A disease of extremes, acute myocardial infarction runs a treacherous and unpredictable course. There are only "good-risk" cases in retrospect.

Evidence continues to accumulate in support of the contention that anticoagulant drugs used early and efficiently, and continued for a minimum of four weeks under strict laboratory control, are capable of halving the death rate and reducing the incidence of thrombo-embolic episodes commonly observed during the first six weeks of the illness.

Necropsy experience substantiates the claim that anticoagulant therapy reduces the frequency of thrombo-embolic lesions.

The overall reduction in mortality cannot be attributed solely to the decrease in frank thrombo-embolic deaths. It appears that the severer grades of cardiogenic shock are favourably influenced by these drugs.

A claim can also be made for the prompt use of anticoagulants when a succession of attacks of acute coronary insufficiency suggests that myocardial infarction is imminent. There is also a justification for their use in selected patients on a long-term basis in the hope of preventing recurrences amongst those who have already sustained one or more myocardial infarcts.

No anticoagulant is uniformly successful. None is devoid of risk. Their successful use demands close clinical supervision supplemented by reliable laboratory facilities. Efficiently used, anticoagulants make a distinct contribution to the treatment of acute myocardial infarction.

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Scientific Research in British Universities 1953-54 (H.M.S.O., price 10s. net) is a massive 500-page paper-backed book issued by the Department for Scientific and Industrial Research in agreement with the Agricultural and the Medical Research Councils. The information in it has been collected direct from the heads of University Departments by the British Council. The Universities are taken alphabetically, and each department is listed, with the names of the head of the department and the permanent staff and a broad description of the research in progress during 1953-4. Under London University, the medical schools and institutes of the Postgraduate Medical Federation are separately scheduled. There is an index to the names of all research workers mentioned, and for the first time a detailed subject index.

DISTRIBUTION OF MICROFILARIAE OF O. VOLVULUS IN THE SKIN ITS RELATION TO THE SKIN CHANGES AND TO EYE LESIONS AND BLINDNESS

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In the course of experiments undertaken in 1953 to investigate the quantitative aspects of the transference of *Onchocerca volvulus* from man to the vector, *Simulium damnosum*, in the British Cameroons, it became necessary to estimate the number of microfilariae in the skin which might be available for ingestion by the fly when taking up its blood meal. Skin snips taken from different parts of the body were weighed on a torsion balance, teased in saline on a slide, and the number of microfilariae issuing forth in a wet film were then counted. The results obtained in the British Cameroons had far-reaching implications concerning the clinical and epidemiological aspects of the infection, and, consequently, similar investigations were carried out in conjunction with ophthalmological studies in areas of Northern Nigeria where blindness is common. In 1954 these combined investigations were repeated in the British Cameroons.

Little attention seems to have been paid to the number of microfilariae to be found in a sample of skin, except that it seems to have been generally assumed that the number could be taken as a very rough measure of the intensity of the infection. The prevalent impression seems to have been that the microfilariae were of very uneven distribution, and that the number in adjacent portions of skin was extremely variable.

Buckley (1949), whilst in East Africa, made a quantitative study by counting the number of microfilariae issuing from skin snips which appeared on inspection to be of about the same size. The snips were taken from many corresponding sites on both sides of the trunk and limbs of a native of Kenya. Buckley concluded that the distribution was very uneven, was without pattern, and that because of the discrepancies the method he described could not be relied upon for a quantitative estimate of the degree of infection.

Blacklock (1926) and Mazzotti (1951) investigated the distribution in a qualitative manner by recording whether skin snips taken from different sites in different individuals were positive or negative. In Sierra Leone, Blacklock found microfilariae most commonly in the loins, next in the thighs, then in the scapular region, and rarely in the ankles. In Mexico, Mazzotti found them irregularly in the entire skin in the upper half of the body and pelvic girdle and rarely in the skin of the lower extremities.

Material and Methods

Samples of the skin were removed by inserting (almost horizontally) in the skin a very fine entomological pin

mounted in a needle holder; the point was then raised, lifting a cone of skin about 2 mm. in height and diameter. This cone was removed with a new safety-razor blade, so that a piece of dermis about 2-3 mm. in diameter was removed with a slightly larger circle of epidermis. No blood was present on the snip, though the vessels in the bed from which it had been removed later oozed very slowly.

