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THE RELATIONSHIP OF LUPUS ERYTHEMATOSUS AND ERYTHEMA MULTIFORME, WITH AN ILLUSTRATIVE CASE.

BY JAMES GALLOWAY AND J. M. H. MACLEOD.

THE case which forms the basis of this contribution is one of unusual interest at the present time, when the nature of Lupus erythematosus is under discussion, and its relation to tuberculosis on the one hand and to Erythema multiforme on the other is being debated. The patient whose case is about to be described presented lesions on the face and hands which were of such a nature as to form a connecting link between a circinate Erythema multiforme and acute Lupus erythematosus, lesions on the fingers suggesting "folliclis," and lesions characteristic of Erythema induratum on the legs.

DESCRIPTION OF THE CASE.

The patient, Beatrice S—, aged 27 years, first came under our observation in the out-patient skin-department at Charing Cross Hospital in August, 1906.

She was a somewhat delicate-looking woman who led the sedentary life of a dressmaker. Her father was alive, and was said to be healthy. Her mother was also living but was not in good health, the nature of her illness being unknown. The patient was the sixth of a family of eight, and the others were healthy. There was no history of tuberculosis in the family or the immediate antecedents.

The patient had enjoyed excellent health till four years before she

came to the hospital, when she accidentally discovered the first traces of Bazin's disease in the form of one or two nodules on the front of the left leg. They seemed to be situated just below the skin over the tibia. These nodules were painful after the patient had been standing, and finally the pain became so considerable as to prevent her walking. The pains were not continuous; they were shooting in character, but were not of the severe type which suggests involvement of the bone, and did not prevent sleep at night. The skin over these nodules gradually became red, forming erythematous patches, oval in shape, and of about an inch in the long diameter; as the erythema made its appearance the pain decreased. These patches were still obvious, though they had diminished in brightness and in size. There was neither ulceration nor discharge of pus from these lesions; a coarse desquamation followed the erythema. Following the appearance of the two nodules noted, several smaller lesions appeared on both legs, and passed through a somewhat similar course of development.

Fourteen months before coming to the hospital a red nodule the size of a split-pea developed on the ulnar side of the back of the right hand. Several others of similar character made their appearance shortly afterwards on both hands. At length these nodules showed themselves on the fingers, and became reddened in colour and surrounded with a good deal of erythema. On one occasion one or two of the nodules suppurated, and after poulticing a certain amount of pus was discharged. The suppurative lesions healed entirely, but the others persisted.

The lesions on the face appeared in 1905, at about the same time as the affection of the hands. The patient described herself as having been in fairly good health during the whole of this period, the condition of her skin causing her comparatively slight discomfort and annoyance. She had suffered, however, for as long as she could remember from a weak peripheral circulation, which manifested itself in cyanosed and clammy hands, cold feet, and a marked tendency to chilblains.

In October, 1906, the patient was exhibited at the Dermatological Society of London (*vide Brit. Journ. Derm.*, 1906, vol. xviii, p. 406), when the following notes were made: A number of lesions of Bazin's disease, in various stages of evolution, from deep-seated nodules to

depressed pigmented scars, were present on the calves of the legs. In addition to the lesions on the legs there was on the face an actively spreading eruption of erythematous, scar-leaving patches, of the nature of Lupus erythematosus. These patches were observed around the eyes, on both cheeks, near the angles of the jaws, and on the sides of the neck. The lesions on the neck were recent, and presented a wavy, raised border. The fingers were also affected, especially those of the left hand, where there were several persistent, congested patches, of a purplish tint, and a number of small white atrophic scars.

A physical examination was made of the patient about this time, which failed to reveal any definite physical defect in the chest. She was given a course of cod-liver oil and malt and various soothing applications for the skin, and told to take every advantage of the fresh air in the country where she lived. In spite of living in the country and the treatment the disease went on spreading, and as new lesions kept appearing on the hands and face it was decided to admit her into hospital, which was done on October 25th, 1906.

A general examination was made on her admission, and it was at first noticed that she appeared to be sound in every respect except for the skin-affection; an exception was subsequently taken to this note, as will be mentioned, on a more careful examination.

The patient was kept in bed after admission for some days, and was quite comfortable and appeared to be fairly healthy. The skin-lesions especially gave her less discomfort, and the temperature, pulse, and respiration records were all perfectly normal.

