Irritation Cancer

Its bearings on the Cancer Problem as shewn

by

Kangri Epithelioma

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Kangri Epithelioma

Introduction.

During the years 1905 - 1914 I had the great privilege of being associated in India with the Doctors Neve in the work of the Kashmir Mission Hospital.

The most outstanding of all the peculiar diseases in that part of the world was the Kangri Burn Epithelioma. I found that my ordinary ideas on epithelioma required re-adjusting, and in 1906 I set to work to collect specimens and cut sections of the tumours.

General.

Kashmir is a part of the Indian Empire governed by a Maharajah who is a ruler in his own right with a British resident Officer attached. The country consists of mountains, and valleys ever rising higher. Lawrence's "Kashmir" states on the authority of the geological survey of India, that one half of the country is over 13,000 feet above the sea. As the latitude is about that of North Egypt and Gibraltar, it will be realized that the cold in Winter is intense.

The people of the country are poor, the

average daily wage before the War was 4d., per day in English money. One-tenth of the population was Hindu, and nine-tenths Mohametan. The people, for Indians, were fair; blue eyes, fair skin, and light to red hair, not uncommon.

Agriculture is the chief pursuit. Clothes are not easily obtained, the native garment called a phyrean, (pronounced peran), is like a smocked frock of one hundred years ago - loose sleeves, loose in the body, a hole for the head. The hole, through which the head is poked is fastened with a knot button, and covered in by a shawl twisted round the neck.

Under the phyrean and next the body the Kangri charcoal fire basket is carried in Winter. This basket acts like a hot water bottle except that it really is, and can be made, intensely hot. Typical phyreans, squatting positions and lying positions are shewn in photos one and two, also Kangri in front of woman, photo 1. Tiny children of two years old carry about these fire baskets and use them, so that children of three years of age shew well marked ephilis ab igne as the result of the heat. The squatting position which these people usually occupy

produces ephilis ab igne over the inner side of the thighs from the junction of the upper one-third and lower two-thirds, to the knee; and on the front of the abdomen and chest to the nipple line.

Ephilis ab Igne.

This condition is described as "Scars and patches of pigmented skin with dry scaly slightly raised black macules and papules all shewing pigmented epithelial overgrowth. The macules and papules are one or two centimetres across, and project upon the surface the fraction of a millimetre."

The scars referred to above are burns of the second and third degree. They take place most frequently in the early years of life.

During 1906 and 1907, a large number of specimens of ephilis ab igne, epithelial horns and epitheliomata were sent to Dr. E. F. Bashford, O.B.E., of the Cancer Research. These included as many border-line ulcer epitheliomata as we could collect. Dr. Bashford reported that the many sections cut did not help to define the border line condition.

Microscopic Appearances.

Microscopic sections of the condition of ephilis ab igne shew a general irritative overgrowth of all layers of the dermis which increases quite markedly the thickness of the skin.

Three other conditions are present

1. Increased pigmentation.
2. Marked downgrowth of the papillary layer into the stratum reticulare (malpigii).
3. Small celled infiltration below the downgrowing papillae.

In regard to these various points

1. The increased pigmentation is almost exactly comparable to that due to sun burn, except that it is not homogeneous as that is. The areas of pigmentation in ephilis ab igne are irregular in shape with lobulated areas standing out, as it were from a central core or patch, lenkoplakia the areas of a-pigmentation and of increased pigmentation (ephilis) resembled each other in a remarkable way.

The subject of the relation of these patches to the start of epithelioma will be referred to later on.

2. In regard to the downgrowth of the papillary layer the attached micro photograph No. 3 shews such a papilla in an advanced case of ephilis. It shews overgrowth, irregular mitotic figures of the nuclei and crowding of the cells of the germinal layer the palisade layer of cells as such seem to have all but disappeared. Early degeneration of the cells with vacuolation is a constant factor.
3. The small celled infiltration of the rete malpigii or stratum reticulare is well marked. The more rapid the growth

downwards of the papilla the greater the small celled infiltration. The infiltration is almost always extra specially well marked at the apex of the papilla, presumably where the downgrowth is most active.

Kangri Epithelioma.

In 1906 we made a careful survey of the tumour surgery of the previous twenty-five years. With a total of 4902 tumours which were operable, 1720 were cancer or sarcoma, the rest non malignant. Of the 1720 malignant tumours no less than two-thirds were epithelimoata namely 1189. These 1189 epitheliomata were distributed about the body as follows :-

Abdomen & Thighs	848	Hand	16
Breast	48	Feet	10
Leg	46	Rectum	6
Chest	21	Lip	5
Face	19	Ear	5
		Tongue	4

These are the chief sites.

The average age of the 1189 patients as far as could be ascertained was 53½ years. The basis of the age calculation was naturally rough and ready, as the patients almost invariably are totally illiterate.

In the year 1910, we operated upon 105 kangri burn epitheliomas. 30 more cases were received in an advanced state

where surgical interference was not warranted. 64% of the cases were in males.

Clinical.

We found at once that these tumours of the kangri epithelioma presented two distinct types.

a. Crateriform excavating.

b. Foliative cauliflower and horny.

The b type was more common than the a. I was able to secure some good drawings by a competent artist of these tumours, which are forwarded with this paper. The original tumours I was unable to bring home as well as the microscopic slides owing to the War. On the whole I think the drawings shew the structure and condition almost better than a preserved specimen, as the drawing were done on recently removed specimens washed in alcohol.

a Variety of excavating ulcer is the tumour almost always seen in this country, and prevalent on the lip, tongue or skin. One such typical ulcer is shewn in the drawings. This type of ulcer was seen in only prox 17% of all cases in 1000 consecutive epitheliomata and is therefore in marked contrast to the epithelioma usually seen in this country.

b The horny foliative tumour in its pure

horny form was seen in about 23% of 1000 consecutive cases, the remaining 60% were mixed ulcer and horn, the ulcer was not crateriform but of a cauliflower type.

Anatomical.

One of the first questions we set ourselves to solve was the question of the horn. The text book teaching was that the horn was a mixture of inspissated pus and skin debris. We have never seen such a horn. Every horn examined by us is made up of regular layers of stratified horny epithelium, stained in the usual way, and often shewed remains of cell nuclei in the horny layers. Micro photos 8 and 11.

These horny tumours were solid and firmly adherent to the skin, they were a pre-epitheliomatous condition. Directly epithelioma supervened the flat layers of horny cells degenerated, long spicular crystals developed. The horny tumour became undermined and was shed. (Micro photo 7).