The piece of skin was then weighed on a torsion balance, made by the White Electrical Instrument Company, Ltd., London, and designed to weigh up to 10 mg. with an accuracy of 0.02 mg. With this balance, weighing was completed in perhaps a quarter of a minute. The snip was then teased out with stout needles, in about 30 c.mm. of saline on a slide, and examined unstained without a coverslip for motile microfilariae which emerged from the fragments. It was our practice to tease for about one minute, then to count the microfilariae. An equal volume of human serum was added, and, after drying, this film was fixed in methyl alcohol and stained with hot Mayer's haemalum for later examination. A thick blood film was made from 50 c.mm. of blood obtained by finger-prick, dehaemoglobinized, and fixed and stained in a similar manner.

In the British Cameroons snips were taken from the skin over the ankles, calves, thighs, the deltoid region, the fore-arms and hands, and from the trunk, and often from the buttocks, from the skin at the outer canthus of the eye, and from the conjunctiva. Later, when the pattern of the distribution had become clear, the snips were limited to the calf, buttocks, deltoid region, outer canthus of the eye, and the conjunctiva of one side, unless some special feature suggested further examination.

Over 200 cases were examined by multiple skin snips.

Results

It is convenient to present the results in such a manner as to illustrate the relation of the distribution of the microfilariae to local anatomical factors, then the relation of the general pattern to the skin changes, and, finally, the relation to eye changes and to blindness.

Local Factors Influencing Distribution

1. *Concentration of Microfilariae in Neighbouring Areas of Skin.*—In order to determine whether the distribution of the microfilariae was as uneven as has been supposed, separate but contiguous skin snips were taken from an area 1 cm. square on the shoulder, on the thigh, and on the calf of a man with a heavy infection. Care was taken that the snips in the groups taken from each region were as nearly as possible of the same size, so as to ensure that about the same area and depth of skin was removed in each snip. In the group taken from the left thigh two additional snips, one larger and the other much smaller, were taken. The results given in Table I show that the concentration of microfilariae is uniform in an area of the skin 1 cm. square,

TABLE I.—Showing the Number of Microfilariae of *O. volvulus* Found in a Wet Film Made From Weighed Separate but Nearly Contiguous Skin Snips Taken From Within an Area 1 cm. square From the Skin Over the Left Deltoid Region, the Left Thigh, and the Left Calf

Region	Weight of Skin Snips (mg.)	No. of mf. in Wet Film	No. of mf. per mg. of Skin
Left deltoid	1.47	5	3.4
	1.53	5	3.9
	1.74	12	6.9
	1.15	5	4.4
			Mean 4.7 ± 1.5
Left thigh	2.75	92	33
	2.24	55	25
	2.63	76	29
	2.12	75	35
	0.46	16	35
	4.60	164	35
			Mean 32 ± 4
Left calf	1.22	268	220
	1.23	228	185
	1.10	241	220
	0.60	115	192
			Mean 204 ± 18

and that within the limits of the size of the skin snips taken, limits within which a reasonable skin snip is likely to fall, the weight of the snip, and therefore its thickness and area, does not influence the result.

2. *Concentration of Microfilariae in the Different Types of Local Skin Lesions.*—The relationship of the concentration of the microfilariae and the different types of skin lesions is considered when the general pattern of the developing infection is discussed, but it is convenient here to state that we found the concentration to be very closely related to the condition of the skin at the point at which the snip was taken. Skin snips taken from areas of skin showing no obvious abnormality were found to contain few or no microfilariae. On the other hand, skin snips taken from areas which had undergone the change of lichenification contained a number of microfilariae which was roughly proportional to the intensity of the change. When skin snips were taken from advanced cases of onchocerciasis from areas in which the appearance of the skin resembled that presented by tissue paper which has been crushed and then flattened the concentration fell. Fibrous scarring, particularly when followed by leucoderma, is accompanied by a pronounced fall in the concentration. Keloid scarring also contains lower concentrations than the surrounding skin.

