 100; at thirty, it is 92; at thirty-five, it is 74; at forty, it is 54; at forty-five, it is 39.

In leaving the subject of twins, it is natural to refer to malformations and monstrosities as showing weakness or disorder of the reproductive powers, but on this point I have no good detailed evidence to adduce meantime. Yet it is well known that a great body of opinion is in favour of the view, and there are many facts pointing in the same direction. In the course of these lectures, I have frequently mentioned such opinions and facts, but the subject is well worthy of special study. Here I would only refer to the frequent combinations of idiocy and malformation, of idiocy and twins, of idiocy and premature or post-mature maternity, of malformation and twins, of interbreeding and malformation, of interbreeding and sterility, as combining to form an argument that may, if worked out, be found to be conclusive on this question.

Experiments in producing malformations and monstrosities in the common fowl have been very fruitful in results, and demand caution in judgment as to the potency of such influences as age of the mother. Especially interesting in this view is the recent discovery of Daresse that mere delay of incubation, in the case of the eggs of the common fowl, is a cause of malformation in the chick.

REMARKS

ON THE

LOCAL ORIGIN OF MALIGNANT GROWTHS.*

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MR. PRESIDENT AND GENTLEMEN,—The subject before us is, as I understand it, the nature and scope of the local influences which induce malignant action. We accept, as being too obvious to need demonstration, the statement that cancer has both exciting and predisposing influences. The question, whether cancer be a local or a constitutional disease, seems to me, when put in such terms, to be almost childish; and I confess that I shall feel greatly disappointed if, in the discussion which is to follow my remarks, it should be in any way assumed that this is the matter in debate. Malignant processes of cell-growth are, I submit, not in any sense specific; they are modifications of the normal conditions of cell-life, and they depend not in the slightest degree upon the introduction of any new germs from without. They are the results of the sum of influences to which the organism has been exposed during its personal career; and it follows, as a matter of course, that these must have been some of them constitutional, and some of them local. It is with the latter that we have to deal to-day, and with these alone. It may, however, clear the matter somewhat if I first say a few words on the doctrine of cancer, and as to the general conditions which predispose to malignant action. In doing this, and indeed throughout my paper, I shall use the term cancer in its old sense, as denoting all forms and varieties of malignant disease.

The general result of modern histological inquiry has been, I believe, to lead us to regard the malignant process as, in the main, a local reversion to foetal modes of growth. A certain group of cell-elements succeeds in freeing itself from the central control of the

organism, and develops for itself upon a plan which is really retrograde, and which produces structures, which are not only in themselves useless, but which possess the power of infecting their neighbours. These growths are beyond the influence, or almost so, of the various agents which have been found effective in controlling inflammation. I am not sure that this insusceptibility to the action of drugs is not the principal characteristic of cancer. The infection of the glands, of the viscera, and of the organism generally, is a power which cancer shares with inflammatory processes. The more we investigate, probably, the more clearly we shall see that all inflammations are really infective; and that, from every structure in a state of inflammatory disease, particulate elements are shed, which, being carried in the lymphatic and vascular channels, may reproduce processes more or less similar in distant parts. The attempt, therefore, to distinguish between inflammation and malignant new growth, by reference to the infective power of the latter, thus breaks down. It is only because the results of general infection are, in the case of cancer, conspicuous and incurable, that we have come to regard this phenomenon as almost pathognomonic.

As it will be part of my assertion to-day, that inflammatory processes may pass by almost insensible gradations into those of malignancy, it becomes of much importance to get rid of false impressions as to the features which distinguish them. If we could find some remedy, the internal administration of which should cause a malignant ulcer to heal, or a malignant growth to melt away, as we witness when mercury or iodide of potassium is given for syphilitic formations, we should soon cease to notice any clearly marked clinical distinctions between cancer and inflammation. Nor, in truth, is the cancerous growth wholly beyond the reach of the remedies for inflammation. It is possibly true that none of the internal remedies—such as mercury, antimony, arsenic, and the like—have any appreciable influence upon it; but the local application of cold, and the local use of such agents as lead and spirits of wine, which repress cell-growth, have, if vigorously employed, an unquestionable power in retarding its development.