The following statement has been made in regard to kangri burn epithelioma "It is at first essentially a local disease and if treated by excision quite early, an absolute

cure is obtained." One reason for this is that the rete malpigii or stratum reticulare is altered in character and becomes firm fibrous tissue, as a result of the irritation of ephilis ab igne and the horn. This fibrous tissue presents a temporary local barrier. Dr. A. Neve in 1900 pointed out "that it is comparatively seldom that the muscles of the thigh are involved, but that early infiltration of the structures below the epithelioma is the rule in epitheliomata of the abdominal wall". In 1890 the same authority pointed out the "early spread of epithelioma of the abdominal wall to the peritoneum". Operative deaths in the early years were unfortunately due to vain endeavours to remove epitheliomata which had reached the parietal peritoneum by direct continuity.

My own observations on several hundred cases of epithelioma of the abdominal wall prove two very important points

1. That the cancerous process spreads to the peritoneum by direct continuity. Although we opened the abdomen in quite a number of cases, and the falciform ligament and liver were inspected, we could never satisfy ourselves either by sight palpation or microscopic section that cancer spread via the falciform ligament to the liver and abdomen. We are, therefore, unable to uphold Mr. Sampson Handley's opinion.

2. Cumeo and Porier in their work on the lymphatics of the body pointed out the irregularity of the lymphatic drainage areas on the front of the abdomen. These areas of lymphatic drainage bear no relation to the umbilicus or the linea alba. Epitheliomatous tumours of almost any part of the front of the abdomen may cause epitheliomatous glands in the axilla or groin, not unfrequently in both right and left axillae or right and left groins and on several occasions in all four situations (verified microscopically). The deep sternal thoracic glands and the deep iliac glands were seldom or never affected except as a terminal condition.

As a result of these experiences we were forced to conclude that epithelioma of the anterior abdominal wall was a much more serious condition than epithelioma of the thigh. When the rapidity of growth and early spread to glands is considered, we find the same condition in Britain especially when we compare operative results as between epithelioma of the hand and that of the tongue which is so very fatal. It must, therefore, be concluded that anatomical consideration as blood and lymph supply alter the whole prognosis of epithelioma.

Microscopic appearances.

The palisade layer of epithelial cells seems the basis or birth place of the superficial epithelium. Upon the palisade cells' health and vigour the strength of the dermis depends.

During the long terms of Winter irritation from the kangri heat, this layer of the dermis becomes more and more irregular. The nuclei become relatively larger, the cells vary in size and the outline is irregular. Instead of one regular layer, you find many irregular layers. Evidences of active proliferation of these cells is found in the relative increase in the number of mitotic figures, the mitosis is irregular and the pigment content of the cells is early increased in quantity.

In the prickle layers the protoplasm stains irregularly and vacuoles appear. The granular layer and stratum lucidum are much less distinct than in the normal skin.

In the horny layer the nuclei though degenerate stain well (unlike healthy skin), but the gradual transformation and deposition of kerato-hyalin and eleidin does not seem to be affected. The horns found on the skin in Kashmir are real horns, hard and firmly attached. They seem to be only local overgrowths of a type similar to the hard corns produced by work in the palms of the hands. Below the horns the papillary down growths are well marked. Micro photos 3, 6,

10, shew the gradual change in the palisade cells, and in a papilla from ephilis to well marked epithelioma.

Despite the many sections cut and examined by Dr. Bashford and myself, no definite microscopic, physiological, or pathological condition was ever found which enabled one to state emphatically that a certain appearance indicated "a border line" condition. In fact there is no pathological division dividing cancer of the skin from chronic irritation and its sequelae.

The advent of epithelioma upon chronic irritation produced

1. A total disorganization of the palisade layer of cells
2. Disappearance of the basement membrane below the palisade layer of cells
3. Complete cessation of the normal chemical relations of the skin protoplasm to keratohyalin and eleidin, hence the appearance of cancer led to loosening of the horn.

As a result of this latter circumstance, horns firmly adherent were removed surgically, but any horn partially loose or with undermined base was removed, and the glands of the area at the same time on the certain assumption that epithelioma was present.

It seems fairly certain therefore, that

the normal chemical changes in the skin are entirely altered by the advent of epithelioma.

Methods of spread of epithelioma will not be described, as they are absolutely comparable to conditions prevailing in Britain.

General considerations.

The literature of cancer produced during the past 20 years is colossal. Unfortunately nothing has been evolved as to etiology by which the spread of this fell disease may be overcome or arrested.

Bacterial or Germinal Theory.

We have some interesting side lights upon this in regard to kangri epithelioma. In the first place the people are intensely dirty. Leprosy, cholera, typhoid, typhus, the diseases Dr. John Wyllie used to describe as pathognomonic of "Human pigsties" exist in Kashmir in severe form. Yet it was practically unheard of to see two cases in the same family or Village for that matter. I noticed in Hospital a son aged 40 - 50 take the cotton trousers of his old father, saturated with pus and discharge from an epithelioma, and after giving the trousers a rinse, put them on and wear them. His father died

of epithelioma of the abdomen. I cannot say for certain if this man developed epithelioma or not, but this sort of dirty habit was not unusual.

Sarcoma in certain rodents is infectious in cages (Rockfeller Institute Reports), but there is a total lack of evidence of infection in Kashmir. The same may be said of cancer houses, there is no evidence. (Ulster Branch B.M.A., B.M.J., Volume 1, page 1171; Imperial Cancer Research 1913 - 1914, B.M.J., Volume 2, page 256,) of such.

With a large percentage of the population nearer our Hospital and a greater number of attendances during the last 10 years, the incidence of epithelioma per 1000 cases has decreased quite considerably.

The foregoing matter also deals a heavy blow at any theory of heredity. We found no evidence of an hereditary tendency. It is hard to divide heredity from infection or contagion. This would be extraordinarily difficult in Kashmir. Families live huddled up in one room during the cold.

Careful enquiries and many visits to Villages have entirely failed to give just cause for any statistics of heredity. In the higher mountain Villages where cold and conse-

quent herding is greater, there is not more kangri epithelioma than in the Plain Villages where it is warmer. We may therefore say that there is no sign

1. Of Cancer heredity.
2. Of evidence to support an infectious origin.

Food and Cancer.

With regard to this ingenious theory we find a Kashmiri with a wage of 4d., per day singularly abstemious, he lives almost entirely on rice and vegetables. Meat, fowl or an egg is a luxury which he may have every now and then, fruit and nuts in season. A more simple and less irritating diet it would be hard to find or suggest.

The association of fish and leprosy as suggested by the late Dr. Jonathan Hutchinson, and food and cancer seem singularly out of place in Kashmir.

Shortly after starting the investigation in regard to kangri epithelioma, the other Medical Officers and myself began to watch for border-line ulcers to send to the Imperial Cancer Research.

We then began to notice certain types of skin more liable to severe ephilis ab igne

than others.

1. Patients with ichthyosis were totally untouched by the kangri in regard to the production of ephilis ab igne, and there was no tendency to kangri burn epithelioma.

2. The type of skin which reacted most to the irritant was the fair type.

3. The type most affected was the albino (mostly partial). Epithelioma and horns formed readily in these patients. The only case seen in 10 years with two simultaneous and distinct epitheliomata growing at the same time was in a partial albino.

