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LUPUS ERYTHEMATOSUS: A CLINICAL STUDY OF SEVENTY-ONE CASES.

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In presenting this communication upon a subject which has received so much attention as Lupus erythematosus we feel that we owe an explanation. We have recently had under observation, at the London Hospital, a very large number of patients suffering from this disease, and, realising that it is still one of the most obscure and difficult to explain, we feel that an analysis of the results of a systematic examination of so large a mass of material will be of value. It is obvious that much that is familiar to Dermatologists will be found in the following pages, but we have, we believe, new observations to record upon the condition of the urine in the more acute cases, and we give a detailed account of a case which proved fatal, and in which we were fortunately able to obtain an autopsy. We intended making a systematic examination of all our cases with tuberculin, but we were obliged to postpone this on account of the demands made upon the beds of the hospital for acute cases. We regret the omission the less, owing to the fact that

since we began our work the valuable paper of Dr. Walther Pick, of Prague, on the tuberculin reaction in Lupus erythematosus discoides has appeared.

1. Sex.—It is universally recognised that Lupus erythematosus is more common in the female than in the male, and the statement usually made is that two-thirds of the patients are females.[1] Of the seventy-one patients we have examined only eleven were males, the proportion being, therefore, 84·6 per cent. females and 15·4 per cent. males. We are unable to explain this difference.

2. Age.—We find that the disease commences early in life in a much larger proportion of cases than is commonly believed in this country. The following table gives the ages at which the disease began in our seventy-one cases :—

	Males.	Females.	Total.
Between the ages of 11 and 15 years . .	1	7	8
,, ,, 16 ,, 20 ,, . .	1	11	12
,, ,, 21 ,, 25 ,, . .	5	9	14
,, ,, 26 ,, 30 ,, . .	1	17	18
,, ,, 31 ,, 35 ,, . .	1	5	6
,, ,, 36 ,, 40 ,, . .	0	6	6
,, ,, 41 ,, 45 ,, . .	0	2	2
,, ,, 46 ,, 50 ,, . .	1	2	3
,, ,, 51 ,, 55 ,, . .	0	1	1
,, ,, 56 ,, 60 ,, . .	1	0	1
	11	60	71

Of the eight patients under sixteen two were 11 years old, one aged 12, two aged 13, two 14, and one 15 at the time of onset. With the exception of a boy in whom the disease started at the age of 11, all were females.

In the oldest case we have seen, the onset of the disease occurred at the age of 58. The patient was a male.

In sixty-two of the seventy-one cases the disease began before the thirty-first year, and in twenty-eight before the twenty-first year.

3. Varieties of the Disease.—Before entering upon the evidence of tuberculosis in our cases, or discussing other supposed etiological factors, it will be convenient to consider the varieties of the disease, because our observations show important differences in the two forms. We recognise that there are two great classes, "circumscribed or discoid" cases, and "disseminated" cases. In the "dis-

coid" variety there are a few isolated foci, which gradually extend and may produce lesions of large size. In the "disseminated" cases there are multiple small foci which, by coalescence, form large areas. In some cases, however, we have found it very difficult to determine the exact mode of development, and we think that it may be impossible to do so unless the disease is followed from its inception. We have eleven patients, all females, in whom we have satisfied ourselves that the disease developed as multiple small foci, cases in which the disease is very widely spread, and has run a rather acute course, and these we have classed as "disseminated." In some of them there have been acute outbreaks while the patients have been under observation. With one exception, the lesions have been of the erythematous type. In the fatal case, described later, the eruption developed with great rapidity, resembling, as do so many of these diffuse cases, an exanthem. We have not seen the severe type of the affection described by Kaposi.[2]

Two cases which we have included under the discoid or circumscribed variety presented the features which Dr. Crocker has described as "telangiectic" in the patches upon the cheeks, but upon the nose the disease was of the common form.

In two cases the lesions were unilateral, in one female patient remaining so for ten years, and in a male, for two years.

4. Tuberculosis in the Family.—There was a history of tuberculosis in the family in thirty-four cases, rather less than one-half. In thirteen instances brothers or sisters had died of phthisis, in eight the mother, and in four the father had died of phthisis. In nine cases there was consumption on the mother's side, and in six on the father's. In one case both families were affected.

As will be seen, tuberculosis was more common on the mother's side than on the father's.

It will be noted that we have only taken evidence of pulmonary tuberculosis, and, of course, even here we are obliged for the most part to rely upon the patient's or relative's history. We found so much difficulty in getting accurate information, and so many sources of possible error, that we have omitted statistics of glandular, bone or joint disease from this inquiry. The information that children of patients had died from meningitis was obtained in two cases, but here again it was impossible to eliminate non-tubercular disease.

