"VIRGIN SOIL"—AND AFTER.**A WORKING CONCEPTION OF TUBERCULOSIS IN CHILDREN,
ADOLESCENTS, AND ABORIGINES.**

BY

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THE expression "virgin soil" in connexion with tuberculosis is generally used to describe the unprotected state of persons belonging to isolated communities so far cut off from human agglomerations as to have escaped all effective contact with the tubercle bacillus. The marked susceptibility of such persons when exposed to infection is generally admitted, and is quite similar to the susceptibility of wild animals when first domesticated or brought into confinement. For the medical practitioner in this country, however, the real interest of this great susceptibility of "virgin soil" to tuberculosis lies in its bearing upon the tuberculosis of infancy, childhood, and adolescence; and it is the importance of this aspect of the question that constrains me to submit a few general reflections on the subject.

The tuberculosis of early life differs in certain important respects from the tuberculosis of later life; and, great as has been the fall in tuberculosis at all age groups, coincident with the rise in the general standards of living within the last fifty years, these differences do not tend to disappear. In infancy and early childhood those individuals—happily much less numerous than formerly—who develop tuberculous disease still do so in three main forms: "primary foci" at portals of entry; adenitis of the cervical, mesenteric, and tracheo-bronchial glands; and, where the initial infection has been heavy or circumstances unfavourable, in the form of a generalized infection manifesting itself as disseminated tuberculosis, caseous pneumonia, or tuberculous meningitis. These three main types are matched by similar manifestations in the tuberculosis of "primitive" adults brought into contact with infection for the first time, and are comparable with the experimental tuberculosis produced in laboratory animals. They represent what I have ventured to call "natural" as opposed to "modified" tuberculosis.

As will be readily seen from the types above enumerated as characteristic of "virgin soil," tuberculosis, even in its "natural" phases, presents marked contrasts in severity, depending not merely on differences in natural resistance, but to a very large extent upon variations in the numbers of bacilli involved, the frequency of repetition of infection, the hazards of anatomical localization, and the time factor or incubation period intervening between the entry of the bacilli and their multiplication to numbers sufficient to produce disease. And, in view of the gradual and steady rise in the percentage of positive tuberculin reactions in the apparently healthy as the children grow older, we are in a position to know that, in the vast majority of instances, infection may occur, even at these susceptible ages, without passing on into disease. This is a point on which stress must be laid. Many appear to believe that tuberculous infection in virgin soil invariably causes acute and progressive tuberculosis. Nothing could be more untrue. All of us were once virgin soil to the tubercle bacillus, no matter how high our resistance may have since become. The fact is that in all except those cases in which the initial dose has been large, the process of "modification" starts at once and proceeds *pari passu* with the infective process, the resistance outstripping the disease or lagging behind it according to circumstances, so that the tissues soon cease to be virgin soil. The characteristic of tuberculosis in virgin soil is not necessarily a high morbidity, but a high case mortality. Latent infection tends to be well tolerated, but the disease, when it occurs at this stage, is usually severe.

Perhaps the most interesting age period in relation to tuberculosis is that which follows infancy and early childhood and leads on towards puberty. This age period may appear from a study of tuberculosis mortalities in the Registrar-General's reports to be one at which the resist-

ance is high and the liability to tuberculosis minimal. It is undoubtedly a period in which the tendency to the infantile or fulminating type of tuberculosis has for the most part disappeared, and in which the tendency to the adult form of apical phthisis has not yet become marked. That is why it is the period of lowest tuberculosis mortality. But, from the point of view of the student of tuberculosis, it is a "larval" period, during which the fate of the individual is often in the balance, a period so little understood and so full of unsolved problems that it can hardly be discussed without raising controversial questions. This "larval" period, though characterized by a low mortality, has a fairly high and a fairly characteristic morbidity, depending upon the gradual fruition of successfully localized but not successfully arrested "infantile" lesions, and appearing in such forms as cervical adenitis, hip-joint disease, spinal caries, and all the various affections of bones, joints, and lymphatic glands; tuberculous conditions which cause a great deal of suffering and deformity, make prolonged claims on bed accommodation, but do not, as a rule, lead to a fatal issue. These lesions of the "larval" period are, in fact, found to be consistent with an astonishing absence of constitutional disturbance if the patient, and the affected part, be kept at rest and "secondary" infections prevented. A glance round the "surgical tuberculosis" wards at Alton or Llangwyfan will convince the observer that advanced tuberculosis of bones and joints, if properly managed, is quite consistent with rosy cheeks, well-nourished limbs, and a fine state of general health.