3. *Concentration of Microfilariae on the Dorsal and Ventral Aspects of the Trunk and the Extensor and Flexor Aspects of the Limbs, and its Relation to the Skin Lesions.*—Since the skin changes occur earlier and become more severe on the extensor aspects of the limbs and on the dorsal aspects of the trunk, and since the concentration of microfilariae was found to be closely related to the condition of the skin sampled, the pattern of the distribution of the microfilariae and the skin lesions was investigated in two cases in detail. Skin snips were taken in pairs from many corresponding sites on the trunk and limbs, one snip of each pair being from the ventral or flexor aspect of the trunk or limb, the other being taken from the dorsal or extensor aspect. Similar results were obtained in both cases: these showed clearly that the concentration of microfilariae and the lichenification of the skin are more pronounced on the dorsal aspect of the trunk and the extensor surface of the limbs than on the ventral aspect and the flexor surface.

4. *Concentration of Microfilariae in the Skin in Relation to the Nodule.*—(a) *The immediate vicinity of the nodule:*—It has been generally believed that the microfilariae were more numerous in the immediate vicinity of the nodule, and in three cases snips were taken from the skin over the nodule and from sites near by. The results showed that the skin over the nodule contained fewer microfilariae than that about 10 cm. from the nodule. This finding is the converse of the usual belief, and the fall in the microfilarial concentration may be due to the local changes in the skin over the nodule consequent on stretching and atrophy. (b) *The same anatomical quarter as the nodule:*—Despite the finding of a higher concentration 10 cm. away from the nodule than over the nodule itself, it was evident from the examination of those with early or light infections that in those in which there was only one or two nodules, and in which the microfilarial concentration in the skin was low, the few microfilariae present might be found only in the same anatomical quarter as the nodule.

5. *Concentration of the Microfilariae in the Skin Compared with that in Deeper Tissues.*—One of the cases examined had an inguinal hernia which was operated upon by Dr. E. A. Fejer. The samples of tissues removed at operation were weighed and treated as skin snips. No microfilariae were found in the fibrous tissue of the hernial sac: the concentration was low in the capsule and pulp of an enlarged femoral gland at the site of operation which did not contain adult worms, and the wall of a nodule containing gravid worms removed from the iliac crest of the same side contained a concentration of the same order as in the near-by skin.

6. *Lack of Variations During the Day and Night and from Day to Day.*—Since *S. damnosum* bites only during the day,

it seemed advisable to see whether the microfilariae might show a corresponding periodicity similar to the correlation of the biting habits of *Chrysops silacea* and the daily periodicity of *Loa loa*. Two cases of infection were examined by day and by night and several were examined on more than one day. No marked changes in the concentration of microfilariae were found. It is clear that the concentration of microfilariae does not differ greatly during the night and day or from day to day.

Relation to Skin Lesions

A relation between the general pattern of the distribution of the microfilariae in the skin and the development of the skin changes was found in each individual examined, with perhaps such minor modifications as have been described, and this relation was general throughout the particular community exposed to infection.

In an early or lightly infected case the microfilariae may be found only in small numbers in the same anatomical quarter as the nodule.

In a case of moderate intensity the microfilariae are most numerous in the ankles, calves, and buttocks, then in the thighs and the waist, and are usually few or are absent in the shoulders, arms, and face. Though the nodules are most commonly found near the pelvis, this distribution of the microfilariae in such cases of moderate intensity seems to be largely independent of the exact position of the nodules. In some cases, however, there may be a local increase in the same anatomical quarter as the nodule compared with the corresponding quarter on the other side of the body. The concentration of microfilariae is proportional to the degree of lichenification, and is higher on the dorsal and extensor surfaces of the trunk and limbs than on the ventral and flexor surfaces.

As the case becomes more advanced, the skin of the ankles becomes fibrosed and the concentration of microfilariae falls. An example is shown in Table II. Later, the calves become fibrosed and smooth, with an extension of the local fall in the concentration.