No one has ever doubted that there are constitutional states which predispose to cancer. In the first place, it is obvious that the structure in which it begins must be alive; and, in the next, it is clear that all living tissues are not equally liable to it, nor the tissues of all living organisms. It occurs in the lower animals as well as in man, but not with equal frequency in all. Possibly it is very rare in wild animals, and happens almost solely in those in whom the average duration of life is prolonged through artificial protection. Amongst the lower animals, as with ourselves, it is an appanage of old age. Senility, either of the structure concerned or of the entire individual, appears to be almost necessary to its production. When exceptions to this occur, they are probably due to the influence of inheritance. Speaking generally, there is no clinical fact more decidedly marked than that the tissues of young persons, however much exposed to the influences which in more advanced years are prone to evoke the disease, are not liable to take on a cancerous mode of growth. Whatever its character, and however prolonged its influence, we do not expect to see local irritation produce cancer in any person under middle age. When exceptions occur, they are to be exceptionally explained.

Sometimes it is not so much senility of the entire organism as what we may term local senility, an old age of the tissues concerned, which is premature, and does not correspond with that of the body as a whole. Nor, indeed, is it correct to say that the degree of senility is the measure of the proneness to cancer, for it is not in conditions of advanced senile atrophy that cancer is most apt to occur, but rather in its commencement. Tissues and organs which are just passing out of use, which are just commencing to decline, are those which are most prone to develop it. Of this law, the female breast offers us the best and most instructive example. It is quite possible that it is under this head that we ought to place part, at least, of the influence which previously existing local disease appears to exert in evoking cancer. Moles, and other forms of congenital excess, as well as certain innocent forms of new growth not congenital, are, as is well known, liable to be attacked by cancer. It may be that these growths run through their life more rapidly than normal structures, and thus, on the score of senility, become liable to cancer more early than the rest. It may be also, and it not improbably is, that this, too, is the way in which long-continued local inflammation sometimes acts; exhausting, as it were, the vital vigour of the part affected, and reducing it to the level of those of much older individuals. In this way, local inflammation may play the part both of predisposing and of exciting cause.

A few words must be said as to the causes of variety in the can-

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cerous process. It would appear to be the fact that the different tissues are all of them liable, with greater or less frequency, to take on this mode of morbid growth, and that in each the new product derives peculiarities from the precise place of its birth. The expression "place of birth" does not, I am aware, cover the whole ground; for the cells in which the first cancer-nodule arises are not only its home, but its parents also. The peculiarities which a cancer takes at its origin it keeps throughout its course. However widely it extends locally, how dissimilar soever may be the structures which it invades, it still keeps its original character. Nowhere is this better illustrated and proven than in the instance of epithelial cancer of the integument of the face. I will class the disease known as "rodent ulcer" as being unquestionably a form of epithelial cancer. Now, the facts appear to be pretty nearly these. If malignant action originate on any part of the skin of the face—the ears, lips, mouth, and mucous membrane of the eye, excepted—it will be of a kind which proceeds slowly, and always remains local, having no power to implicate either the lymphatics or the blood. This is the so-called "rodent ulcer." But if malignant action be originated on the lips (the red prolabium), or in or on the ear, it will be of a much more rapid kind, and will cause early implication of the lymphatic glands. It will kill its victim in a year; whilst the "rodent ulcer" may easily take twenty years before it causes death. Everything depends upon the precise tissue in which the disease takes its birth; for the "rodent ulcer" may involve the lips secondarily, but it does not, on that account, acquire any modification of its character. I could not produce to you any better example of this fact than that which this portrait illustrates. It shows us a malignant ulcer which has destroyed the outer angle of the mouth and part of the lower lip, but which had existed ten years when the portrait was taken, and had shown no tendency to implicate the glands. The explanation of this apparent discrepancy is that it began, according to the patient's clear testimony, not on the prolabium, but on the skin near to it.

As I have just asserted, the clinical observer may, without resort to the microscope, easily find proof of the law adverted to, and may note that each special tissue, almost, I might say, each individual region, gives peculiarity to the cancer which originates in it. But the histologist can carry things much further, and can explain the peculiar progress of different forms of cancer which have begun, so far as naked eye observation can go, in the same structure. He can show us that, although varieties of malignant action may begin in one and the same organ, or in one and the same region, they do not necessarily begin in identical structures. There is no organ, no part of an organ, which is not complex as regards its ultimate constitution; and with this complexity comes the possibility of variety in the precise spot in which morbid action takes its origin. Thus, in connection with true carcinoma of the breast, we have recently had it suggested by Dr. Thin and others that, when the process begins first in the epithelial lining of the ducts, it may, and probably does, differ in not unimportant features from that which begins in the acini. So, in the case of the integument of the face, although almost all forms of malignant disease originating there take on the clinical features of rodent ulcer, and are slow in progress, yet we have marked exceptions. When these exceptions occur, they are, doubtless, to be referred to the fact that the disease does not always begin in the same elements. I will not, in the presence of Dr. Thin and Mr. Butlin, and with the recollection of the amount of skilled labour which has been expended upon the question, presume to say in which of the skin-elements the common type of rodent ulcer has its birth. It is not, however, necessary to be sure of that before venturing to feel confident that when remarkable deviations from type are witnessed, they are due to deviations from ordinary rule as regards origination-tissue. When sarcoma begins in the skin of the face, whether pigmented or not, I presume no one will doubt that it starts in elements which are not the same as those in which epithelial cancer begins. I do but extend the line of this argument, when I infer that the peculiarities of various forms of epithelial cancer itself are due to the same cause. I show some drawings of a form of epithelioma of the face, clinically very different from what we usually observe.