It is not suggested that the whole of this period of childhood and adolescence is consistently the same in relation to tuberculosis. The earlier the age, the closer the assimilation to the "generalized" tuberculosis of infancy; the later, the more marked the tendency to "adult" pulmonary types. On the whole, however, childhood and adolescence is the period of non-pulmonary localization combined with a surprising degree of "tolerance" to the disease.

Now if the visible and easily detected manifestations are so well tolerated at this stage, it is not difficult to realize that invisible and hidden lesions may go completely unrecognized. Suppose, for instance, that the neck were as safely concealed from view as the roots of the lungs and the mediastinum, how often would cervical adenitis escape our notice? It is this very quality of "tolerance" to tuberculous lesions that stamps this "larval" period with its peculiar importance and its characteristic dangers. For the hidden dangers of this period are just as characteristic as its "tolerance," and are best appreciated in terms of the latter.

We may assume that, so far as milk-borne bovine tubercle bacilli are concerned, the primary lesions are, for the most part, easily detected, being situated in the cervical or the mesenteric lymph nodes, which receive the lymph drainage from portals of entry in the tonsillar and pharyngeal regions and the intestinal tract. The difficulties of detection are much greater, however, in the case of infections with human tubercle bacilli, which, being for the most part breathed into the lungs with the inspired air, set up minute "primary" focal lesions—usually only recognized, at this stage, at post-mortem examinations, but actually very common—from which the bacilli pass on to cause far larger and more important lesions in the tracheo-bronchial glands.

The preponderating importance of these insidious thoracic lesions in initiating generalized tuberculosis is shown by the fact that A. Stanley Griffith has found human tubercle bacilli in 73 per cent. of cases of tuberculous meningitis. We learn, too, from the combined pathological and radiological observations of Opie, that, at a later stage, when the primary lung lesions have become calcified and reached a stage of good x-ray visibility, a large percentage of adult lungs show evidence of having been infected with "primary foci" in childhood. It is probable that many enlarged tracheo-bronchial glands escape detection in x-ray films through being too small to project visibly into the lung fields or through being obscured by neighbouring structures, nor is it possible to say that a glandular enlargement seen in an x-ray picture is necessarily tuberculous;

but the combined evidence of radiology and post-mortem pathology points strongly to the conclusion that many apparently healthy children and adolescents have latent tuberculosis in the tracheo-bronchial glands.

Now the sinister aspect of these latent lesions of hidden glands lies in the fact that, during the period of childhood and adolescence, they continue to contain caseo-necrotic foci which may easily be awakened into dangerous activity or from which small infective emboli may enter the blood stream. It is one of the fortunate circumstances of human development that this age period is, in most cases, a time of life free from personal responsibility and admitting of plenty of open air and exercise followed by adequate rest. At no other time is life, on the whole, so healthy and natural as at school age. But if we look more closely into the question we find that the stresses of this age period are definitely associated with increased liability to the acute forms of tuberculosis. Inquiry into the case-histories of children suffering from "surgical" tuberculosis will very often elicit a history of injury as the determining cause of the disease. The very distribution of "surgical" lesions carries with it the same suggestion, tuberculosis being commonest in the structures most liable to stress and strain—the spine, the hip-joints, and the knee-joints. Again, in the case of the thoracic lesions of childhood, it is exceedingly common for these to have their onset determined by other respiratory infections, especially those causing congestion of lymphatic glands or causing thoracic strain through excessive coughing; examples being whooping-cough, influenza, and measles.

Turning to physiological stress, the earlier onset of puberty and sex character in the growing female is definitely associated with an earlier liability to tuberculosis than in the later-developing male. Even at the end of the adolescent period we find the same liability to break down under stress in the acute tuberculosis frequent in young males on entering strenuous industries—for example, coal-mining, an industry not otherwise characterized by any marked tendency to produce tuberculosis—and in the risks to young females after parturition and lactation.

And this leads me to the point which I wish specially to emphasize. We have clear evidence that, among healthy children and adolescents, just as among healthy adults, there is much latent tuberculosis. Tuberculin tests, radiological examinations, and post-mortem records prove this to be so. But within these groups of latent tuberculosis we ought to distinguish in our minds between the "larval" lesions of childhood and adolescence and the "compensated" lesions of later life. The former would appear to be far more liable to break down and cause autogenous reinfection than the latter. It is quite possible, on the other hand, that the "compensated" lesions, permitting of a gradual loss of immunity, may be consistent with a greater liability to exogenous re-infection; and the marked association of the pulmonary phthisis of middle age with certain industries suggests that this may be so; but this latter question is an intricate one requiring separate consideration.

