most part, in the "larval" rather than in the "compensated" phase of latent tuberculosis. This is a situation which is likely to reproduce itself in the more recently occupied parts of Africa as well as in other countries where hitherto isolated communities are being brought into increasing contact with European civilization. It would be well if industrialists in such countries studied the methods of prevention arrived at, through long experience, by the Johannesburg Chamber of Mines.

The importance of a correct appreciation of the factors underlying the phenomena of tuberculosis in "virgin soil—and after" is not, then, confined to the management of children and adolescents in this country, but has a wide bearing upon the future of industrial populations in our dominions, colonies, and dependencies.

I hope that the suggestions here set forth, but for which no originality is claimed, may serve to stimulate further thought and further investigation into some of the basic problems of our most formidable bacterial disease.

THE RADIATIONAL TREATMENT OF CORNEAL ULCERS.

BY

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In a previous paper in this *Journal*¹ a preliminary account was given of the application of ultra-violet light to ophthalmological diseases. Subsequent experience, extending to well over a thousand cases, has wholly confirmed the opinion then tentatively put forward; but the results of radiational treatment applied locally to ulcerative conditions of the cornea merit a separate and more detailed account.

The action of ultra-violet light is primarily abiotic—that is, destructive. The most obvious effect produced in the radiation of a cell is the photochemical denaturation and subsequent coagulation of its proteins. This, with other reactions, involves the production of a certain amount of trauma, which may lead to the partial or complete destruction of the cell, an effect which is now well recognized in the desquamation of the outermost layers of the skin after radiation. In the tissues of the eye a precisely similar reaction takes place; with small intensities of radiation the cells are injured, with great intensities they are destroyed. It is this end, under proper control, which is desired in the treatment of ulcers of the cornea, and the active response which the traumatism of light evokes repairs, and more than repairs, the damage which is done.

Histological studies carried out on the cornea of rabbits² which were subjected to radiation with ultra-violet light in doses considerably above those which may be used clinically, show no observable change after radiation until four hours have elapsed, when, in both the superficial and basal cells of the epithelium, some spacing out and oedema are evident. The nuclei of some of the more superficial cells then show the presence of acidophil granules, which take on a sharply defined eosin stain. After six hours these same changes are much more generally evident, and the arrangement of the superficial layers becomes somewhat irregular. The pathological changes are most striking after twelve hours. A large number of the nuclei of the epithelial cells take on the red stain markedly; some remain granular, in others the granules appear to have coalesced to form amorphous red "inclusion bodies," and a nucleus may contain a very large number of the former or be entirely converted into one or two of the latter. At a later stage these inclusions tend to bulge out the nuclear membrane, giving the nucleus a polymorphic shape, and finally they may be extruded altogether into the cytoplasm. Thereafter, if the cell is a superficial one, it appears to be cast off. At any stage before this the process may stop and the cell return to normal in appearance and staining reaction. From twelve to twenty-four hours after radiation desquamation is proceeding in the central area, around

which there is frequently, but not invariably, a heaped-up region of proliferating epithelium. Meanwhile the substantia propria shows somewhat similar changes, which gradually decrease in intensity in the deeper layers, and from the limbus an infiltration spreads, composed very largely of eosinophils, although some polymorphonuclear cells are present. After thirty-six hours this limbal infiltration becomes more marked, blood spaces of considerable size are seen, and the eosinophils, which preponderated initially, are largely replaced by a massive invasion of polymorphs.

About fifty hours after radiation the epithelium near the periphery becomes more regularly arranged, and over the desquamated area a single layer of cells, the nuclei of which show no acidophil properties, begins to appear. The process of regeneration goes on with surprising rapidity and little evidence of cellular activity until, at seventy-six hours, the epithelium is two or three layers thick. At the limbus vascular infiltration is at its height; large new blood spaces, frequently surrounded by young fibroblasts, are present in great numbers, while the whole tissue in this region, and for some considerable distance into the cornea, is infiltrated with blood cells. This marked vascular reaction at the limbus seems to be a secondary feature, and is not evident histologically until the abiotic changes are well advanced; it is probably stimulated by the absorption of the products of protein disintegration. In seven days the cornea is again entirely normal.

Therapeutic Effects.