It is needful here to say a few words as to the *Inheritance* of cancer in its bearings upon the doctrine of its local origin, since an adverse argument has been founded upon it. It has been urged, with much plausibility, that a disease which is capable of inheritance must be a constitutional one. No doubt, to some extent, this is true; but the argument must not be pushed beyond its legitimate scope. The laws of inheritance, as with property, so with disease, concern convection, and not origin or production. The inheritance of a fortune is a very

different thing from its acquisition, and gives us no clue as to how that may have been accomplished. The causes of cancer, as we meet with it in practice, may perhaps be usefully classed as three, senility of tissue, local irritation, and inheritance. Of these, only the first two can rank as true causes; the latter, although practically of great importance, is only a mode of perpetuation of that which the other two have originated. Senility gives proclivity, local irritation excites, and subsequently hereditary transmission may perpetuate. The facts as regards chimney-sweeps' cancer give perhaps the best illustration of what I mean. Before this malady was practically suppressed by Act of Parliament, I believe it was commonly noted that when the trade of sweep went, as it often did, in a family, proneness to suffer from soot-warts, and for soot-warts to degenerate into cancer, increased in successive generations. Grandsons and great-grandsons were attacked at earlier ages, and with much greater frequency, than those who were new to the trade. Here, then, we observe the liability to a form of cancer, produced in the first instance by a local cause, perpetuated and intensified by hereditary transmission. We witness the genesis of cancer, and see the shares taken by local irritation and inheritance, and how entirely secondary the latter is as regards the former. If we ask what it is which is inherited in the case of the transmission of cancer, probably the nearest approach to an answer which can be given will be to say that it is a peculiarity in cell-structure generally; not germs, not a blood-malady, but a special type of cell organisation, permitting, with greater ease than in other persons, the injurious influence of local causes. Even in the sweep, whose forefathers have suffered from soot-cancer, the transmitted tendency still waits for the exciting cause; and the disease occurs, not in internal and, therefore, protected parts, but on the same part as it did in his great-grandfather, and under the direct influence of exactly the same cause. Not that I would for one moment doubt that, in some instances, the inherited proclivity may be so strong, that it does not wait for the help of any exciting causes, but manifests its power in the production of a cancer which may be considered spontaneous. It is probably in this way that we ought to explain almost all cases of cancer occurring in very early life; and it may be the fact that, in a few of these, something more definite than mere tissue-proclivity may be transmitted, possibly even germinal matter, especially in those cases in which the parent was the subject of the malady. Thus, then, although I fully admit that in the examination of our patients we must make large allowance for the influence of inheritance, I wholly deny that we can allow it rank as a true cause of cancer.

It is time that I should cease from these general and somewhat speculative considerations, and come more closely to the details of the matter in hand. I trust, however, that what I have said will not be found to have been wholly beside the mark, but that it has really cleared the way for that which is to follow. My wish has been that our minds should be brought to that point of view in which we may see that it is, after all, just possible that what we call cancer is only a modification of the inflammatory process; or, at any rate, to put the proposition in a more restricted form, that it is almost always preceded and initiated by changes which are of that character.

I have adverted, in passing, to several matters of clinical experience on this point; but it may be well now to enumerate *seriatim*, but as briefly as I can, the several classes of fact which we have to consider. Many of these possess no kind of novelty, and have, indeed, been often before cited and discussed with almost identical objects to those which induce me now to reproduce them.

First, let me ask whether it is not within the experience of surgeons that there are certain rare and exceptional forms of chronic ulceration which histologists will not accept as cancer, but which run a clinically malignant course. To this group the so-called rodent ulcer belonged for many years. It was "a peculiar ulcer of the eyelids," "Jacob's ulcer;" and able microscopic observers assured us that no elements could be found in its growth which differed from those of chronic inflammation. The more developed processes of modern research have, however, changed this; and we now know that the differences between epithelial cancer and rodent ulcer are those of degree, and not of kind; and clinical observation, thus supported by the microscope, without hesitation places it as a form of cancer. I am entitled, then, to claim the rodent ulcer as resulting from a form of morbid action which stands halfway between common inflammation and cancer.