A few days after admission the following notes were made as a result of more critical examination:

Condition of skin.—*Face*: "Situating symmetrically on both sides, involving mainly the skin in front and behind the angle of the lower jaw, extending over the cheek in front and back to the lateral line of the neck were ringed and circinate erythematous patches. The erythematous areas of skin were slightly thickened, presenting closely in appearance those of chronic Erythema (multiforme) exudativum. Interspersed among the erythematous patches on both cheeks were small, ringed areas, about half an inch in diameter, where the skin was atrophic, nearly scar-like. The patient stated that these atrophic patches had appeared at points which discharged and

which she had poulticed last March (1906). In addition to the general areas involved there were small, outlying, erythematous lesions both on the face and neck.

"The whole of this condition dated from December, 1905."

Hands : Both hands were involved, nearly symmetrically, but the right was more seriously affected than the left. The lesions consisted of erythematous areas which tended to atrophy and became more severe towards the tips of the fingers. Interspersed among these areas of erythema were small nodular lesions, but these occurred also where the skin appeared to be normal. They appeared to produce points of atrophy about one eighth to a quarter of an inch in diameter, and resembled the lesions described as "folliclis." Actual necrosis had occurred at the tip of the left little and ring finger and the right little finger and thumb.

The whole of this condition dated back to August, 1905.

Legs.—Left : There were small lesions resembling those of the hands at the extremities of the fifth and fourth toes. The leg presented six areas where the skin and subcutaneous tissue had been affected. The colour of these lesions was bluish-red, and their shape rounded. The surface tended to desquamate, but there appeared to have been actual ulceration of one on the front of the shin. At the back of the leg near the centre of the calf several nodules had coalesced, forming an irregular indurated area.

Right : The toes were unaffected. The leg showed a few pigmented scars, with small thickened skin-eruptions on the posterior surfaces at about the junction of the middle and lower thirds of the leg. The affection of the lower extremities dated back to 1902.

Back.—Between the shoulder-blades was an area showing a papular and circinate seborrheic eruption quite different in type from that already described.

The scalp also presented in a mild degree the signs of seborrheic dermatitis.

The examination carried out on the admission of the patient appeared to show that she was not only well-nourished but was in good health, with the exception of the skin-lesions described. On account, however, of the importance of the case, especially the possible relationship of the skin-affection to internal conditions, a critical physical examination was carried out.

No signs of disease of the internal organs were discovered with the exception to be noted. It is especially important to observe that the blood, on repeated examination, was normal in its characters, and in view of the relation of erythematous lesions to diseases of the kidney it is noteworthy that no abnormal constituent was found in the urine during her residence in the hospital.

Condition of the lungs.—On her admission attention was drawn to the condition of the upper part of the right lung. Careful examination now showed that the air-entrance at the right apex was not perfect, and that in addition there appeared to be slightly deficient resonance as compared with the left side. These signs were so slight that some doubt was expressed as to their significance. The patient had never given any history of lung disease, no symptoms were described, and during her residence in the hospital there was no rise of temperature, no cough, no expectoration, nor any of the ordinary signs of chronic pulmonary affection. Nevertheless, the comparative inefficiency of the lung at the apex of the right upper lobe was repeatedly noted. Thus on November 9th there was a note to the effect that "the normal breath sounds were imperfect at the right apex in front, to a less extent below the clavicle; behind they were diminished in vigour as far as the fifth rib. There was slight comparative dulness at the right apex in front and behind." A note to the same effect was entered on November 19th.

The progress of the patient while in bed was satisfactory. She was comfortable, improved in general condition, and the skin-lesions in the face and extremities faded in colour. The seborrhoeic dermatitis at the back had vanished as a result of mild sulphur treatment by November 6th. In spite, however, of the general improvement of the skin-lesions, occasional fresh erythematous patches appeared.

On November 15th, two small patches about the size of threepenny-pieces made their appearance immediately beneath the right eye.

Appreciating the importance of a correct diagnosis in the case, and in view of the discussion as to the ætiology of the skin-lesions of the type described, it was determined to give the patient a diagnostic injection of tuberculin.