I should say that albinism was rather more frequent in Kashmir than elsewhere, but was not common even there.

We saw a good many partial albinos in Kashmir. The disease was looked upon as somewhat of a disgrace, and we were visited with a view to treatment. It seemed that there were quite a few cases.

Leucoderma is a common disease in Kashmir and one could not help contrasting the peculiar a-pigmented patches seen in this disease with the pigmented patches seen in ephilis. Their forms were extraordinarily alike, so much so, that they seemed an equal and opposite reaction.

Whilst we were in the midst of our observations Sir George Lenthal Cheatle, K.C.B.,

C.V.O., published some very interesting papers B.M.J., February 2nd., 1908. These shewed that 54 out of 56 epitheliomas of the dorsum of the hand started in the border between the nerve distribution area of the radial and ulna nerves. Dr. Henry Head had previously shewn that this was the special area for tropic lesions produced by section of the radial nerve in his own forearm. Sir George Cheatle also demonstrated definite nerve changes in the post. root ganglion of the nerve at the border of whose distribution epithelioma had developed.

We were struck by this paper and our attention at once was attracted to the case of epithelioma in the cervix uteri. Here the nerve supply is remarkably poor. The cervix uteri can be manipulated gripped with a volcellum without pain etc. Yet epithelioma here is one of the disasters especially prevalent in the female.

The Middlesex Hospital Special Cancer Department reports shew 97% of all uterine cancer as having origin in the cervix . Turn again to the incidence of rodent ulcer and epithelioma upon the face. Here we find the points of maximum incidence in angles and borders between the distribution of the

various facial nerves.

Again in the rodent ulcers depicted in the enclosed illustrations from Sir G. Cheatle's paper from the B.M.J., 1905, note how the ulceration areas in large rodent ulcers correspond to nerve distribution. Especially is this the case in regard to the great auricular nerve.

Looking at our own tumours in this light we soon found that the pigmented ephilis patches so like the patches of scleroderma or lenkoplakia developed horns or epithelioma upon their edges.

Upon the thigh it was most marked that whilst the ephilis ab igne was acute along the inner border of the adductor longus, the epithelioma usually originated further forward at the line of junction of the sensory areas supplied respectively anteriorly by the Int. division of the anterior cutaneous and posteriorly by the obturator nerve.

What about the theory of developmental rests? One can understand the idea as applied to dernoid cysts, and epithelial cysts, and patent branchial clefts, the condition is obviously straight forward.

In regard to cancer it cannot be a

rational explanation.

These so called developmental rests occur along the original segmental lines of development. These lines also serve to define nerve distribution. Along these segmental lines are the areas of division of the various nerve distributions.

Why should cancer occur so frequently at the pylorus, at the angle of the mouth opposite the cricoid cartilege, at the junction of the pelvic colon and rectum?

They are all seats of irritation, but not more than other parts of the alimentary tract.

Duodenal ulcer rarely if ever becomes malignant, pyloric ulcer frequently.

It seems to me that the one outstanding anatomical fact underlying the pathology of these conditions is the border-line between the segmental nerve distribution.

Why should micro photographs 5, 9, 12, 13, 14, shew this intense overgrowth of epithelium producing cauliflower like masses? It surely must do so by growing without nervous control.

In the literature of cancer, I have not

been able to find any physiological or pathological experiments to shew if irritation cancer is more likely to develop on denervated areas as compared to those in which the nerve distribution is normal. Some old war injuries may help to solve this problem, and failing this, it seems to me that a fruitful field for further examination exists in regard to this matter.

I do not think that the suggestion put forward by American Authorities; that excavating rodent ulcer and excavating epithelioma as compared with cauliflower growths of either sort are due the former to squamous epithelial cells and the latter to the epithelium of the sweat glands; is worth minute discussion. Both positive and negative evidence rest entirely on supposition.

Summary.

A. Ephilis ab igne is associated with

1. Increased pigmentation.

2. Overgrowth of the palisade layer of epithelial cells.

3. Down growth of the papillae into the rete malpigii.

4. The areas most intensely affected bear a striking resemblance to the areas of superficial nerve distribution.

B. Kangri burn epithelioma

1. Is frequently secondary to horny growth.

2. The horns are composed of layers of squamous epithelial cells, being an exaggeration of the normal horny production on the hand.

3. The points of cancer incidence correspond to the edges of the ephilis ab igne patches.

4. That the incidence of cancer at once stops all the chemical changes by which the protoplasm of the squamous epithelial cells is changed into eleidin and kerato-hyaline.

5. That cauliflower epithelioma with horny growths is more common in Kashmir than in Britain.

6. That several points in the history, incidence and growth of this cancer, point to a nervous origin of the growth, either disease, or insufficient control, and give fruit for thought and require further investigation.

Description of Photos and Drawings.

A. Drawings.

1. A typical squamous epithelioma ulcerating and excavating. The rather unusual type.

2. Typical kangri epithelioma of the usual type and section. Mixed cauliflower ulceration and horny production.

3. Ditto. Ditto. Horns showing stratification, advanced condition.

4. Ditto. Horn all but entirely shed, cauliflower growth marked.

5. Typical horns of the two common varieties Sections supplied in micro photographs.

Micro Photographs.

1. Kashmiri woman. Typical phyereans. Kangri in front.

2. Men and boys using kangri in bed, sitting up, all in squat position.

3. Papillary down growth in severe ephilis ab igne, well marked small celled infiltration.

4. Epithelioma on edge of horn shewing dinutigration of superficial epithelial structures. Small celled infiltration at either periphery.

5. Typical cauliflower epithelioma, immense and irregular epithelial overgrowth.

6. Second stage of papillary degeneration, epithelioma just starting.

7 & 8. Very early epithelioma under horns 7 later stage than 8. Horny structure well shewn in 8.

9. Advanced epithelioma (cauliflower) under horn which has now been shed.

10. Third stage of papilloma; well marked epithelioma.

11. Shews small horn and structures beneath the whole in an early stage.

12,13,14. Shew typical ulcers with characteristic overgrowth all over the place.

General

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11. Points of Incidence compared Lancer, Leucoderma, Seleroderma.

Sir G.M. Cheatle K.C.B., C.V.O.,
B.M.J., April 18th. 1903.
" Dec. 12th. 1903.
" April 29th. 1905.
" Feb. 22nd. 1908.

Practioner.

Inflamatory changes in Post. Root Ganglia 1905 and 1908.

Reprinted from the British Medical Journal, April 29th, 1905.

THE POINTS OF INCIDENCE COMPARED IN CANCER, LEUCODERMA, AND SCLERODERMA.

With Illustrations.

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In my two previous communications[1] upon this subject I have referred to three points: the genesis, the incidence, and the spread of cancer when considered apart from the secondary deposits.