It may be worth while to glance for a moment at the varieties which this ulcer may present. We are far too apt, in this instance as in many others, when a peculiar pathological process has had the misfortune to receive a distinctive name, to assume that it is always

one and the same in its features. I could produce much evidence to show that different examples of rodent ulcer vary very greatly in the degree in which they resemble either chronic inflammation on the one hand or the ordinary type of epithelial cancer on the other.

I think there are other forms of disease which still stand in the position which rodent ulcer occupied not long ago, and which some forms of it still possess, of being literally and absolutely halfway between inflammation and cancer. Some of the forms of ulceration of the rectum, with thickening and stricture, locally incurable, but not constitutionally infective, come into this category. So also does the disease to which French surgeons give the name of *œsthiomène*. In this malady, the ulceration is steadily aggressive, very slow in progress, not attended by anything which, strictly speaking, can rank as new growth, and without tendency to implication of the lymphatic glands. It is not influenced, so far as I know, by internal medication; and although, both as regards it and the common forms of stricture of the rectum, it is quite true that they often originate in syphilitic subjects, they are not under the influence of iodide of potassium. In this clinical feature, they correspond with what we know of all forms of malignant disease, that they are amenable only to local treatment.

I am sure that I have repeatedly seen syphilitic ulceration with inflammatory hypertrophy glide into cancer so imperceptibly and gradually, that I could not tell when the one ended and the other began; and my impression is strong, as I have several times before publicly stated, that parts formerly affected by syphilitic inflammation possess a special degree of proneness to take on malignancy.

A gentleman was under my care some time ago for syphilitic laryngitis, with extensive destruction of parts and narrowing of the glottis. Swelling occurred about the thyroid cartilage; and, in the performance of tracheotomy, I had to pass through what appeared to be a gumma, which had an abscess in its middle. Granulation-masses sprang up around the tracheal cannula; these resisted all treatment; and, after some months, the persistent growth of a large bossy mass obliged us to realise that at length we had to deal with a malignant neoplasm.

Many years ago, Mr. Cock described, in the *Guy's Hospital Reports*, a peculiar tumour of the scalp, which, originating in a sebaceous cyst, finally assumed the features of a locally malignant growth. Of these, I show now some remarkable illustrations. In one of these, the ulceration, attended by free warty, or cauliflower growth, had involved almost the whole scalp; yet it was excised by my colleague, Mr. Rivington, without return or implication of glands.

The cancer which occurs in scars, and to which, if I mistake not, Mr. Cesar Hawkins was one of the first to draw attention, is another illustration of the power of local peculiarities in evoking malignant action, and also in stamping peculiarity upon it. I believe that in this form of cancer, as in the rodent, there is seldom any gland-disease.

The almost absolute restriction of cancer of the lip to males—that is, to those who smoke—is so definite as to suggest the possibility of constructing a sexual classification of cancer. This might be done in considerable detail by reference to the local influences to which the several parts of the body are in the two sexes relatively exposed, and would supply testimony of great strength in support of the doctrine of local origin.

In a paper upon the antecedents of cancer of the tongue, many years ago, I insisted upon the great frequency with which syphilitic inflammation is its precursor, and probably its cause. Every year's experience confirms this impression, and furnishes but too numerous illustrations of the difficulty which even the best trained observers find in recognising the stage at which syphilitic ulceration, sclerosis, or papilloma, may pass into the condition of declared malignancy. The cases of cancer of the tongue which are not preceded by some form of syphilitic inflammation are, in fact, exceptional. I must hold, also, that the results of operations for cancer of the tongue very strongly confirm the theory of its local origin; for, in a large majority of cases, if the operation be done early and boldly, there is no return in the organ.

I ought to say a few words respecting the association of cancer of the penis with phimosi and other local causes of irritation, and also as to those cases in which cancer follows injuries, and in which it begins in the substance of other new growths; but I must pass these topics over with a bare mention. I must not, however, neglect to remind you of the fallacy of supposing that the influence of external irritation is confined to external cancers. If this doctrine be true for the various forms of malignant action beginning in the skin, or in those mucous tracts which are open to our inspection,

we may safely assume that it is true also, and perhaps with not less cogency, of those parts which are concealed.