In thirty-seven instances it was definitely stated that there was no consumption in the family, and this negative evidence is, we think, as valuable as the positive evidence recorded above. In the non-tubercular cases, we have the remarkable instance of two sisters in whom the disease started at the age of 26 years. Both of them have been under observation for some time, and their family history is well known to one of us. There has been no sign of tuberculosis in either of the patients, or in any member of the family.

5. Evidence of Tuberculosis in the Patient.—We are here upon surer ground, for we have not only examined all the patients ourselves, but in doubtful cases have had the advantage of the assistance of members of the staff of the London Hospital, to whom our best thanks are due. There was evidence of tuberculosis in eighteen cases.

Tubercular glands, or the scars of glandular abscesses, were found in one male and ten females. Tubercular disease of the hip-joint was present in one female aged 16 years.

Definite evidence of tuberculosis of the lungs was found in one male and seven females. In the fatal case, which is described later, we found a well-encapsuled nodule at the apex of one lung, over which the pleura was thickened and adherent. The nodule was the size of a pea, and there was no other sign of tuberculosis in the body.

There was no evidence of tuberculosis of the abdominal or renal organs in any of our patients.

The proportion of tuberculosis in all our cases is, therefore, just under 25 per cent.

Roth[3] found evidence of tubercle in 185 out of 250 collected cases.

Boeck[4] gives the proportion as 83 per cent. Kopp[5] found eighteen tubercular cases in thirty-eight, and Veiel[6] thirty-nine out of 119, figures which show remarkable variations.

6. The Relationship of Tuberculosis to the Variety of the Disease.—We find that the disseminated form of lupus erythematosus is associated with tuberculosis to a much greater degree than the discoid variety. In five of the eleven patients whom we have classed as suffering from this form of the disease, we found evidence of phthisis, and two of these have also strumous glands. In three

others the glands are affected, but there is no evidence of pulmonary disease. In three cases there was no sign of tuberculosis.

A history of phthisis in the family is present in eight out of ten of the disseminated cases. In the remaining instance the patient knows nothing of her family, her parents having died when she was very young.

As an instance of the severity of the disease which may be met with in association with tuberculosis, we may mention the case of a young woman, aged 28, admitted to the London Hospital in 1890. She was in an advanced stage of phthisis, and while in hospital developed a hæmorrhagic form of lupus erythematosus. There were large hæmorrhagic patches upon the cheeks, ears and also round the mouth. The case proved fatal, but unfortunately there was no autopsy. The condition is figured in the collection of drawings presented to the London Hospital Medical College by Dr. Stephen Mackenzie.

In our fatal case the sole tubercular lesion was a small calcareous nodule at the apex of one lung. Eight of Kaposi's fatal cases died from tuberculosis.

Of the sixty cases which we have classed as circumscribed or discoid, we found evidence of phthisis in three instances, and strumous glands or the scars of abscesses in seven. In one case there was tuberculous disease of the hip-joint.

Eighteen per cent., therefore, of the discoid cases were found to be associated with tuberculosis as observed clinically. In twenty-four instances, nearly 40 per cent., there was a history of tuberculosis in the family.

Dr. Walther Pick's observations upon the tuberculin reaction in cases of lupus erythematosus discoides[7] are of the highest importance in this connection. Eighteen of forty-three cases of this variety of the disease in Neisser's clinic at Breslau showed signs of tuberculosis. Twenty-nine cases were injected with tuberculin in doses from one-fourth to twenty milligrammes. With the larger doses a general tuberculin reaction was obtained in fifteen patients, but in all of them there was clinical evidence of tuberculosis, apart from the skin affection. In only one case there was a local reaction. Pick, therefore, concludes that we have no right to look upon lupus erythematosus discoides as a tubercular disease.

7. Acroasphyxia, Chilblains, &c.—A feeble circulation, livid, cold hands and the tendency to the formation of chilblains are known to be common in lupus erythematosus. Acroasphyxia was present in one male and six females. A history of the actual presence of chilblains was found in three males and nine females. We have been careful to eliminate from these numbers cases in which there were definite patches of lupus erythematosus on the extremities.

8. Other Diseases.—We obtained a history of scarlet fever in five cases, but there was no evidence to suggest a direct connection between the skin disease and the fever. In all the patients the fever had occurred long before the onset of the lupus erythematosus. As will be seen later, the relationship of the renal disease set up by the exanthem has to be considered in view of some of our observations.

In two cases there was a history of rheumatic fever. In one of these there was stenosis of the mitral valve, and this, in our opinion, led to a peculiar lividity of the skin lesions.