In my last paper I pointed out that on the trunk rodent ulcers appeared on points at which nerves became cutaneous; which points also correspond to the maximum points described by Dr. Henry Head. I said I had not sufficient cases to enable me to determine whether the same thing was occurring in the face. Dr. Sequeira has kindly supplied me with the points of incidence in 138 cases of rodent ulcer on the face; the two do not coincide, but it will be seen later that rodent ulcers in the face appear most commonly on points at which nerves become cutaneous, notably the infraorbital, infratrochlear, temporo-malar, and lachrymal. Further, it will be seen that it is on the points at which the smaller branches become cutaneous that rodent ulcer appears commonly on the face and body.

Since writing my last paper I have had the advantage of more than one conversation with Dr. Head, and I learnt from him that maximum points are chiefly of importance when two or more are affected with disease—say herpes zoster—on the same nerve area, hence demonstrating a central cause; but should only one maximum point be affected, then the disease is due to a probable peripheral cause. Now, I can only show cases on the trunk where one maximum point on the same nerve area is the seat of a rodent ulcer; hence, according to Dr. Head, the change ought to be peripheral rather than central—that is to say, if I am right in suggesting a relationship between the two facts. In future I shall not use the term maximum point, but only refer to it as a point on which the nerve becomes cutaneous.

I propose in the present article to consider only the points of incidence in which the cancer process begins on the skin. And I wish to draw attention to the fact that the point of incidence must have an important etiological bearing on the actual genesis of cancer.

I shall confine my example of cancer to rodent ulcer, partly because squamous epithelioma is even more rare on the trunk and because there are no complicating factors connected with secondary deposits, which do not, as a rule, occur in rodent ulcer.

I publish all the reproductions of rodent ulcers on the trunk which so far I have been able to collect. As I have already said, points of incidence of primary cancer occur at points on which the nerves become cutaneous, and in this article I wish to strengthen that statement by pointing out that the points of incidence in rodent ulcer on the face and trunk are common to the points of incidence of the so-called neurotrophic diseases—leucoderma and scleroderma; and hence I wish further to indicate that the points of incidence in the latter diseases correspond also to those points at which nerves become cutaneous. In the simple and more localized forms of leucoderma and scleroderma there is, as a rule, only one maximum point of a nerve area affected, and therefore, according to Dr. Head, the neurotrophic factor is probably peripheral.

[1] British Medical Journal, April 18th, 1903, and December 12th, 1903.

Head and Face.

Fig. 1 represents a diagram of the points of incidence in 138 consecutive cases of rodent ulcer of the face collected with most careful investigation by Dr. Sequeira[1] from his large clinic at the London Hospital, and I must thank him for allowing me to publish this work in my paper. Dr. Sequeira's own observations I have placed away from my paper not because they are unimportant, but because I do not wish to complicate the sequence of my observations.

Now, it will be seen that the points of incidence on which rodent ulcers are most common in Dr. Sequeira's cases are identical with points of incidence in cases of leucoderma seen in Figs. 2, 3, and 4, and with the nasal point of incidence in scleroderma in Fig. 5, all of which points are seen to be skin areas at which small branches of the fifth nerve become cutaneous—namely, the infraorbital, infratrochlear, temporomalar and lachrymal nerves (see Fig. 6).

Perhaps the most striking thing in comparing them is to note the relation of the diseases to the ala of the nose and eyelid, where the incidence of rodent ulcer is also most frequent (Fig. 1).

Before leaving the cases represented by Figs. 3 and 4 I would like to remind the reader that I have previously pointed out that the primary growth of cancer in lip and eyelid occupies the same oral and palpebral regions respectively as does leucoderma and scleroderma in these regions.

Trunk.

Figs. 7 to 15 inclusive represent different cases of scleroderma; Figs. 16, 17, and 18, 2 cases of leucoderma; Figs. 19 and 20 are anatomical figures showing the distribution of cutaneous nerves in the trunk reproduced from Professor Cunningham's *Textbook of Anatomy*, with the kind permission of the publisher, Mr. Young J. Pentland, Edinburgh.

With these figures I am now going to compare all those rodent ulcers of the trunk the reproductions of which, so far, I have been able to collect.

Compare the rodent ulcer scar in 21 with the case of scleroderma in Fig. 11 and the anatomical diagram, Fig. 20.

Before leaving Fig. 11 I would like to remind the reader that the lesions shown in the drawings of the ears represent also points of incidence in rodent ulcer, and their spread in front of the ear corresponds to the spread of rodent ulcer when it occurs in front of the ear. The position of the rodent ulcer in Fig. 22 compares with the point of scleroderma in the lower photograph in Fig. 7 and the anatomical Fig. 20.

Fig. 23 represents a rodent ulcer the site of which compares with the same picture as the rodent ulcer represented in Fig. 22.

Fig. 24 is a rodent ulcer which arose in the internal division of the posterior branch of the third dorsal nerve. Compare Fig. 20.

Of the extensive rodent ulcer seen in Fig. 25 I have no history, but its area of occupation corresponds to the posterior branches of the first to the seventh dorsal nerves. See Fig. 20 and compare with Fig. 9.

The rodent ulcer in Fig. 26 compares in position with the top patch of scleroderma on the right side of Fig. 9, also compare Fig. 20. The position of the rodent ulcer in Fig. 27 compares with that of the upper patch of scleroderma in Fig. 8. See also Fig. 20.

The rodent ulcer in Fig. 28 began on the spot where the first sacral nerve becomes cutaneous. See Fig. 20.

Dr. Pusey, U.S.A., who kindly sent me the photograph reproduced in Fig. 29, did not state the exact point of its incidence, but the distribution occupies the areas supplied by the internal divisions of the posterior branches of the dorsal nerves of both sides from about the third to the twelfth. Compare with similar distribution of leucoderma in Fig. 16.

Fig. 30 is a rodent ulcer which started on the right side on the coccygeal nerve area.

The rodent ulcer of Fig. 31 began at the point of the arrow seen in the figure; compare the point of incidence of scleroderma in Figs. 12 and 15, and compare it also with an anatomical diagram (Fig. 19).

Fig. 32 represents a rodent ulcer in the axilla—compare with scleroderma in Figs. 12 and 14, and leucoderma in Fig. 18, and the nerve supply in Fig. 19.

Fig. 33. A rodent ulcer on the point at which the second dorsal nerve becomes cutaneous in Fig. 19.

Fig. 34 shows a rodent ulcer and its point of incidence in the figure below it. Compare with scleroderma in Figs. 10 and 14 and with Fig. 19.

Fig. 35. Rodent ulcer; although I cannot find a case in which to compare the point of incidence with leucoderma and scleroderma the ulcer evidently began in the same line (longitudinal with the body) as the scleroderma in the upper photograph in Fig. 7 and in Figs. 10 and 14. Compare the fourth dorsal nerve distribution in Fig. 19.