In bringing these remarks to a close, allow me, Mr. President, to give expression to the pleasure which it has afforded me to be permitted to introduce this subject. It is one which has engaged a large share of my thoughts during the whole of my professional life; and more than twenty years ago, I read before the Hunterian Society a paper which contained, in the main, the same arguments which I have to-day brought forward. I then held, as I have now done, that cancer is, in the main, a disease local in its beginnings; and I insisted on the paramount importance of this doctrine as the only safe basis for surgical treatment. The general opinion of the profession has, if I mistake not, much advanced in this direction since then. It was helped much by the discussion which took place in 1874 before the Pathological Society. On that occasion, Mr. Campbell de Morgan, in a most able speech, introduced the subject, and upheld the doctrine of local origin. In the debate which followed, I had the honour of taking part, and I then re-stated, in the strongest terms which I could find, my concurrence with his opinion, and my belief that, in nineteen cases out of twenty, cancer begins as a local growth, and that the infection of the system may be prevented if the removal be sufficiently early and sufficiently free. Some years later, in a second paper before the Hunterian Society, I introduced and defended the expression "precancerous stage of cancer." I hoped that a readily used phrase of this kind might avail something in attracting the attention of the profession at large to the subject. At the same time, I suggested and recommended that our operative measures might often be justified before the diagnosis of cancer could be established, and that sound surgery might find its most beneficent vocation in the anticipatory excision of suspected parts. An ingenious argument in support of the doctrine of the constitutional origin of cancer has been based upon the fact that it so almost constantly recurs after removal. But, before we can allow any weight to this contention, we must inquire where it recurs. If the recurrence be in the lymphatic glands, or in other parts in close proximity to the growth, it proves only that excision was delayed too long, and that infection had already been accomplished. We do not allege that syphilis originates in the system because the excision of a chancre seldom prevents the full development of the disease; nor would a farmer who allowed a thistle to seed before it was cut down, have any right to infer from next year's crop that his field had a constitutional tendency to the production of thistles.

Let me now briefly glance back upon what I have been stating in relation to the discussion which is to follow. I have tried to urge respecting cancerous new growth that it by no means occupies a position of such absolute isolation as has been supposed, and that, when not the result of inheritance, it is not only sometimes, but almost invariably, preceded by conditions of cell-change which are identical with those of chronic inflammation. For this I have proposed the name *Precancerous Stage*. I have further suggested that there are cases in which the changes never advance beyond this introductory condition, and the malady remains ill characterised to the last. Into the details of the microscopic changes, and how, in the various tissues, chronic inflammation gradually slides into cancer, I have not entered. I have avoided this important aspect of the subject for several reasons: partly because I feared it might be of comparatively little interest to some of my hearers; partly because the clinical evidence seems to me sufficient, and even more convincing than any which the microscope can offer; but in still greater part, because I knew that there would be those to take part in the discussion of much greater knowledge upon it than myself. If the discussion should not prove a copious and valuable one, it will not be because I have exhausted the subject, for I have left not only this topic but several others wholly untouched. Nor will it be, I think, because I have expressed my own opinions with undue rotundity or caution. I have stated them broadly, and, perhaps, even with some rashness, believing that to be at once the best method of conveying my own meaning and of eliciting the opinions of others. There is, however, another and far stronger motive for being outspoken in this matter. It is the conviction which grows with each year's experience, that in the rules of practice which would spring out of the full and hearty adoption of the doctrine of the local origin of cancer rests our only hope of being able to save those who consult us, from the horrors of this dreadful malady. "Too late! too late!" is written in legible characters upon three-fourths of cancer-cases when they come under the notice of the operating surgeon. When the doctrine of the precancerous stage shall be widely adopted, and when surgeons generally shall recognise the propriety—let me say the duty—of operation for purposes of prevention, then, and I believe not till then, shall we witness a equ-

siderable reduction in the mortality of cancer. In no other direction is any hope of improvement to be discerned. I made this assertion twenty years ago before the Hunterian Society, and I feel it to be a duty to repeat it now with all the emphasis that I may be permitted to give it.