One woman, aged 53, with signs of phthisis, had also suffered from Graves' disease, which is now in abeyance.

9. Place of Onset.—In forty-seven of the sixty circumscribed cases we have information as to the place where the disease was first noticed. In eighteen instances it began upon the cheeks in what has been called the "flush" area. In fifteen the nose was first involved. In three cases the neighbourhood of the eye, in three the ears, and in three the scalp. In two the disease began as an oval patch in front of each ear, and has not spread on to the cheek. In one case the disease began and has remained limited to a ring round the mouth. In one case the forehead, and in another the chest, were involved first.

In the disseminated cases the face was the first part attacked.

10. Limitation of Areas.—We have many photographs of our patients, and have made diagrams of all of them, many of which show well the rapid extension of the areas in some of the more acute cases. The gradual enlargement of the spots in the discoid cases until a certain limit has been reached, and the involvement of identical areas by the coalescence of numerous small foci in the disseminated cases suggest an anatomical basis. Such an anatomical basis may be vascular or nervous. The areas, however, do not correspond with the distribution of the vessels, and we are, therefore, compelled to

explain them by the influence of vaso-motor nerves. As yet we do not know anything about the vaso-motor areas of the skin and we suggest that lupus erythematosus may be a clue to them. The remarkable limitation of the areas is not only seen upon the face, where it is most marked, but also upon the trunk, particularly upon the shoulders and the nape of the neck. We examined the Gasserian and spinal ganglia in our fatal case, but with negative results, our experience in this respect corresponding with that of Kaposi in 1882.

11. The Influence of Local Irritation.—In one of our disseminated cases the application of poultices to the abdomen for the relief of pain was followed by a crop of small patches of lupus erythematosus, the nature of the disease being confirmed by microscopical examination. In another of the same variety, the application of the Finsen treatment was followed by an increase in the size of the spots and the development of fresh spots at the margin of older lesions. In a discoid case we have seen definite increase in the size of the spots follow the light treatment. In another discoid case scratching started a fresh area. This experience is in accord with that of Mr. Malcolm Morris, who had a case in which a mosquito bite was the determining cause of the lesion,[8] and a case was reported by Whitehouse in which the application of a cantharides plaster was the exciting cause.

12. Albuminuria in Lupus erythematosus.—We have examined the urine on many occasions in twenty-seven cases, ten of the diffuse type, and seventeen of the discoid. We found albumen present in seven; five of these were disseminated cases, and the disease was in an active stage. In our fatal case the urine was loaded with albumen, and contained casts and blood. At the autopsy we found parenchymatous nephritis. In two other cases we found casts in small number. Of the seventeen discoid cases examined we detected albumen in two instances only. In one of these there was mitral stenosis, and we attributed the albuminuria to the cardiac lesion. The other case was a woman of middle age, whose urine was pale, of low specific gravity, and we believed, from the hypertrophy of the heart and the high tension pulse, that there was chronic interstitial nephritis.

Of the five disseminated cases with albuminuria two gave a history of scarlet fever, one of them being the fatal case above alluded to, but the kidney lesions found post-mortem appeared to be of recent origin.

We do not feel that we have enough cases to be dogmatic, but it is certainly significant that in half of the disseminated cases examined we found albumen in the urine, and especially where there was active disease, while in the discoid and more chronic form we found only two cases of albuminuria, one of which was explained by the cardiac lesion found and the other was a woman of middle age with granular kidney.

In four instances the urine passed was of low specific gravity whenever examined, but as we did not have the patients under observation in hospital we were unable to estimate the quantity passed and the proportion of solids, and, moreover, we could not eliminate the fallacies which might be introduced by taking tea, alcohol, &c., which might produce diuresis.

In connection with the fatal case in which we found nephritis, may be mentioned one of Dr. Brooke's, in which a similar condition was present. Here the patient had extensive tubercular abdominal disease, but the kidneys were free from tubercle. It is only right, however, to mention that Dr. Brooke looked upon the nephritis as a coincidence.[9]

13. Notes of a Fatal Case.—Grace C., a folder of note-paper and envelopes, came to the Skin Department of the London Hospital on February the 20th, 1902, suffering from Lupus erythematosus. The patient was eighteen years old. Her father and mother are alive and well, and she has one brother and one sister in good health. Her maternal grandmother died from phthisis. The patient suffered from measles and whooping cough in early childhood, and when twelve years old she had scarlet fever. The attack was said to be mild, and she was discharged from the fever hospital at the end of six weeks. When she was sixteen she is said to have had an attack of "rheumatism," but her general health was good until October, 1901.