Figs. 36 and 37 are rodent ulcers on points comparable to scleroderma in Fig. 14, leucoderma in Fig. 17. See also Fig. 19.

In Fig. 38 the rodent ulcer occupies the region of the ilio-inguinal nerve's distribution on the skin. See Fig. 19 and compare with the indistinct distribution of scleroderma on the right side in Fig. 13.

The observations contained in this paper strengthen the opinion which I have already expressed, namely, that the incidence of cancer may be due to the direct or indirect nervous influence of the area in which it occurs: as we now believe is the case in leucoderma and scleroderma.

Further, if I am right in believing that the rodent ulcers on the face and body coincide in incidence with scleroderma and leucoderma, and that these points of incidence are due to direct or indirect nervous influences, then I am right in saying that the tenability of part or all of the cleft-inclusion theory is threatened. In support of this I point out that the points of incidence of rodent ulcer on the trunk are not usually on the position of clefts as we know them.

As I have already said, I have never seen a rodent ulcer appearing on two or more points at which the same nerve root becomes cutaneous on the trunk, but only a rodent ulcer on one of the points. Hence the nervous influence, if

[1] Dr. Sequeira says: Fig. 1 is reduced from a large diagram on which the point of origin of 138 rodent ulcers of the face has been marked. It shows (1) a greater tendency for the right side of the face to be affected; (2) that the common sites are the alae nasi, the inner and outer canthus of the eye; (3) that nearly all arise in the middle of the face; (4) that there is no special predilection for Head's "maximum points."

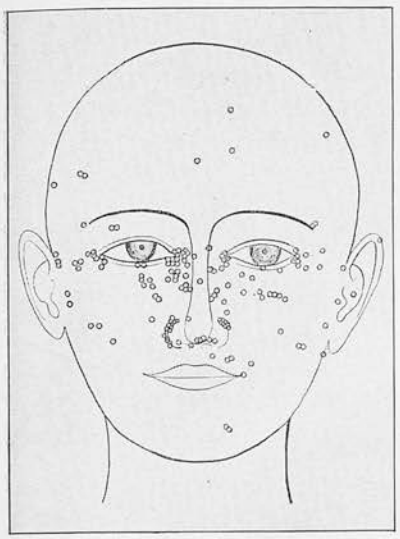

Fig. 1.—Dr. Sequeira's diagrammatic representation of the points of incidence in 138 cases of rodent ulcer.

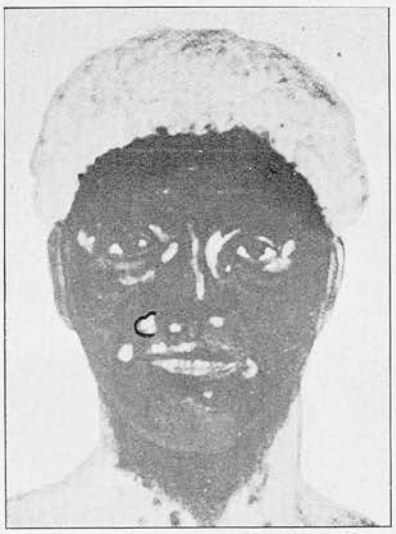

Fig. 2.—Leucoderma. Royal College of Surgeons Museum.

Fig. 3.—Leucoderma. Royal College of Surgeons Museum.

Fig. 4.—Leucoderma. Royal College of Surgeons Museum.

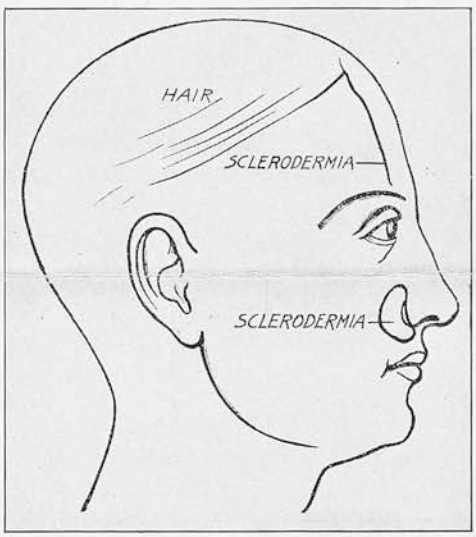

Fig. 5.—Scleroderma. Dr. Whitfield's case.

Fig. 6.—The 1st and 2nd division of the 5th nerve. The auriculo-temporal nerve is abnormal. Fritz Frohse

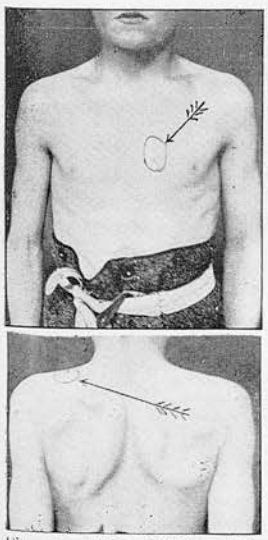

Fig. 7.—Scleroderma. Dr. Whitfield's case.

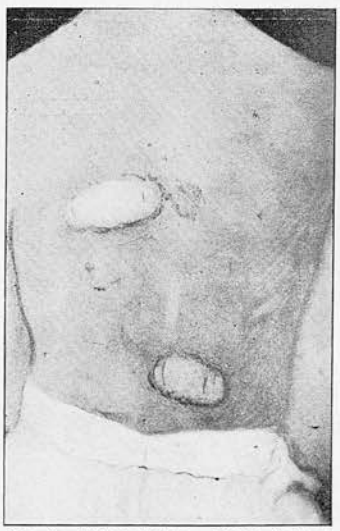

Fig. 8.—Scleroderma. Royal College of Surgeons Museum.

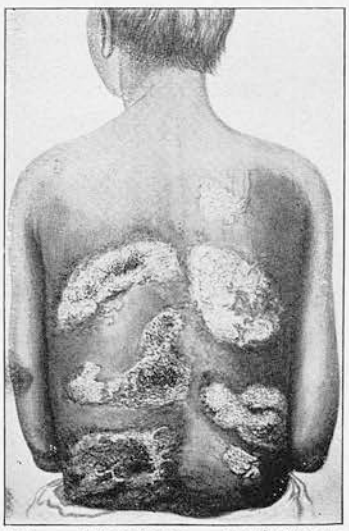

Fig. 9.—Scleroderma. Royal College of Surgeons Museum.

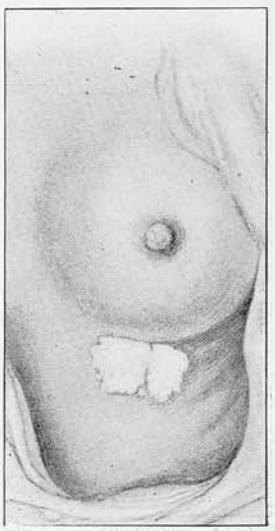

Fig. 10.—Scleroderma. From Mr. Hutchinson's collection at the Polyclinic.