Sir JAMES PAGET said that he had been quite conscious that the opinion had been of late years increasing, that cancer was in its origin local. But this did not preclude the adoption of the idea of "constitutional element" in the formation. It was necessary to define the term "constitutional," which used to be regarded as synonymous with "something in the blood," whereas at present the word was more fairly used as expressing something that was prevalent through the whole body. In the subject of cancer there was undoubtedly something preceding the cancer present in the part in which it would subsequently appear, although that person was not more likely than others to have cancer in any other part. If it were necessary that that were to be held as being essential to the doctrine of the local origin of cancer, then it was necessary to meet a class of facts which were opposed to it. The negative evidence of inheritance with regard to disease was absolutely worthless. Scarcely any man certainly knew that his great-grandparents did not have such or such a disease, and many inherited tendencies without being aware of it. Sir James referred to a person who died of cancer of the stomach, whose two daughters and many of their children (to the total of twelve or fourteen in all) also died of cancer in different organs. In such instances as this, no local tendency was transmitted; no malformation was transmitted; but that which was transmitted was something general—something which, in each of these persons, was planted in a different organ from the others, and was determined in each individual to this or that part. He would not say that the transmission was in the blood, lymph, or tissues, but that it was a general influence. At the same time, he fully admitted the existence of a precancerous stage, the importance of which Mr. Hutchinson had urged. In support of his view, he quoted the case of a patient who had recurrence of cancer in the opposite breast to that which had been the primary seat of the growth, and had been removed twelve years before. Was not this explained by the same general condition pervading her? and was it not that, in turn, each breast had been subjected to the same local influence? Similar support was afforded by the occurrence of cancer in the scars of burns of long standing. Whilst, then, not doubting that many facts supported the local development of a cancer, it was impossible to exclude the general or constitutional influence, without which the local influence would not operate to produce the disease. The presence of these two factors occurred in other diseases—*e.g.*, the tendency to gout was inherited and was present in the child, but the local manifestations of the disease were only evolved in later life. Thus it was also that syphilis might be latent for years, until some injury caused its manifestations.

Dr. THIN (London) remarked on the absence of all positive knowledge regarding the changes by which a physiologically healthy epithelial cell acquired the properties of stimulating an abnormal increase in the number of cells present in a part. The newly formed epithelial cells of a cancer differed in their vital properties, and in their chemical constitution, from healthy epithelial cells. Their contact was not tolerated by the adjacent vascular tissues, on which they acted like an irritating foreign body, and the action of staining reagents showed that they differed chemically from normal epithelium. It had been imagined that, as a preliminary condition to the changes which they underwent, the cells reverted to their embryonic condition. He found no evidence of this supposed reversion. As regards the changes which epithelial cells underwent in becoming a distinctly cancerous epithelium, he could not recognise them as being changes which were peculiar to the embryonic state, or to any stage which characterised epithelium in the healthy body. The hypothesis which seemed to him to explain best the perverted vital action in epithelial cells which led to cancerous formations, was the assumption of a feeble differentiation of the epithelial layers in the embryo. According to this theory, the liability to cancer must be carried back to the earliest stage of embryonic life, when one set of cells took on the epithelial character, and another that of the connective tissue. If, at this period, the vital qualities of the epithelium were feebly developed, the epithelial structures would, throughout life, be liable to take on perverted action under causes more or less slight. Local irritation would be liable to cause cancerous growths in persons whose epithelium had remained permanently weakened by original fault of development. It was in this way that it was possible to explain how, in some cases, local causes

alone seemed to produce cancer, whilst, in other cases, the cancer appeared to be in the constitution of the individual; and also how the cancerous diathesis ran strongly in certain families. He was unable to follow Mr. Hutchinson in regarding rodent ulcer (or rodent cancer) as representing a transition between inflammatory conditions and cancerous changes. The specific cancerous changes were as highly developed in rodent ulcer as they were in any other form of cancer. The reason why, at one time, confusion had existed regarding the pathology of rodent ulcer, was not to be found in the fact that the cancerous changes were imperfectly developed, but in the fact that the special type of cancerous development was associated with the formation of an epithelium which had a small round nucleus and a yielding perishable protoplasm. The preservation of this peculiar epithelium, and of the relation of the groups which it formed to the neighbouring tissues, required special measures in making preparations; but, if those measures were taken, there was no difficulty in observing the complete independence of the new growth, and in being satisfied that there was no transition between the epithelial clusters and the products of inflammation. Nor did, in his opinion, the peculiar disease of the female genital organs, to which Mr. Hutchinson had referred (the *ecthiomene* of Huguier), afford an example of a half-way condition between inflammation and cancer. He had carefully examined some of these cases, and had satisfied himself that they were not connected with cancerous change.