It is probable that the therapeutic effect of ultra-violet light when applied to the cornea in inflammatory, ulcerative, and degenerative conditions depends on the following factors. In the first place, pathogenic micro-organisms in the most superficial layers of this tissue will be directly killed. The lethal action of short-waved light upon such organisms is well known, and in a transparent tissue like the cornea this bactericidal power will be much more effective and extend more deeply than in an opaque and highly absorbent tissue like the skin. Where there is much inflammatory reaction and infiltration present in the superficial corneal layers, however, the greater part of the abiotically active rays will be absorbed, and in this case any lethal effect will necessarily be slight and practically restricted to the surface; but in proportion as some degree of transparency remains, bactericidal action will be greater and extend more deeply. In the second place, the superficial cells of the diseased corneal epithelium are killed and cast off with contained bacteria. Thirdly, the intense vascular reaction at the limbus and the invasion of the cornea by blood cells and inflammatory oedema will flood the diseased area with bactericidal influences. Fourthly, the stimulation to rapid and healthy regeneration of the exfoliated epithelium is a beneficial factor in any type of ulcer, but one which becomes of first importance in chronic and recurring conditions. Finally, it is probable that the absorption of the products of disintegration of the proteins of the cells will exert a favourable influence over the local immunological mechanism.

The Biological Action of Ultra-violet Light upon the Lens.

We have seen that the traumatization with the subsequent active response which ultra-violet light rays evoke, when used in clinical doses, is the action which is desired in the cornea. In the lens, however, the case is different. This is an avascular tissue in which active repair is comparatively lacking, and consequently any damage which may be done to it tends to be cumulative. Coagulation of the proteins of its cells is recognized clinically as cataract, a condition which has been produced experimentally by radiation with ultra-violet light.³ With radiation of such intensity as does not produce an opacity, changes take place in the colloid system of this tissue which result in the proteins becoming more labile and their subsequent coagulation by other influences more easy. Moreover, the autoxidation system of the lens, upon which it probably depends in large measure for the maintenance and regulation of its metabolism, is damaged by ultra-violet light; while, in addition, the permeability of the capsule is

altered, thus further increasing the susceptibility to pathological changes. It has been urged that, in the comparatively small doses in which ultra-violet light is used clinically upon the eye, there is little fear of causing permanent damage to the lens; but it is to be remembered that small doses, such as have no apparent effect, produce physico-chemical changes which predispose to the formation of cataract. In addition, in many diseased eyes the possibility of a complicated cataract without any artificial stimulus is by no means remote. In any technique of local phototherapy, therefore, it is essential that the lens be excluded from the path of the incident rays.

Clinical Technique.

In the treatment of corneal ulcers by ultra-violet light the first essential is that the beam should be adequately controlled so that it may be limited to the diseased area; in this way unnecessary traumatism to the healthy parts of the cornea is avoided, and the lens is excluded altogether from the path of the rays. For this purpose I have introduced an "ophthalmic radiation lamp," which has been already described in detail elsewhere.⁴ In principle it is a modified Gullstrand slit-lamp fitted with a mercury vapour lamp instead of the usual nitra lamp, and provided with an optical system of quartz, mounted on a freely movable arm. The last lens in this system is capable of accurate focusing and fine adjustment in two planes by means of an Arruga screw arrangement, and the precise incidence of the beam is controlled by observation through a Zeiss binocular corneal microscope. Interposed in the beam is an adjustable diaphragm and a system of filters, by means of which the nature of the light employed can be varied. For therapeutic purposes the ultra-violet light is employed unfiltered, but a screen which cuts off the abiotically active rays (such as uviol glass or Crookes's B) is useful for examinations for diagnostic purposes; with these all the advantages of a slit-lamp with red-free light are attained. With such an instrument a beam of considerable intensity and any desired size can be used, its incidence can be adequately observed and controlled, and in all cases it is easy to avoid the lens by inclining the beam at a sufficient angle. The most convenient procedure to adopt is to instil cocaine into the eye, which is followed by fluorescein, which is again washed out by cocaine. The patient is then set down to the radiation lamp, and, a uviol filter being interposed in the beam, of light, the nature and extent of the ulcerative process are examined through the microscope. A remarkably beautiful and well-pronounced fluorescent effect is produced in this way, and the depth and extent of the disease are clearly delimited. The beam is adjusted so that it plays upon the ulcerated area, and no other region of the cornea, and the uviol filter is thereupon turned off and the unfiltered light allowed to play upon the eye. If the patient is unable to keep his eye open during the whole time of the treatment there is no disadvantage in interruptions, for intermittent exposures, within very wide limits, are additive in their effects, and have the same accumulative action as a single long exposure.

Other methods have been proposed from time to time. Koepp (1919) and Birch-Hirschfeld (1922) employ a carbon arc as the source of light, but this emits a very large amount of heat; infra-red rays readily penetrate into the tissues of the eye and are potent for harm, especially to the lens, while any attempt to filter them off necessarily reduces the intensity of the abiotic rays. Ascher (1922) uses a quartz rod as a director along which the ultra-violet rays are guided, but although such a method is very suitable for radiating the conjunctiva it is impossible in this way, in the case of cornea, to control the beam of light with sufficient accuracy.

Dosage.