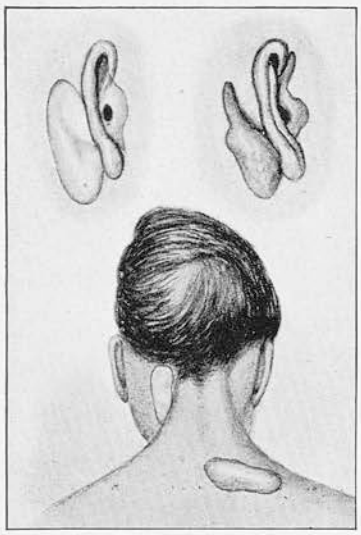

Fig. 11.—Scleroderma. From Mr. Hutchinson's collection at Polyclinic.

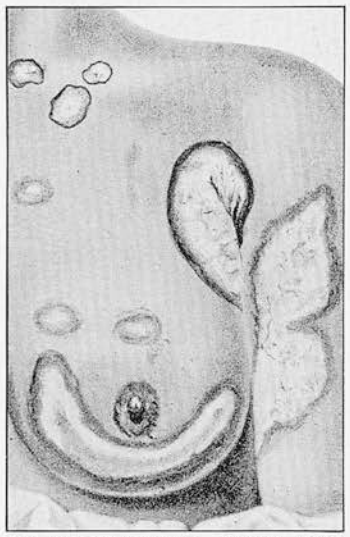

Fig. 12.—Scleroderma. Kaposi, *Handatlas der Hautkrankheiten.*

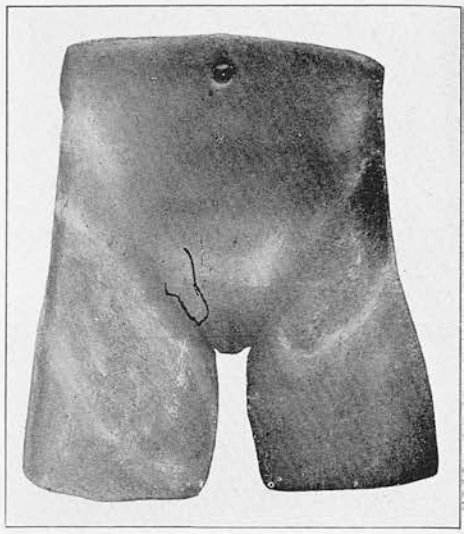

Fig. 13.—Scleroderma. Royal College of Surgeons Museum.

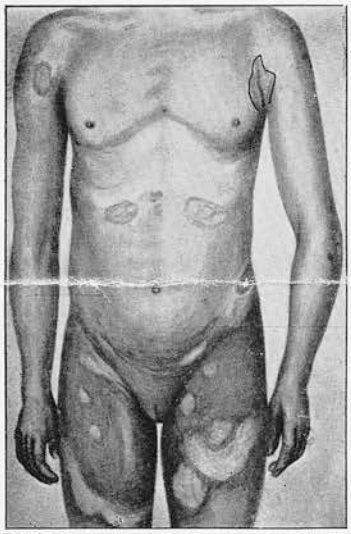

Fig. 14.—Scleroderma. Royal College of Surgeons Museum.

Fig. 15.—Scleroderma. From Mr. Hutchinson's collection at the Polyclinic.

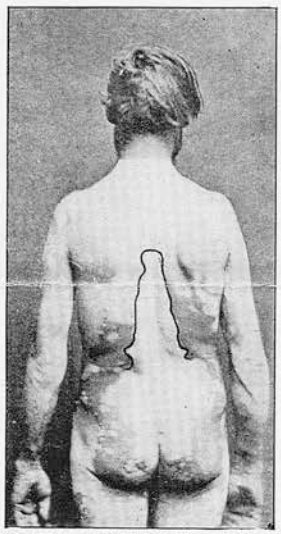

Fig. 16.—Leucoderma. From Mr Hutchinson's collection at the Polyclinic.

Fig. 17.—Leucoderma. From Mr. Hutchinson's collection at the Polyclinic.

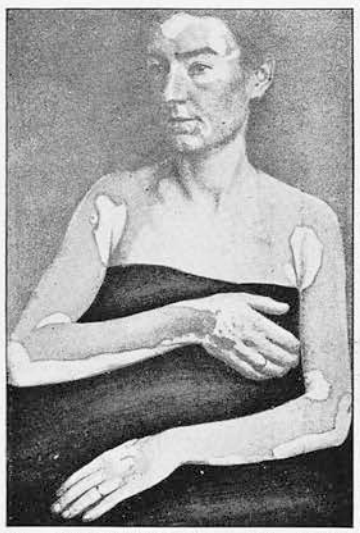

Fig. 18.—Leucoderma. Dr. Montgomery's case, from the *Journal of Cutaneous Diseases*, January, 1904.

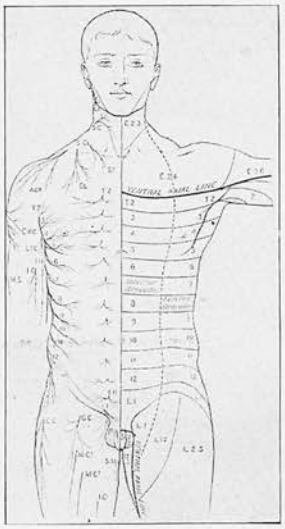

Fig. 19.—Cutaneous nerves of trunk. From Prof. D. J. Cunningham's *Textbook of Anatomy.*

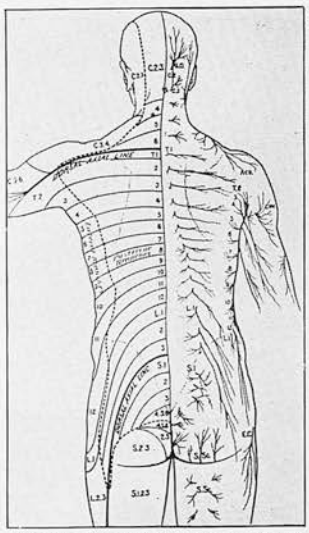

Fig. 20.—Cutaneous nerves of the trunk. From Prof. D. J. Cunningham's *Textbook of Anatomy.*

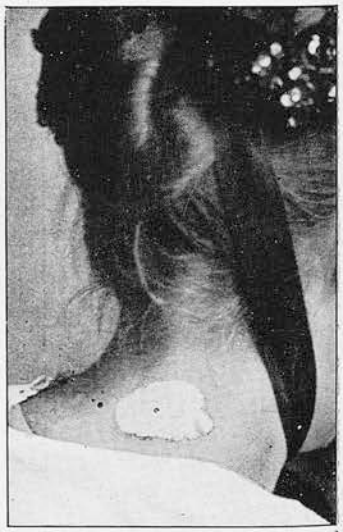

Fig. 21.—Scar of rodent ulcer cured by *x* rays. Dr. Jacob's case.