In the "burnt out" case the microfilariae may be few, though the residual skin changes may be extreme. When the skin is severely affected by fibrosis, atrophy, scarring, or leucoderma, or when the condition described as "crushed

TABLE II.—Showing the Concentration of Microfilariae of *O. volvulus* in Skin Snips From an Advanced Case of Infection With Marked Skin Changes and Fibrosis over the Ankles. (Nodules Left Side of Chest, Outer Surface of Both Thighs, Both Iliac Crests, and the Right Trochanter)

Site on Right Side	No. of mf. per mg. of Skin	Site on Left Side	No. of mf. per mg. of Skin
		Conjunctiva	0
Deltoid	8.1	Outer canthus	0
Forearm	1.0	Deltoid	1.1
Hand	0	Forearm	1.5
Costal margin ..	3.8	Hand	1.8
Buttock	71	Erector spinae	31
Thigh	95	Buttock	38
Calf	82	Thigh	74
Ankle	0.6	Calf	66
		Ankle	1.7

tissue paper" or "lizard skin" occurs, few microfilariae are found.

In general the number of palpable nodules increases throughout the progress of the infection.

Relation to Eye Lesions and Blindness

This was investigated in 1953 at Dadin Kawa and Gbulki in Northern Nigeria, and in 1954 at Bonjongo and Bimbia in the British Cameroons.

Anterior Segment Lesions.—At Gbulki, infected patients were classified in four groups according to the severity of the onchocercal keratitis and iridocyclitis—that is, those with: (1) no eye lesions, (2) early lesions of the anterior segment, (3) advanced lesions of the anterior segment, and (4) advanced lesions of the anterior segment in persons with "burnt out" skin lesions. In groups 1, 2, and 3 we found a progressive rise in the concentration of microfilariae in the legs and lower trunk associated with a spread of microfilariae to the shoulders, face, conjunctiva, and anterior chamber of the eye. This rise in concentration of microfilariae is followed by a fall in persons with "burnt out" skin lesions (group 4). The skin changes bore a similar relation, and there was a progressive rise in the number of nodules and in the average age of the four groups, reflecting the duration of their exposure to infection. The relation of the distribution and concentration of microfilariae to the skin lesions and to the changes in the anterior segment of the eye are shown in Fig. 1.

FIG. 1.—Showing the relation of the distribution and concentration of the microfilariae of *O. volvulus* to the skin lesions and to the changes in the anterior segment of the eye in the inhabitants of the village of Gbulki. The concentration is given as the number of microfilariae per mg. of skin over the calf, buttock, deltoid region, and the outer canthus of the eye, and of the conjunctiva. The areas with marked skin changes are shaded. The mean number of nodules found in the individuals in the four groups is 1.9 ± 1.3 , 4.2 ± 3.2 , 5.4 ± 2.7 , and 4.4 ± 2.3 .

The incidence of onchocercal eye lesions at Gbulki is so high that we were unable to collect a series of patients to serve as controls in the older age groups. At Bonjongo, however, eye lesions were less common and usually less severe. We were therefore able to collect a series of patients and to compare the distribution of microfilariae in those with anterior segment lesions and those with no eye lesions in the same age groups. These findings were analysed in two age groups, and Fig. 2 records the findings in those aged

FIG. 2.—Comparing the distribution and concentration of the microfilariae of *O. volvulus* in those with no lesions of the eye and in those with lesions of the anterior segment in the age group 30-49 of the inhabitants of the village of Bonjongo. The concentration is given as the number of microfilariae per mg. of skin over the buttock, deltoid, and the outer canthus of the eye, and of the conjunctiva. The areas with marked skin changes are shaded. The mean number of nodules found in the individuals in this group is 4.6 ± 2.1 and 9.3 ± 4.9 .

30-49. Similar results were obtained in those over 50. In both age groups the intensity of infection is higher and the spread of microfilariae more advanced in those with anterior segment lesions than in those whose eyes are not involved, showing that the resulting intensity of infection and not merely age and duration of exposure is the causal factor.

Posterior Segment Lesions.—The possibility of a corresponding relationship existing between the posterior segment lesions and the distribution and concentration of microfilariae is more difficult to assess because some anterior segment changes prevent examination of the fundus. At the places we visited no conclusive association between the development of posterior segment lesions and the spread of microfilariae to the head region could be demonstrated. Further evidence to which we refer in the discussion suggests that the pathogenesis of anterior and posterior segment lesions may be different.