In radiating the cornea extreme care must be exercised with the dosage. I have found experimentally that the intensity of light required to produce a response is very slightly less than that required to produce an erythema upon the skin.⁵ It is to be noted that, as occurs in the skin, the response varies with different individuals; consequently the ideal method is to test the erythema dose

on the skin of the arm of each individual patient, and to commence radiating the cornea with a dose slightly less than this. In many corneal ulcers, however, it may be inadvisable to wait the twenty-four hours necessary for the development of the cutaneous reaction, and in these cases it may be necessary to start treatment immediately with an average dose. This may be taken as representing a period of radiation lasting three to three and a half minutes with the apparatus described, where the mercury vapour lamp is of the atmospheric pressure (K.B.B.) type, and runs on 220 volts, 2 to 3 amperes. Once the initial dose is obtained and its reaction observed subsequent doses are based upon it, but any increases are to be graduated with care, for it must be remembered that a small increase will make the difference between a mild and a violent photophthalmia.

Since the beam is always kept at a focus upon the cornea, the distance of the lamp from the cornea is constant, and the dosage can be altered only by time. Allowance must be made, however, for the obliquity of the rays, for it is evident that if the rays are not falling normally upon the cornea their intensity per unit area will decrease with the degree of obliquity. Actually, the energy varies quantitatively as the cosine of the angle of incidence of the beam, this angle being that which the incident ray makes with the normal to the tangential plane. The following table gives the factor by which the time of exposure determined for a normal ray should be multiplied in order to give an equivalent exposure with oblique rays:

Angle of incidence.		Cosine.	Factor.
0 (i.e., normal)		1.000	× 0.00
15 degrees		0.966	× 1.03
30 "		0.866	× 1.16
40 "		0.766	× 1.30
45 "		0.707	× 1.40
60 "		0.500	× 2.00

Some hours after the administration of a small exposure to a normal cornea there is a pricking sensation as of a foreign body in the eye, a sensation which is frequently accompanied by the appearance of haloes,⁶ and which is followed by the symptoms characteristic of photophthalmia. After intense doses the pricking sensation gives way to pain, accompanied by marked photophobia, lachrymation, and blepharospasm. The appearance of haloes is due to corneal oedema; the pain is due to the irritation of the corneal nerve endings after the trauma to the epithelium. It follows that in those conditions where the epithelium has already been destroyed (as in the majority of ulcers) pain does not occur, provided the rays have been allowed to play on the ulcerated area only. The latent period which elapses before the reaction starts is about eight hours. In practice, therefore, when dealing with cases when a subsequent reaction is expected, it is well to conduct the treatment during the afternoon so that the symptoms begin to assert themselves during the night. If the patient has the eye bandaged up so that the lids do not abrade the radiated area, he frequently experiences no subjective symptoms at all, especially if a small dose of aspirin or bromide be given before going to bed to ensure sleep.

Clinical Indications.

Corneal ulcers of practically every kind respond well to radiation with ultra-violet light, but, inasmuch as the more simple types of ulceration tend to heal up with the usual methods of treatment, it is in the more severe, the chronic, and the recurrent forms that the beneficial effect of treatment can be seen to the best advantage. In the more simple forms healing without any opacity is usually obtained; and the method has been found extremely useful in cases of foreign bodies in which infection has already become evident. With the more severe types of ulceration radiational treatment is the method of choice. In hypopyon ulcers, for example, a greater chance of recovery is offered than can be expected from cauterization, with, at the same time, less permanent damage to the cornea. In a series of 190 cases of this type of ulcer published recently by Hoffmann at Königsberg the percentage of excisions of the eye was reduced to 4.6 from the percentage of 32 which obtained before radiational treatment was introduced. Chronic ulcers, also, associated with a varying degree of deep keratitis and corneal opacity, and sometimes with

iridocyclitis, in which the eye has reached a torpid and sluggish state, and which have progressed over long periods in spite of the usual treatment, may frequently be made to heal over and remain quiet after a course of three, four, or more exposures to light. The deep lesions of acne may also be very favourably influenced.

There are, however, two conditions wherein the beneficial effects of treatment are very evident: recurrent ulcers, and phlyctenular ulcers. With regard to the former, especially those marginal lesions associated with a continually relapsing conjunctivitis, the ulcer itself readily clears, an end which is, of course, usually easily brought about. But after the epithelium round the ulcer has been desquamated in the photophthalmic reaction following exposure to ultra-violet light, the new layer seems so healthy and resistant that it is enabled to withstand the liability to break down on future occasions. As a general rule the ulcer heals up after the first or second exposure, and in the milder cases heals up leaving a transparent facet; but it is preferable in most of these cases to give a third or fourth exposure, bringing about a mild reaction each time, involving a traumatism and renewal of the epithelium in order to render the possibility of recurrences more remote.