A red spot, however, had been noticed upon her nose in the latter part of 1900, and in October, 1901, a small scaly patch appeared upon the left cheek, and in the course of a month the eruption had extended over a large part of the face. At the time the patient stated that she felt ill, but there were no special symptoms. New patches continued to appear, the scalp, trunk, and hands being involved as well as the face. In February, 1902, the patient began to complain of headache, and also of abdominal pain which was said to be of a

"colicky" character sometimes, and at others as if the abdominal wall were being stretched. There was swelling of the legs, and blood was passed in the urine. Early in March the patient was admitted into the hospital.

On admission, the skin of the face below the orbits was the seat of an erythematous eruption, which involved the upper part of the nose and extended in two triangular areas upon each cheek, but more so upon the left side than upon the right. On the left side also the lower part of the cheek and the adjacent part of the chin were affected, while the corresponding areas on the right side were free. The circumoral ring was quite pale. On the upper eyelid on the right side there was a small patch about half an inch across, and upon the eyebrows and the lower part of the forehead there were several small circular spots. The margin of the lobule of the left ear was involved, and there were oval patches in the sulcus behind each ear. All the patches were of a dull red colour, they were covered with fine brownish scales, and were slightly raised. Near the centre of the triangular areas on the cheeks—the oldest lesions—there was evident atrophy of the skin.

The neck was quite free, but over each clavicle there were several small circular spots from a quarter to half an inch in diameter. Two isolated spots of rather larger size, one over the sternum opposite the third right intercostal space, and one near the inner side of the left nipple, were the only parts of the integument of thorax affected. On the lower abdomen in the eleventh dorsal area there was a crop of small spots, and these formed a definite band upon the left side. This band appeared after the application of a poultice for the relief of pain on February the 27th. On the back there were symmetrical circular small spots on each side of the spine, extending from the level of the *vertebra prominens* to the seventh dorsal spine. Just below the angle of the left scapula, there was a crop of small spots similar to those upon the abdomen.

The hands were free, but there were numerous characteristic spots upon the dorsal surface of the fingers upon both sides. The feet and toes were free.*

At the autopsy we found a patch upon the right labium majus.

* The patient was in the condition described when she was shown at the March Meeting of the Dermatological Society of London.

Elsewhere the skin was anæmic, and there was œdema of the lower extremities.

The patient complained of dyspnœa upon exertion ; the respirations were twenty-eight per minute. The movement of the upper part of the chest on the left side was impaired, and there was dulness upon percussion at the left apex posteriorly. There were no abnormal sounds at the apices, but a few moist râles were audible at both bases posteriorly.

The pulse was sixty-six per minute, and its tension was slightly raised.

The cardiac impulse was felt just outside the left nipple line. The second sound was accentuated over the aortic area, but there were no bruits.

The patient complained of abdominal pain, and a sensation as if the abdominal wall were being stretched. There was no enlargement of the liver and spleen.

The optic fundi were normal.

Menstruation commenced at the age of 15, the periods occurring about every five weeks. For some months there had been amenorrhœa. The patient complained of some difficulty in micturition. The quantity of urine passed was 46 ounces per diem. The urine was of a smoky colour, its reaction acid, and the specific gravity 1·020 There was one-tenth albumen upon boiling, and there were blood and granular and hyaline casts in the deposit.

On admission to hospital the temperature was normal.

The patient was obviously very ill when admitted, and she gradually got worse. More spots appeared. A peculiar oblong patch developed upon the upper lip on March the 17th, and also fresh spots upon the forehead. The condition at this time is well shown in the accompanying photograph.

On the 20th of March the patient vomited, and the temperature rose to 104°. She complained of pain in the left side, and fluid was later found in the left pleural cavity. On the 28th she was much worse. The back was now œdematous, and there was a little fluid in the abdominal cavity. Eight ounces of semi-purulent fluid were withdrawn from the left pleura. This fluid was submitted to Dr. Bulloch, who found pneumococci. The quantity of urine fell to 12 ounces in the twenty-four hours. It was loaded with albumen,

and contained blood, hyaline and granular casts. Fresh spots continued to appear upon the skin until near the end, but the patches became of a paler colour.

On the 30th of March there was a sudden attack of breathlessness, but the pulse remained good. The patient complained of pain in the chest, and died with severe dyspnœa.

The autopsy was performed forty hours after death, but as the body had been kept at the freezing temperature decomposition had not set in. The skin eruption was of a pale brown colour. A small patch was found on the right labium majus.