Discussion

It is convenient to consider these findings first in their bearing on the mechanisms controlling the distribution of the microfilariae in the skin, on the transmission of the infection by the vector, and on the population dynamics of the parasite in the human host; secondly, to consider the relation of the distribution and the concentration of the microfilariae to blindness; and, thirdly, to discuss the significance of this definitive host-parasite relationship in the possible control of the infection, the prevention of blindness, and the treatment of infected individuals.

Much of this discussion must be speculative, but, since some of the apparently anomalous features of the infection are more easily understood when considered as part of a

definitive host-parasite relationship involving the intensity of the infection in the individual and in the community, it is profitable to discuss the implications in some detail.

Population Dynamics of the Microfilariae

Before discussing the factors which influence the distribution of the microfilariae it is perhaps advisable to consider what little we know of the life history of the microfilariae of *O. volvulus*. We have no direct evidence of the longevity of the microfilariae, but from such information as is available on the results of treatment with suramin, in which it is assumed that the effect of the drug is wholly on the adult worm, and by analogy (with due caution) with other filarial infections in man, it appears that the individual microfilariae probably live for weeks or months. This belief, however, does not help us to determine whether the pattern and concentration of the microfilariae described as a result of our investigations have been built up by the slow accumulation of long-lived microfilariae over a period of years or whether the microfilariae are constantly being replaced with a relatively rapid population turnover. We are thus unable to say, in the case of an individual with an infection established at a particular level of intensity and harbouring an unknown number of functioning adult worms, whether the microfilarial distribution and intensity represents a balance between microfilarial destruction and replacement, or whether the concentration will continue to build up slowly without any effective suppressive mechanism.

We do not know whether the microfilariae lying in the tissue spaces of the superficial layers of the dermis remain static or whether they move rapidly from place to place within the skin. They are seen alive only in the aqueous humour in the anterior chamber of the eye, or in the saline surrounding the tissue in a skin snip, neither of which can be regarded as their normal environment. This problem is unlikely to be solved except by the observation of the microfilariae by direct microscopy of living skin.

Pattern of Distribution of Microfilariae in the Skin

It seems reasonable that in a light infection microfilariae should be found in a higher concentration in the same anatomical quarter as the nodule. That the microfilariae are fewer in the skin over the nodule is perhaps explained by morphological changes in the overlying skin due to stretching or to mild trauma.

The high concentration of microfilariae in the lower part of the leg and in the trunk in an infection of moderate intensity is perplexing, for, though the nodules are predominantly on the legs and pelvis, yet this high concentration in the lower extremities occurs irrespective of the position of the nodules. We think that a simple explanation depending upon a physical agency like gravity or some peculiarity of the superficial layers of the dermis in the legs is too specious, and any explanation must embrace not only the distribution as we have found it in West Africa, but also such results as may be found in the Central American form of the infection. Mazzotti (1951), working in Mexico, showed by qualitative examinations that more skin snips were positive in the upper portions of the body than in the lower; Blacklock (1926) had shown previously in Sierra Leone that more skin snips were found to be positive in the lower portion of the body than in the upper. If any inference can be drawn from their results and from ours in Nigeria, then we suspect that if the concentration of microfilariae in Central America were investigated by means of weighed skin snips it might be found to be higher in the upper part of the body than in the lower. Information on this point would enable us to be more definite about many of the underlying principles of the definitive host-parasite relationship.