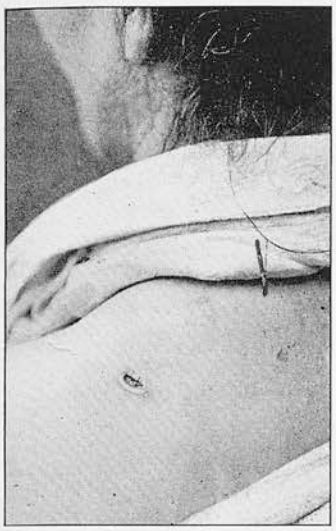

Fig. 22.—Rodent ulcer. Dr. Sequeira's case.

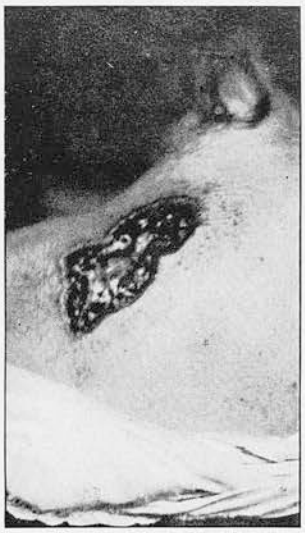

Fig. 23.—Rodent ulcer. From Mr. Hutchinson's collection.

Fig. 24.—Rodent ulcer on left of middle line. Mr. A. Reid's case.

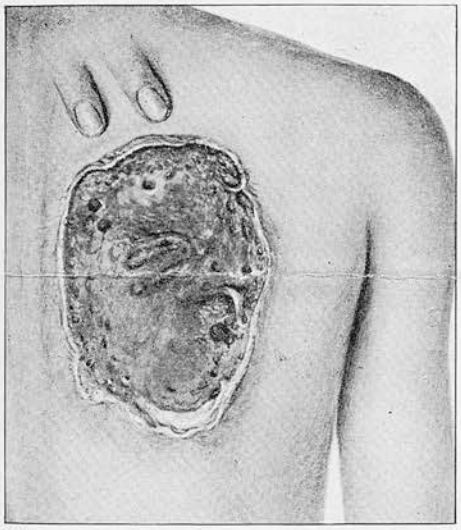

Fig. 25.—Rodent ulcer. From Mr Hutchinson's collection at the Polyclinic.

Fig. 26.—Rodent ulcer on upper and inner extremity of scapula. Mr. A. Reid's case.

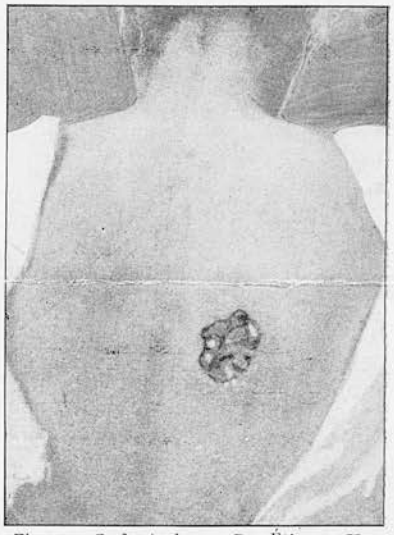

Fig. 27.—Rodent ulcer. Dr. Étienne Henrard's case. From the *Archives d'Électricité Médicale*.

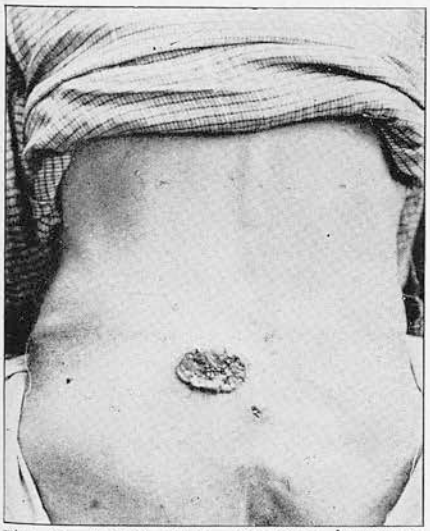

Fig. 28.—Rodent ulcer. Sir Victor Horsley's case.

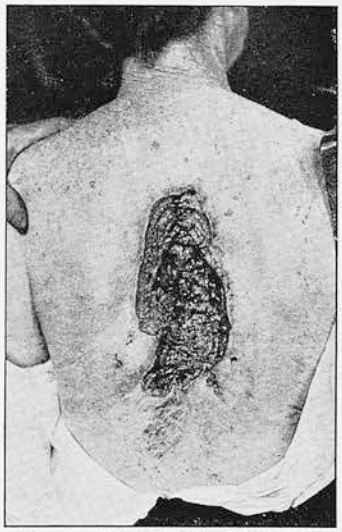

Fig. 29.—Rodent ulcer. From the collection of Dr. W. A. Pusey (U.S.A.).

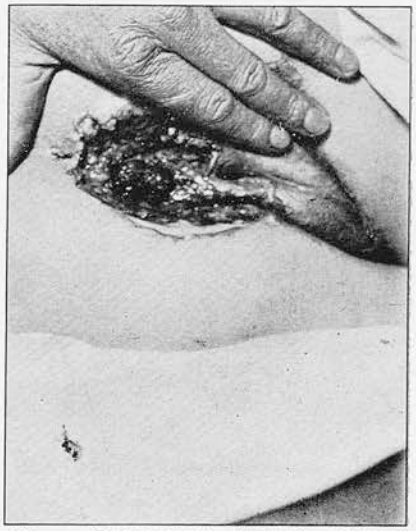

Fig. 30.—Rodent ulcer. From the collection of Dr. Norman Walker (Edinburgh).

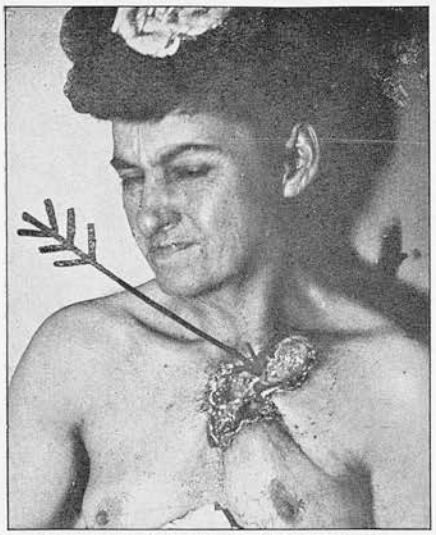

Fig. 31.—Rodent ulcer. Dr. Mill's case.

Fig. 32.—Rodent ulcer. Mr. McAdam Eccles's case.