The left pleura contained a quantity of thick creamy lymph, but no free fluid. The lower lobe of the left lung was in a condition of red hepatisation. At the lower extremity of the right lower lobe there was a wedged shaped infarction, over which there was some recent pleurisy. There was a small calcareous nodule at the left apex, and over this the pleura was thickened and adherent to the chest wall. There was no active tubercle in the lungs. The ary-epiglottic folds were œdematous. The pericardium contained a slight excess of fluid, but there was no pericarditis and no adhesions. The heart weighed 11 ounces. The right ventricle was filled with antemortem clot. The valves were healthy, but there were several minute patches of atheroma at the root of the aorta.

The abdomen contained a slight excess of fluid. The spleen, which weighed $5\frac{1}{2}$ ounces, was healthy, the liver weighed 49 ounces, and showed no abnormality.

The right kidney weighed $10\frac{1}{2}$ ounces, and the left $12\frac{1}{2}$ ounces. Both were in a condition of parenchymatous inflammation. The capsule peeled readily, and the stellate veins were marked. The pyramids were congested, but the cortex was swollen and pale. The microscope showed a condition of glomerulo-tubular nephritis, of a fairly acute type, with slight increase in the connective tissue. The condition was not compatible with a nephritis of long standing, such as would have been found had the affection dated back to the scarlet fever six years before.

The brain and spinal cord were examined, but no naked eye abnormality was found. Both Gasserian ganglia and several of the spinal ganglia were removed and examined with Nissl's and other

stains, but no changes of importance were found. Dr. Head kindly saw the sections and confirmed our observations.

The portions of skin removed showed in the acute patches extensive perivascular infiltration, with a great number of mast-cells. In some there was evident thickening of the epidermis, but no evidence that the sebaceous glands were the seat of the disease.

Conclusions.—The inflammatory nature of the lesions in Lupus erythematosus and their symmetrical distribution suggest a circulating poison or poisons. The hypothesis that the circulating toxine is of tubercular origin in all cases does not appear to be adequate. We found that the two varieties of the disease exhibit striking differences in their relationship to tuberculosis. The discoid form was associated with tuberculosis in 18 per cent., and there was a history of tuberculosis in the family in about 40 per cent. We are, therefore, inclined to agree with W. Pick's statement that we have no right to say that Lupus erythematosus discoides is a tubercular affection.

On the other hand, we found that the disseminated form was associated with the presence of tubercular disease in 70 per cent. of our patients, and that there was a history of tuberculosis in the family in 80 per cent. The more severe forms of the disease appear to be constantly associated with tuberculosis, although in our own fatal case the lesion was obsolete and limited in extent. There is, therefore, strong evidence in favour of Lupus erythematosus disseminatus being of tubercular origin, or, that the presence of tuberculosis modifies the course of the disease and intensifies it. The fact that Lupus erythematosus is very rarely seen in our great consumption hospitals is perhaps not sufficiently recognised. If the disease were solely due to the circulation of toxines of tubercular origin, we ought certainly to find it frequently in institutions where so large a number of patients suffering from tubercular disease come under observation.

The presence of albumen in the urine in a large proportion of the disseminated cases and particularly in those in which the disease was active may be explained in two ways. We know that circulating toxines in the exanthemata and other diseases are excreted by the kidneys, and that they commonly set up nephritis. In the more active forms of lupus erythematosus, in those, in fact, in which we

may assume that there is a greater toxicity, we found albuminuria, which we believe to be of toxic origin. The other explanation is that the kidneys being diseased previously prevent the excretion of toxines, in themselves incapable of causing renal changes, and that their retention in the blood is the cause of a more active form of the cutaneous disease. We are inclined to the former opinion, as we found no reason in some of our cases to suppose that there had been pre-existing albuminuria, and, moreover, the albuminuria was associated with the disseminated form of the disease especially of the exanthematic type.

The situation of the lesions appeared to be determined by (1) nervous influence. The peculiar limitation of the areas affected affords strong support to the angio-neurotic theory of the disease. We found, however, no characteristic changes in the nervous system in our fatal case. (2) A feeble circulation also seems to be a factor, as shown by the frequent association of acroasphyxia and allied conditions, including Raynaud's disease, as in a case of Dr. Pringle's.[10] (3) Local irritation cannot be overlooked as a determining factor, as shown by the appearance of the lesions after the application of poultices, of a cantharides blister, from the irritation produced by the chemical rays of light, and by the bite of a mosquito.

We gratefully acknowledge the assistance so generously given to us in our work by Dr. Stephen Mackenzie. We not only had the benefit of his advice and experience in many points but the abundant resources of the Skin Department of the London Hospital were placed at our disposal for the purposes of this inquiry.

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