Mr. BUTLIN (London) said that, during the past few years, he had often had to ask what was known of the cause of tumours, or of the conditions which precede tumours; and the reply was, that we now were aware of preceding conditions of two different kinds: first, those which were merely interesting; second, those which were very valuable. To the first class belonged traumatism, deep-seated inflammations, and inheritance—all of which, most believed, were strong predisposing causes, some of which were probably exciting causes, of tumours. This knowledge or belief could not at present be put to any practical use, although possibly, at some future time, it might become possible to do so. To the second class belonged certain typical morbid conditions, some of which were hypertrophic, some inflammatory. Thus moles, warts, and excrescences of the surface of the body, passed in certain instances into epithelioma; fissures, cracks, and warts of the lips became epithelioma; chronic inflammatory conditions of the tongue (psoriasis, ichthyosis, etc.) led to epithelioma; and certain chronic inflammatory conditions of the vessels and areola led undoubtedly to deep-seated cancers of the breast. This knowledge could be applied in practice: for, by removing or destroying these preceding conditions, as soon as they presented suspicious characters, the formation of cancer could be prevented in a certain number of persons. He hoped that the knowledge of these preceding conditions of the second kind might be widely and speedily increased: for it lent a charm to pathology which practical surgery had not always thought it possessed. He was strongly of opinion that not only inflammatory conditions of the nipple, but also ill-developed conditions, predisposed to cancer.

Dr. COUPLAND (London) suggested that the fact of long delay in the recurrence of cancer might be explained on the purely local view, by assuming that the organ secondarily infected might be the seat of cancer in a latent state.

Mr. HUTCHINSON, in reply, said that he had but little to add, since most of those who had taken part in the debate had supported the views which he had advanced. If there were any difference between his opinions and those of his teacher and friend Sir James Paget, they concerned the relative importance of predisposing and exciting causes, and were very trifling. He agreed entirely with Sir James in assigning great influence to inherited tendency; but, as he had urged in his paper, such tendency must have been acquired in the first instance. This consideration threw us back in the search for causes upon the two great classes—senility of tissue and local damage. Dr. Thin had asserted that rodent cancer was easily recognised as such by the microscope. This was to be admitted in the late and well characterised stages, but not in the earliest. There was a period in which he believed it was quite impossible to establish such diagnosis; and this assertion was to be applied, also, to the early stages of malignant disease of the lip, tongue, penis, and other parts. In all of these, it was, he feared, true that the microscope, for the most part, became of use just when, to the experienced eye, it became unnecessary; when the precancerous stage was past, and malignancy well declared. Dr. Thin stated that he had examined cases of *ecthiomene*, and found no histological evidence of cancer; and he argued from that circumstance that the disease did not afford a connecting link between cancer

and chronic inflammation. But really this was precisely as he (Mr Hutchinson) had stated the facts. A disease which clinically ran a more or less malignant course showed to the microscope only inflammation products. Whether the disease was called a local cancer or not, depended entirely upon whether a histological or a clinical definition of cancer was adopted. Dr. Coupland had suggested that, when recurrences of cancer after operation were delayed for very long periods, they still did not prove anything more than local origin, since the germinal plasma might possibly remain long latent. This was probably true, but there need be no anxiety on the part of the advocate of the local origin to adopt it to the exclusion of that of separate and spontaneous production. No doubt, constitutional tendency was, in some persons, of considerable strength; and this, together with the abundance of local causes, might well explain occasional multiplicity of new growths, whether simultaneous or after long intervals. He recollected the case of a lady for whom many years ago he excised an eye, on account of melanotic sarcoma. She remained well eight years, and then died of epithelial carcinoma of the vagina and uterus. He did not regard it as an instance of dormant cells, but rather of independent production of a second growth. When the disease, after a long interval, reappeared in the original site, or in the proximal lymphatic glands, then probably Dr. Coupland's suggestion would be the correct one.

AN EXPERIMENTAL INVESTIGATION OF THE ACTION OF CHLORAL, OPIUM, AND BROMIDE OF POTASSIUM.

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(Continued from page 153.)

Extract of Opium.—The experiments with this preparation may be more cursorily given; for, in the main, the results obtained were similar to those which the morphia gave. A 10 per cent. solution of the watery extract was employed. The quantities required to arrest the heart in diastole gave, for the six experiments, an average of 3.26 c.c.; whilst the 5 per cent. solution of the hydrochlorate of morphia, it will be remembered, gave 14.16 c.c. as the average toxic dose. This, of course, would make the opium rather more than twice as poisonous as the morphia. There can, however, be little doubt but that this discrepancy is due to the extract of opium solution being acid, for in an even very feebly acid solution, the ventricle ceases to beat. The quantity table hence loses its value; and, indeed, the qualitative results are vitiated from the same cause, although, with the exception that inhibition was more marked than with morphia, the agreement was tolerably close; thus latent period and "period of diminished excitability" were similarly affected; the behaviour to continuous faradisation was likewise similar; and the results, both of dilution of the poisoned fluid and of substitution of the same by fresh blood, were also similar. The "exhaustion" or "recovery" effect described under morphia was exceedingly well shown, much more perfectly than in the case of morphia; and it was possible, by placing the stimuli, to get either a descending or ascending staircase of contractions.