We know nothing of the early life history of the adult worms, except for an occasional record of their having been found accidentally at operations, lying free in the tissues, usually in the inguinal region. The infective form is deposited by *S. damnosum* (the chief vector in West and

Central Africa) during biting, which occurs predominantly on the ankles and the lower parts of the legs. The developing and adult worms then presumably wander in the tissues much as does the adult *Loa loa*. Their progress is, however, not accompanied by Calabar swellings, and in consequence we do not know how widely they may migrate before becoming encapsulated, but there is no record of an adult *O. volvulus* crossing the eye. While those worms which are found in nodules are adult, it does not follow that encapsulation may not occur until some time after the migrating adult female has copulated and has begun to liberate microfilariae. If the rate of migration of the developing and adult worm were slow, and in consequence it remained in the region in which it was deposited as an infective larva by the vector, or if encapsulation were delayed, then the few adults found in a palpable nodule might be the only detectable representatives of a potentially larger population of worms producing microfilariae but moving slowly in the legs or encapsulated in deeper nodules. In this connexion it is interesting to note that *S. ochraceum*, a vector of onchocerciasis in Mexico, bites predominantly on the head and neck, the sites where the nodules are most commonly found in that area.

We are at a loss to explain why the concentration of the microfilariae should be higher and the skin lesions should be more clearly marked on the dorsal and the extensor surfaces of the trunk and limbs than on the ventral or flexor surfaces. It may depend upon differences in the detailed architecture of the skin in these situations, involving perhaps the vascular supply or the structure of the tissue spaces; similarly, an explanation is lacking for the localized distribution of psoriasis, lichen planus, and other skin conditions. On general grounds it seems unlikely that the microfilariae are attracted to the lesions, and it is more reasonable to assume that the presence of the microfilariae in the skin leads to the production of the lesions.

Relation of Distribution of Microfilariae to Transmission

In an established case of infection in West Africa the highest concentration of the microfilariae is in the legs, particularly in the calves and ankles, the area in which *S. damnosum* bites preferentially. The established case without atrophic skin lesions and the habits of the vector thus combine to facilitate the transfer of the parasite. This mechanism may be regarded as corresponding in space to the periodicity in time manifested by *Loa loa* and *Wuchereria bancrofti* with their appropriate vectors. As the case progresses and the skin changes of atrophy or fibrosis develop, accompanied by a fall in the concentration of microfilariae, this mechanism changes from one of enhancement of transmission to one of suppression.

Relation to Eye Lesions and Blindness

The occurrence of anterior-segment lesions is related to the presence of microfilariae in the anterior chamber and the head region consequent upon a spread of microfilariae from the lower parts of the body. This spread is associated with a high intensity of infection in the human host, and this in its turn probably reflects the duration and intensity of the exposure to which the host has been subjected throughout his life.

Figures being published separately by one of us (F. H. B.) show that where there is a high proportion of infected persons in a community infections are acquired early in life, their intensity rapidly rises, and a rise in the concentration of microfilariae in the head region often occurs. Blindness due to anterior-segment lesions, when expressed as a percentage of infected persons, is 23 times higher in these heavily infected communities than in lightly infected ones, and, furthermore, persons in the younger age groups are more often affected. By contrast, the incidence of blindness due to choroïdo-retinal lesions amongst infected persons is only six times higher in the heavily infected villages than in the villages where infection is light. These findings lend support to our suggestion that the anterior-segment lesions are closely related to an invasion of the

anterior chamber by microfilariae. They also suggest that, although posterior-segment lesions are related to onchocercal infection, the mechanism of their production is different and possibly does not depend on the presence of microfilariae in the eye.

Possible Other Factors in Eye Changes

An understanding of the way in which the intensity of the infection affects eye lesions may well explain the apparent anomaly that onchocerciasis in West Africa is not uniformly associated with blindness. Other causes such as nutritional changes have been postulated in the past to explain such apparent anomalies. The occurrence of blindness in the inhabitants in some areas and not in others, the finding of eye changes in individuals in whom microfilariae were not found in the eye, and their absence in others in whom microfilariae were found thus require explanation.

We believe these anomalies can be explained by differences in the intensity of exposure of the community affecting the duration, intensity, and distribution of the infection in the individual.

Nutritional factors may, of course, as in malaria and sleeping sickness, affect the host-parasite relationship, but such a possibility must remain speculative until further knowledge is acquired.

Relation to Treatment and Control

We have little information at present on the manner in which the pattern of the distribution of microfilariae is altered by treatment with such drugs as the piperazines, which act on the microfilariae, or by suramin, which affects only the adult worm. But it is obviously of considerable importance to know whether after the use of diethyl-carbamazine the infection regains its original intensity after a short or a long interval, an interval which will depend upon the natural population turnover of the microfilariae, appropriate to the stage and intensity of the infection at the time when treatment was instituted.