Acute phlyctenular ulcers occurring in children respond so well to general light treatment⁷ and efficient dieting and hygiene that it is not worth while, as a rule, to coax a child affected with this disease to submit to keeping its eye open in the beam of the slit-lamp. It is in the chronic cases which have gone on for years, leaving an ulcerated, opaque, and vascularized cornea, and involving continued irritation, frequently with acute exacerbations, that the

method has its greatest use. Here again it is best employed along with general light baths. In these cases the eye quiets down and becomes white and comfortable, but the extensive opacities, which are already present with the resulting diminution of vision, remain.

One word may be said with regard to corneal opacities. In order to investigate claims in the literature, a series of nine cases of old corneal opacities were given a fair trial with local radiation. No results justifying the continuation of the treatment were seen anywhere. It is certainly the case, however, that recent opacities, such as those following ulceration, may be improved, and the prophylactic action of the treatment of ulceration by light in the prevention of opacity formation is very marked. Two factors seem to enter into this: the rapidity of healing with new-formed epithelial cells, and the large amount of vascularization which the photophthalmic response excites. To this extent its action would seem to be comparable to that of an irritant, such as dionine.

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FOCI AND NATURE OF INFECTION IN 100 CASES OF RHEUMATIC CONDITIONS.*

BY

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(With Special Plate.)

It is now admitted that a large majority of rheumatic cases are due to some infective cause. Many types of organisms have been accredited with being the causal agents, but it has also been admitted that no one organism has proved to be the causal factor in more than a certain number of cases. Similarly, with regard to the focus held to be responsible in cases of infective arthritis and fibrositis: teeth, tonsils, accessory sinuses, gall-bladder, intestinal tract, and urinary and genital passages have all in turn fallen under suspicion as being the main or primary source of infection, and treatments designed to deal with these foci have sometimes been applied with good results, but more often without success.

It has generally been realized that while unhealthy and abnormal conditions of any of the areas above enumerated may be the cause of arthritis, fibrositis, myositis, neuritis, and other inflammatory conditions, it is exceedingly difficult to determine in any individual case whether the particular area under consideration is really the causal one, or whether it is only one of several equally important foci which may be present, but less obvious, in the patient. The bacteriological investigation of specimens from a patient suffering from some rheumatic infective condition, as indeed from an apparently normal person, will show numbers of varying strains of organisms in cultures made from teeth, tonsils, sinuses, post-nasal secretions, faeces, etc., and many of the isolated bacteria are of a possibly infective type and character. In the normal person they are obviously not so at the time, and the question arises of how to decide which, if any, are of infective importance to the patient under investigation. In the rheumatic case it is usually assumed that streptococci, if isolated, are probably causal, and past experience in treatment has certainly shown this conclusion to be frequently correct;

but the types of streptococci are many and various, and the question again arises as to whether they are all of equal importance to the case from which they have been isolated, or whether one or other strain is the real causal agent of the condition present.

A great deal of work has been done on the bacteriology of rheumatic infection during the past thirty years. Paine and Poynton¹ claimed the organism they isolated and named *Micrococcus rheumaticus* to be the specific infective agent; Andrewes and Horder² later recognized this organism as probably similar to the *Streptococcus faecalis*. Shaw,³ and later Beattie,⁴ demonstrated the presence of streptococci in the synovial membranes of cases of acute rheumatism, and with these experimentally reproduced arthritis and endocarditis in rabbits; Topley and Weir,⁵ however, showed that not only streptococci isolated from rheumatic lesions, but those from non-rheumatic sources, were capable of producing similar experimental lesions in rabbits. Warren Crowe⁶ described a staphylococcal type of organism, which he named *Micrococcus deformans*, and believed it was frequently a specific cause of infection in chronic infective arthritis. Bach and Wheeler⁷ have quoted many cases in which chronic intestinal infection, associated with the presence of atypical coliform organisms, has apparently been causal in certain forms of rheumatism. Ford Robertson,⁸ after giving his reasons for not accepting the *Micrococcus rheumaticus* as an adequate specific agent, detailed several different species—namely, *Streptococcus pyogenes*, *anginosus*, *salivarius*, *B. influenzae*, *pneumococci*, *diphtheroid bacilli*, and *Micrococcus catarrhalis*—which he considered were all capable of being causal agents in rheumatic infections. Some indecision exists, therefore, as to which, if any, of the numerous organisms isolated from a case may be pathogenic to the patient concerned, and, further, as to which organisms should be employed as an antigen in the condition, if vaccine treatment is desired.

In approaching the question of ascertaining the focus and bacteria concerned in rheumatic cases, these difficulties were appreciated, and in view of the satisfactory results obtained by means of the pathogen selective culture method in previous cases already published (Solis-Cohen⁹ and Cronin Lowe¹⁰), this method of bacteriological examination was carried out in a large number of cases which clinically fell into the group of rheumatic infections. An analysis of the findings in 100 of these cases is the subject of this communication.

* Communication read before the Wallasey Medical Society, March, 1929.