On November 22nd $\frac{1}{1000}$ c.c. of the old tuberculin was injected subcutaneously in the left flank at 2 p.m. At 4 o'clock the temperature rose to 100° F., at 6 o'clock to 102° F., at 9 o'clock to 103° F.

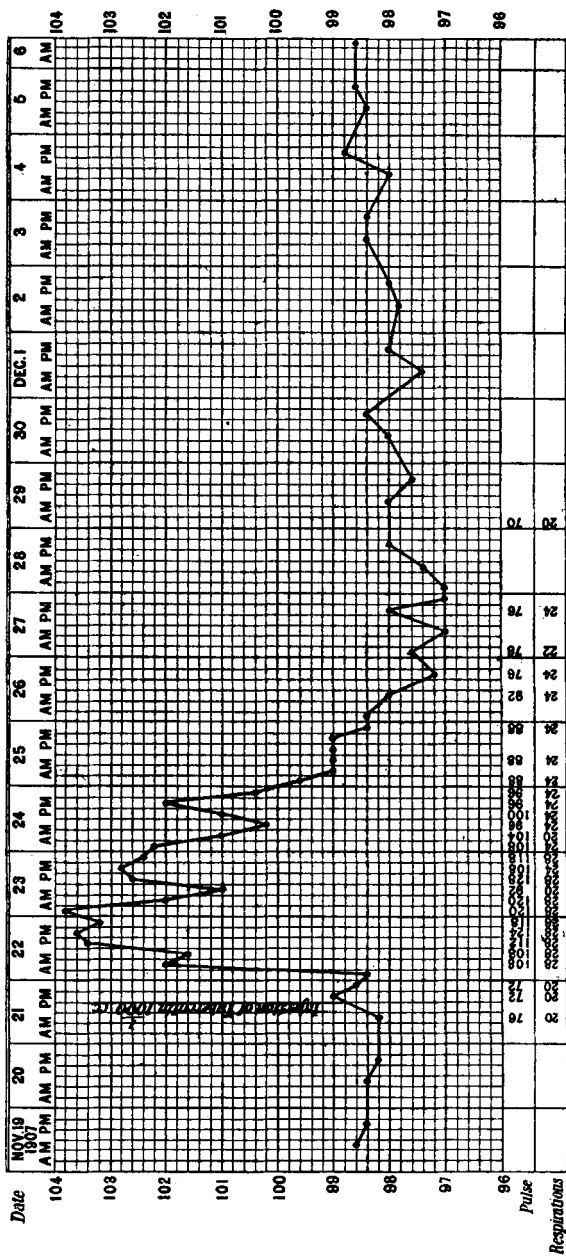


Chart showing the febrile attack due to the injection of tuberculin.

The course of the pyrexial attack is indicated on the appended chart.

The patient felt out of sorts during the attack of fever, but not seriously ill. Shortly after the injection many of the subcutaneous lymph-glands were noted to be enlarged—for instance, in both axillæ, beneath the chin, in the left popliteal space and the left inguinal region. An attack of Herpes labialis also developed.

The condition of the lungs was carefully watched throughout the febrile reaction and afterwards, but it was satisfactory to report that no new physical signs had developed. The indications in the lungs were of the same indefinite character as those already noted immediately after the attack, and also when she left the hospital, ten days after the temperature had definitely fallen. During the residence of the patient in the hospital a gradual improvement of the erythematous lesions was observed; this, however, was not more than could be safely attributed to the fact that she was living indoors and had not been exposed to cold. The patient left the hospital on December 6th in good health and much improved in her appearance, but still presenting evidences of the various cutaneous lesions.

GENERAL DISCUSSION ON THE CASE WITH REFERENCE TO THE LITERATURE ON THE SUBJECT.

The record of this case is given fully as an observation to be added to our knowledge on the subject of erythematous eruptions of the type of Lupus erythematosus. There can be no longer any doubt that symmetrical erythematous eruptions, sometimes exceedingly acute and at other times of a slowly progressive and chronic nature, but in both instances producing destruction and atrophy of the skin, have been observed in relationship with certain visceral disorders. Disease of the kidneys has, perhaps, more frequently been associated with the acute forms of this disorder than disease of any of the other viscera. Cirrhotic disease of the liver, however, has been observed in close association with the more chronic type. There remains the large group known as "Lupus erythematosus," concerning the ætiology of which there is still much doubt and room for investigation. It is now an old suggestion that Lupus erythematosus is in some way or other associated closely with tuberculosis. The great difficulty in establishing even a clinical relationship between these two conditions has served