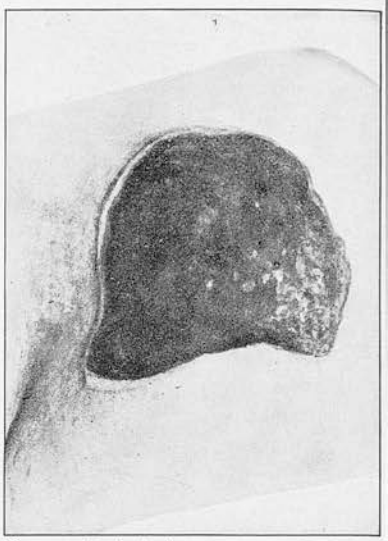

Fig. 33.—Rodent ulcer. From Mr. Hutchinson's collection at the Polyclinic.

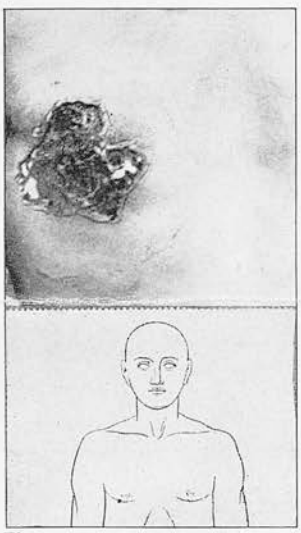

Fig. 34.—Rodent ulcer. Upper photograph shows the distribution on the side of the chest. The figure below shows its point of incidence. Dr. Jacob's case.

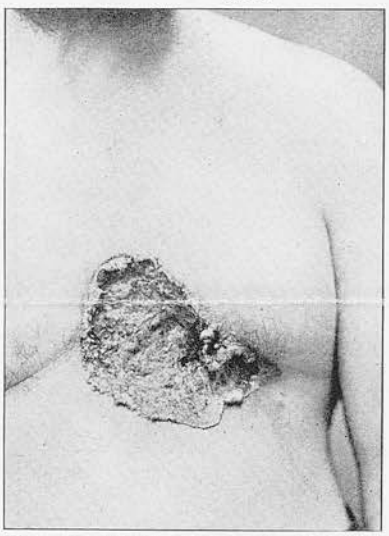

Fig. 35.—Rodent ulcer. Dr. Sequeira's case.

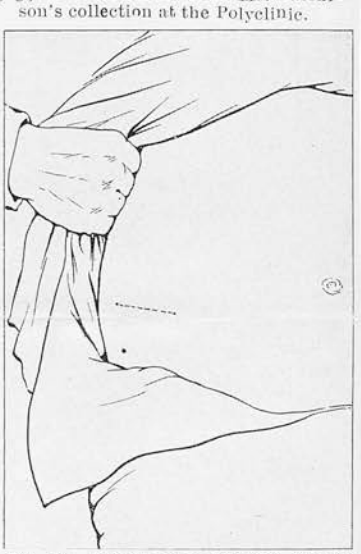

Fig. 36.—Linear scar marking the site of removal of a rodent ulcer. The dot marks the position of the anterior superior iliac spine. Sir Victor Horsley's case.

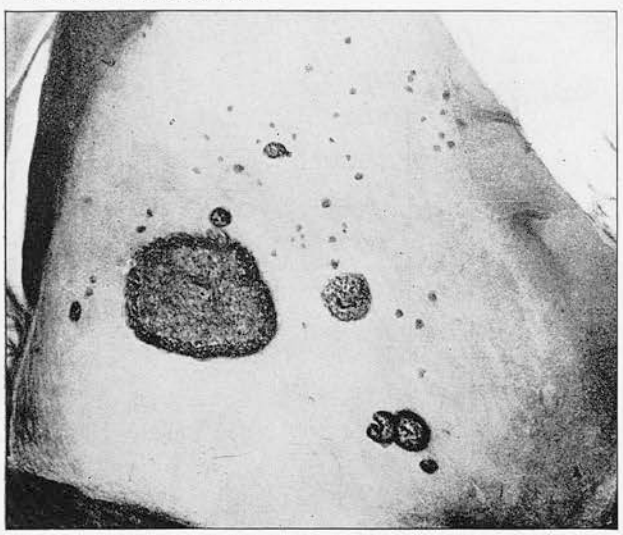

Fig. 37.—Rodent ulcer on right side of abdomen. From Mr. Hutchinson's collection at the Polyclinic.

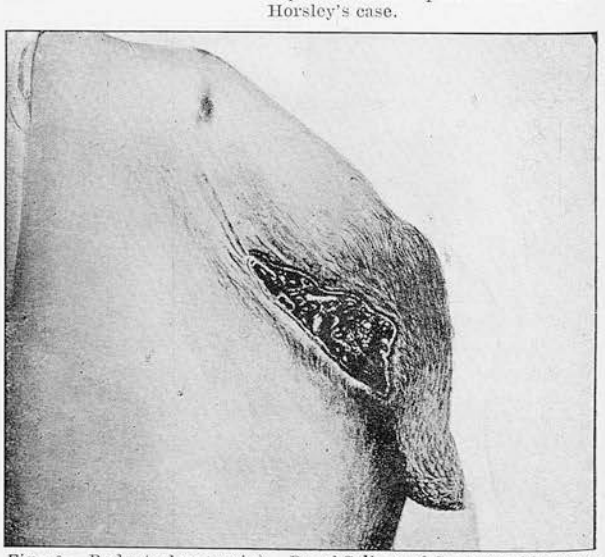

Fig. 38.—Rodent ulcer (groin). Royal College of Surgeons Museum.

present, which affects its incidence is probably either peripheral or a peripheral modification of central influence and not only segmental. The spread of rodent ulcer on the trunk, as it does on the head and face, appears on the whole to resemble the spread of scleroderma and leucoderma, and hence the spread as well as the incidence of rodent ulcer on the body is under a nervous influence which, if present, is peripheral.

Can this investigation throw any light upon the vexed question of the germ theory of cancer?

I have already pointed out that there are areas, around the mouth for instance, which are common to the spread of disease in processes known to be infective and of scleroderma, leucoderma and rodent ulcer. But there are others which are not common to them all, but only to leucoderma, scleroderma, and rodent ulcer.

Moreover, I have shown previously cases in which the spread of rodent ulcers has ceased in areas which had become denervated. And, finally, I cannot obtain sufficient evidence to support the idea that processes known to be purely infective are more liable to select those points of the skin at which nerves become cutaneous. However, on the whole, time is not ripe for a definite statement on this point, although the little evidence I have just given appears to me to oppose rather than support the theory that cancer may be entirely due to the effects of a micro-organism.

Finally, I have to thank Sir Victor Horsley, Dr. Sequeira, Captain Pinch of the London Polyclinic, Dr. Pusey of Chicago, Dr. Norman Walker, and Mr. Hall-Edwards for many pictures of rodent ulcers.