There remains for description the bromide of potassium. The experiments with this drug were made about ten to twelve months previously, and the results given in a paper in the *Medico-Chir. Trans.* for 1882, from which the following is taken.

The heart is arrested in diastole. The average quantity requisite for this was 2.13 c.c. of a ten per cent. solution; this is equivalent to 0.213 grammes of the salt, or 3.28 grains. Inhibition, though less marked than with chloride and iodide of potassium, is still a characteristic feature. Contractility is diminished from the outset, no stage of stimulation preceding; in the end, there is complete abolition of the power to contract. The duration of the contraction is not increased; on the contrary, a pointing of the apex of the trace occurs; this is uniformly the case with potassium salts.

Experiments subsequent to those above mentioned have shown that the "period of latency" is considerably increased, as also is

the "period of diminished excitability." The excitability for continuous faradisation is lessened for bromide of potassium, as it is for the other potassium salts examined (*op. cit.*).

Dilution of the circulating poisoned fluid with an equal volume of fresh blood was tried in three cases with restoration of good spontaneous beats. Replacement with fresh blood would, of course, have been yet more effective.

To discuss the results obtained, we note that, in contradistinction to the somewhat large group of systolic arrestors, these three drugs, chloral, morphia, bromide of potassium, arrest the ventricle in diastole; this, we know, will result from a toxic dose administered to the organism in its entirety; but these experiments show further that these drugs are depressants, when applied directly to the substance of the ventricle; and they demonstrate that, contrary to what one would be led to infer from Labbé's statement, chloral is capable of arresting the isolated ventricle.

The question as to whether the quantitative results here obtained will help us with reference to the toxic dose required for the entire organism, must clearly be answered in the negative. The working of the entire organism is an accurate and delicate adjustment of numerous functions; and, as the strength of the rope is the strength of the weakest part, so the power of resistance of the entire organism is the power of resistance of the most delicate part of the complex structure. The structure of the great nerve-centres is, as a rule, the weakest point, and hence, in general, systemic death results, whilst the peripheral structures still functionate more or less perfectly.

Here, in these experiments, the drug is pushed on to the complete extinction of the peripheral structure, *i.e.*, to a degree beyond, though it is impossible to say by how much beyond, the death point of the entire organism. The curious action of curare in selecting, not the nerve-centres, but the muscle-endings of the motor nerves, shows that it is not always the nerve-centres which first succumb, and stays one from inference as to the relationship of the death-points of central and peripheral structures. Still, much may be learnt from comparative action on a peripheral structure, and, in particular, a definiteness in the results obtained quite impossible else.

Considered thus, we learn, first, the qualitative similarity of action of chloral, morphia, and bromide of potassium; they are depressants, and they are so by inhibition, and by direct diminution of muscular contractility. Compared, we note that, whilst inhibition is a well marked factor for both chloral and bromide of potassium, it is but slight for morphia. Compared further, we note that, for both chloral and bromide of potassium, the action on muscular contractility is depressant from the onset, whilst morphia presents a fairly well marked stage of stimulation, or of heightened muscular contractility, preceding the stage of depression. Further, with reference to morphia, must be noted the really enormous dose required to destroy contractility, *i.e.*, the slight action of the drug on the cardiac tissues. We may here state, moreover, that "contractility" was not appreciably affected till late in the action of the drug, whilst then the decline was rather rapid; in other words, the resisting power was maintained till a considerable percentage dose of the poison was reached. These results are in complete conformity with the statement, previously noted, that morphia affects but slightly the peripheral structures, nerve and muscle; and comparison in respect of quantity will place both chloral and bromide of potassium as far more poisonous to peripheral structures than morphia.

The isolated heart of the frog, we have stated, manifests a twofold activity, *viz.*, contractility and rhythm; chloral and bromide of potassium we find threatening in both of these directions—there is the direct weakening of the contractile power, there is the tendency to inhibit. Is the presumption unlikely that nervo-muscular action generally, which rhythm and contractility may serve to typify, will be similarly affected qualitatively, and that the action of bromide of potassium and of chloral will be generally depressant to nervous and muscular tissues; also that the qualitative relation above seen to hold for the three drugs will apply generally? If so, a more extended inference as to the relative value of the three drugs in question will be possible; but, even if one limit oneself to the consideration of the local cardiac action, it must be evident that a drug such as morphia—which, in the doses employed in medicine, must be practically without local influence on the heart, or which, to a very small extent of this action, must be stimulant rather than depressant in nature—is to be preferred over drugs such as chloral and bromide of potassium, which in their smallest doses appear to be depressant, and which are employed therapeutically in far larger doses than morphia.