to throw much doubt on any relationship whatever between Lupus erythematosus and tuberculosis. It is perhaps unwise to draw the conclusion that there is nothing but a casual relationship between these two diseases, and it is as a guide in the discussion of this subject that the observation just given is recorded. In the case of this patient an eruption presented itself with all the characteristics of the milder variety of disseminated Lupus erythematosus; in addition, on the lower extremities there were lesions, which should certainly be classified under the heading Erythema induratum scrofulosorum (Bazin's disease). Careful examination of the lungs in the first instance failed to give evidence of any defect whatever. It was only when under favourable circumstances, and when a careful and critical examination of the lungs was enabled to be carried out, that the very slight defect in respiration was noted, yet the injection of tuberculin in small doses produced a very sharp and definite reaction.

A study of the recent literature on the subject of the relation of Lupus erythematosus to tuberculosis seems to show that the view that certain cases of Lupus erythematosus are in some way connected when the presence of the tubercular toxin is rather gaining than losing ground, and especially among our French colleagues. Boeck (1) of Christiania, was among the first to insist on the tuberculous origin of the disease, and since then numerous distinguished writers have supported his contention, such as Besnier, Hallopeau, Pautrier, and Brocq. Various arguments have been put forward for and against this theory. It has been said that in the majority of cases of Lupus erythematosus there is either a personal or a close hereditary history of tuberculosis, and a mass of statistics have been collected to establish this statement. Pautrier (2) quotes 35 cases of Lupus erythematosus of which only 3 were free of a personal or hereditary tubercular taint. Brocq obtained a tubercular history in three quarters of his cases. Sequeira and Balean (3) elicited a family history of phthisis in 34 out of 71 cases, and found evidences of tuberculosis in the patient in 18 of the cases; they also noted that the disseminated form of Lupus erythematosus was associated with tuberculosis to a greater extent than the discoid type. Out of 250 cases collected by Roth (4) 185 were tuberculous. Walther Pick (5) found that out of 43 cases at the Breslau clinic, only 18 gave evidence of tuberculosis, and Gunsett (6) gave the proportion of 9 cases with tuber-

culosis out of 19 examined. Statistics of this sort, however, showing such a large variation cannot be regarded as conclusive evidence. It is possible in this connection that in several of the cases where there were no obvious tubercular manifestations some latent focus might have been present which would have been revealed had the patient been given an injection of the old tuberculin. In our case, for example, had the patient not been admitted to the hospital and injected the fact that she was tubercular might have been missed.

Another argument which has been used by the advocates of the tubercular theory is that the clinical appearance of the lesions of Lupus erythematosus may closely simulate those of Lupus vulgaris. This is only true, however, in cases of Lupus vulgaris of the superficial type described by Leloir as Lupus érythématoïde, but the course of such lesions, the fact that they leave a brown staining on pressure with a diascopé, and their histological characteristics show that their resemblance to Lupus erythematosus is a superficial one.

Another point in favour of the tuberculous origin of Lupus erythematosus which has been brought forward, and one which is borne out by our case, is the fact that Lupus erythematosus may occur in association with various types of skin-affection at present classed as tuberculides, such as folliculitis, Lichen scrofulosorum, and Erythema induratum. This point is still further strengthened, since it is admitted by different observers that Erythema induratum is more than a toxi-tuberculide, and is a tuberculous manifestation, possibly due to emboli of tubercle bacilli and endo-phlebitis of the affected region. Positive inoculations in susceptible animals have been obtained from the lesions of Erythema induratum by Thibierge and Ravaut (7) and Colcott Fox (8), and the lesions have been found to react locally to tuberculin injected (Jadassohn [9]), and in a case of Erythema induratum in which an ophthalmo-tuberculin reaction occurred the patient stated that the local lesions became more painful and appeared to be more inflamed (MacLeod [10]). In the case of the papulo-necrotic tuberculide ("folliculitis") also some doubt has been cast on the propriety of regarding the condition as a tuberculide, since inoculations in two cases have given positive results (Leiner and Spieler [11]), and a lesion excised from one of the cases showed a typically tubercular architecture.