It is interesting to note, in several recent observations on intradermal tuberculin tests in "healthy" persons, that among positive reactors there is a tendency for the end-point of reaction to graded dilutions to be higher in youth than in middle age, suggesting a greater degree of allergic hypersensitivity; and yet we have reason to know that this state of hypersensitivity of early age does not necessarily imply any very marked exemption from liability to tuberculosis under unfavourable conditions.

The sequence of events which suggests itself is, in my opinion, as follows: The "larval" stage, with its still unstable lesions, favours the auto-inoculations which lead on rapidly to a high degree of tissue allergy and, much more slowly, to a building up of the cellular proliferations and fibrotic barriers of spontaneous healing. During this "larval" period exposure to undue stress or to unfavourable physiological conditions is liable to produce such marked auto-inoculations as to lead on, not to increased immunity, but to secondary lesions and acute, often generalized, disease.

For those, however, whose lesions are smaller and better localized, or whose lives are exempt from undue stress, the

danger period is gradually passed and the stage of "compensation" reached without breakdown. This, of course, is what appears to happen in the majority of cases in this country; and the resistance acquired in the process is sufficient to ensure the safety of nurses and doctors, and even of the majority of healthy partners of tuberculous husbands or wives, though exposed to many infective contacts.

Such reflections as these have assumed, for me, a new importance in connexion with the industrialization of African natives. The entry of South African natives into industry takes a different course from that which has been usual in these islands. Here, with the growth of our industrial centres which followed the application of machinery to production, the labouring man quitted his agricultural pursuits and transferred himself and his family to the towns, where he and his descendants had to adapt themselves as best they could to urban overcrowding and the bacterial "contacts" associated with it. The result has been a wide diffusion of tuberculous infection, and, after a period of high morbidity and mortality, a steady decline in both.

In South Africa, for the last thirty or forty years, the native labouring man has merely bidden a temporary farewell to his tribal home, and, leaving his dependants behind him, has sought the gold mines or other industries, not as a permanent resident, but for short "contract periods" of nine months or a year, during which sufficient money might be saved to enable him to rejoin the "leisured classes" in the Transkei or in Portuguese East Africa at the expiration of his contract. This system of alternate industrial stress and pastoral leisure has its advantages and its disadvantages. The good effects of hard muscular work combined with plenty of food are evident in the fact that the average native worker gains in weight and condition during his contract period and returns home a fitter as well as a wealthier man. But the system must inevitably lead, also, to the carrying home of the bacterial parasites acquired in industry and their diffusion among the kraals in the native territories. In these native territories, however, the mode of life is no more strenuous than that of the children of school age in this country, and contact with tuberculous infection, when not too intimate or intense, leads to much the same results. What has occurred has been, not a rapidly spreading epidemic of tuberculous disease in the kraals, but the gradual establishment of endemic tuberculosis, leading, in the sunny open-air life of a native population, to a high average of positive tuberculin reactions in "healthy" persons as well as to a fairly large number of relatively chronic cases such as might be found in a country town in Ireland, Scotland, or Wales. The more acute types do undoubtedly occur, but are not frequently seen because they die quickly, and, as likely as not, their deaths are attributed to hostile magic or some other malign influence.

In contemplating this widely diffused and relatively benign endemic tuberculosis the observer is tempted to exclaim, "But this is just like the tuberculosis we meet with at home." The real test, however, lies in comparing the behaviour of the "healthy but infected" adults from these native communities with the behaviour of similar groups of adults of European stock when exposed to the stresses of such an industry, for instance, as that of gold mining on the Rand. Under this ordeal we find that, in spite of the fact that about 80 per cent. of the native mine workers react positively to the intradermal tuberculin test on arrival at the mines, they exhibit a much more marked liability to tuberculosis than the young adult of Dutch or British ancestry in the same industry. And this liability is manifest not only in a higher morbidity and mortality, but in a marked tendency to revert to the generalized and progressive lesions usually regarded as characteristic of "virgin soil." It is obvious that, although arriving at the mines with a sufficient margin of health over infection to pass a stringent medical examination, these natives are in a far less stable condition in relation to tuberculosis than gold miners of European stock. In this liability to break down under stress they resemble the "healthy but infected" children and adolescents of this country, and their condition suggests that they are, for the

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.

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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