But there are just as convincing arguments on the other side, and the

most important of these are the facts that tubercle bacilli have never been found in the lesions, that inoculation experiments on the lower animals have been invariably unsuccessful, and that the lesions do not, as a rule, react locally to tuberculin injection. These show that if the lesions are connected with tuberculosis they are not due to the presence of the tubercle bacilli in the skin, and must be caused by toxins from bacilli at a distance from the skin; in other words, that the lesions can only be "toxi-tuberculides" in Darier's sense of the term. But against this there is the fact that even in the showing of those who advocate the tubercular nature of the disease, in the larger proportion of the cases no traces of tuberculosis were discovered in the patients or in their families. In various cases also in which patients suffering from Lupus erythematosus have died from some intercurrent disease and in which post-mortem examinations have been made, no trace of tuberculosis could be discovered in the internal organs which might have been the focus of the toxin. Kren (12) recently reported such a case in detail.

There is another argument against the tuberculous theory, and that is that so far we are not aware of an eruption of Lupus erythematosus having been caused by the injection of tuberculin for diagnostic purposes, whereas in the case of Lichen scrofulosorum an outbreak has on several occasions been reported as the result of an injection.

From these various observations the obvious conclusion is that certain cases of Lupus erythematosus, both of the disseminated and the discoid type, are independent of the tubercular toxin, and in the cases where there were definite signs of tuberculosis the possibility that some other toxin than the tubercular toxin may be responsible is not precluded.

In the majority of cases in our experience no association with tuberculosis could be detected, and considering the prevalence of tuberculosis it is to be expected that Lupus erythematosus might occur in a tuberculous subject in a certain proportion of cases, but there is insufficient proof that the association is more than a casual coincidence.

The close relation which exists between Lupus erythematosus, especially noticeable in the acute forms of the disease, and Erythema multiforme has been from time to time insisted upon. This view we have already discussed in a paper in this journal entitled "Erythema

multiforme and Lupus erythematosus: their relationship to General Toxæmia" (13). Wilfrid Ward (14) has also published observations which seem to indicate that the absorption of pyogenetic toxins may result in one of the forms of toxæmia concerned in the production of Lupus erythematosus.

It seemed to us that it might be of some service in settling this question if a histological examination were made from typical cases of Lupus erythematosus and Erythema multiforme and the results compared.

COMPARISON BETWEEN THE HISTOLOGICAL CHARACTERISTICS OF ERYTHEMA MULTIFORME AND LUPUS ERYTHEMATOSUS.

With the object of comparing the histology of Erythema multiforme exudativum and Lupus erythematosus, a number of sections from two cases of Erythema multiforme, one of a lesion of the iris-vesicular type, the other of a red raised patch, were studied and compared with sections from a discoid patch of Lupus erythematosus excised from the face.

The histological appearances in the sections from the two cases of Erythema multiforme may be briefly summarised as follows: Marked changes were present in the epidermis and the superficial layers of the corium such as occur in an acute inflammatory process.

The blood capillaries of the papillary and sub-papillary layers were dilated, but their structure was well maintained. A serous exudation had occurred from them which rendered the collagen in that region œdematous and distended the tissue spaces. The œdema was so marked immediately below the epidermis that it had flattened the papillary layer and made it almost vesicular in places. Around the vessels there was inflammatory cellular infiltration, consisting chiefly of mononuclear cells with a small proportion of polynuclear leucocytes. Some of the mononuclear cells were spindle-shaped and were organising. There was an occasional mast-cell, but no plasma-cells were detected. The cellular infiltration was also collected around the vessel of the sweat-coil.

In the epidermis the basal layer was blurred owing to the presence of the sub-epithelial œdema and the cellular infiltration. There was marked œdema of the epidermis also. The inter-epithelial lymphatics

of the prickle-cell layer were widened, and to such an extent in places that the inter-epithelial fibrils had been broken and a vesicle formed. The prickle-cells were also œdematous, some of them having their spongioplasm distended with fluid and giving rise to the condition known as "reticulation," others having lost their fibrillary connections and lying free at the margin of the vesicle as swollen homogeneous cells—the "balloon-cells" of Unna. Where the œdema was not excessive the granular layer was defective and cornification interfered with, and there was slight scaliness of the surface. In one portion of a vesicle a number of cocci had gained entrance from the surface, and their presence was associated with numerous pus-cells and leucocytic *débris*.

These changes, both in the corium and the epidermis, were evidences of an acute inflammatory condition of the skin, which suggested as a cause a toxin reaching the skin *via* the blood-vessels.

The histological appearances of the sections of Lupus erythematosus discoides were briefly as follows: The epidermis and the corium were both involved. In the corium the blood-vessels of the papillary and sub-papillary layers were affected. Some were dilated and surrounded by a dense cellular infiltration, others were so packed with cells as to suggest a thrombus; in a certain number of them the endothelium of the vessel-wall seemed to have disintegrated in places, and the capillary was only indicated by a space in a cellular focus. The upper parts of the pars reticularis and the papillary layer were œdematous in places, but not to the same extent as in the sections of Erythema multiforme. The collagen in the papillary layer had become rarefied and was broken up in places, and the elastic tissue was also defective, this being especially the case where the cellular infiltration was densest. The cells were grouped chiefly about the capillaries of the papillary and sub-papillary layers and around the sweat-glands and pilo-sebaceous follicles. These cells consisted of mononuclear cells, some round, others spindle-shaped, a few polynuclear leucocytes, which were irregular in shape and breaking up, a certain number of mast-cells, and here and there groups of plasma-cells. The epidermis was not markedly œdematous. In places proliferation of the prickle-cell layer had taken place. There was also a tendency to hyperkeratosis, chiefly noticeable at the mouth of the hair-follicles, where horny plugs were formed.

Where the underlying capillaries were much dilated and the œdema had spread up into the epidermis the granular layer was defective and imperfect cornification had resulted.

The type of infiltration in the corium, the condition of the fibrous bundles, the marked dilatation of the blood-vessels, and degeneration and obliteration in places of their walls, and the acanthosis and hyperkeratosis in the epidermis, were evidences of an inflammatory process which was not so acute in character as that in the Erythema multiforme but was acting over a longer period. They suggested the presence of some form of toxin or irritant acting in a situation where the vaso-motor control was feeble, so that the toxin did not set up an acute inflammation but collected where there was a certain degree of vascular stasis.

A comparison of the two sets of sections leads to the conclusion that, histologically at all events, the differences between the two were more of degree than of kind; and that whereas in the one case there was a virulent toxin acting on the skin in situations where the circulation was fairly good, in the other a less virulent toxin was acting for a longer period in situations where, for anatomical or other reasons, the circulation was feeble and caused a mild or chronic inflammatory disturbance followed by an imperfect repair and resulting in atrophy.

Brocq (15) has recently described Lupus erythematosus as a peculiar type of reaction of the skin in certain individuals which may be called forth by a variety of causes such as the tubercular toxin, uterine disturbances, digestive troubles, nerve troubles, atmospheric conditions, etc. This individual peculiarity or idiosyncrasy of the skin seems to us to play an important part in the etiology of the disease. Its exact nature is uncertain, but it might possibly be the vaso-motor instability of a feeble peripheral circulation. In our patient there were marked evidences of a feeble peripheral circulation, and Lupus erythematosus has been in numerous instances shown to be connected with circulatory disturbances, such as chilblains (West [16], Perry [17], Adamson [18]) and Raynaud's disease (Pringle [19]).

In *conclusion* we consider: (1) That certain cases of Lupus erythematosus and certain types of Erythema multiforme are so closely related that they may be regarded as the ends of a chain, in which all transitional stages may be encountered.

(2) That they are both due to toxins of various sorts and of different degrees of virulence.

(3) That in Erythema multiforme we have a virulent toxin acting on an individual with a comparatively healthy circulation; whereas in Lupus erythematosus the toxin is less virulent and acts on an individual with a defective peripheral circulation, and tends to affect situations where, from anatomical reasons, the circulation is accomplished with difficulty.

(4) That in the case of Erythema multiforme the reaction is acute and transient, while in Lupus erythematosus it is prolonged, and as it occurs on a tissue with a defective circulation it leads to destructive changes and atrophy.

(5) That the exact nature of the toxin or toxins which are directly responsible for such cases is still uncertain.

(6) That the above conclusions only refer to certain cases of Lupus erythematosus, and that there are others which probably result from external causes.

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