Our findings suggest that it may thus be practicable to ward off the eye changes in the individual by repeatedly reducing the microfilarial intensity at appropriate intervals by the use of this drug, or by interfering with the population turnover of microfilariae by killing the adults with suramin, or by a combination of both types of drug. Individuals exposed for many years to an intensity of transmission which could in this time produce eye changes may thus be protected even in the absence of control measures directed against the vector by limiting the established intensity of their infection below this critical level. Furthermore, an understanding of the method of the production of eye lesions has an immediate bearing on possible control measures directed against the fly, since repeated temporary reduction of the population of the vector, without attempting complete eradication, may possibly reduce the intensity of human infection below the level which is associated with eye changes and may maintain it below this level.

Summary

The concentration and distribution of the microfilariae of *Onchocerca volvulus* in the skin were estimated in people in the British Cameroons and in Northern Nigeria by counting the number issuing in a wet film made from skin snips weighed on a torsion balance and taken from different parts of the body.

The numerical distribution of the microfilariae was found to have a clear pattern, which in the Cameroons and in Northern Nigeria was related to the distribution and severity of the skin lesions and to eye changes and blindness.

Possible reasons for this distribution are discussed, and, from the relation to eye changes, conclusions are drawn concerning the possibility of the effective control of the infection and the prevention of blindness.

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INTRAMUSCULAR BENZATHENE PENICILLIN IN THE PROPHYLAXIS OF STREPTOCOCCAL INFECTION IN RHEUMATIC CHILDREN

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In 1951 Szabo, Edwards, and Bruce described the preparation and chemical properties of a new penicillin compound—N,N'-dibenzylethylenediamine penicillin G (benzathene penicillin). Elias, Price, and Merriam (1951) showed that this substance marked a valuable advance in depot penicillin therapy, and that useful blood levels were maintained for as long as 144 hours after a single dose of 300,000 units, and for 12 days after 2.5 mega units. O'Brien and Smith (1952) reported that two injections at weekly intervals, or even a single injection of 2.3–2.5 mega units, gave excellent results in the treatment of gonorrhoea, 97% of the cases so treated being apparently cured. Further, fourteen days after the single dose appreciable blood levels of penicillin were found. Such a preparation clearly promised to be of value in the prophylaxis of streptococcal infection in patients who had suffered from rheumatic fever, and Stollerman and Rusoff (1952) reported the results of its use in 135 children. They found that 300,000 units maintained adequate blood levels for at least a week, 600,000 units for two weeks, and 1.2 mega units in most cases for four weeks. No patient developed a sore throat during treatment, but there were instances of temporary "bacteriological relapse" but with no evidence of clinical illness. These claims are so important that it appeared desirable to confirm them.

For this purpose a study has been made of children recovering from acute rheumatism or chorea in a hospital school.

Methods

Throat swabs were plated, within three hours of taking, on 5% horse-blood digest agar containing 1:700,000 crystal violet and incubated overnight in an anaerobic jar at 37° C. One colony from every plate with β -haemolytic streptococci was subcultured on blood agar and was grouped by the method of Maxted (1948). All group A cultures were tested for penicillin sensitivity by a ditch-plate method and sent for typing to the Streptococcal Reference Laboratory, Colin-

dale. Serum penicillin levels were measured by the *Sarcina lutea* plate method (Welch, 1948) modified by diluting the suspension of the organism so that its final concentration in the plates was 1 in 2,000 of the original culture.

The study lasted from March 1, 1953, to February 28, 1954. During this period 53 rheumatic fever convalescent children were admitted and 48 were discharged. Their ages were from 6 to 16 years. The duration of their stay in hospital ranged from 83 to 316 days. The children were accommodated in two wards, where there were also some children with orthopaedic complaints. The number of rheumatic children in the wards at a time varied from 10 to 23, and the number of orthopaedic patients varied from 33 to 35 at any one time. Except for benzathene penicillin, no specific treatment was given during the study. Throat swabs were taken at weekly intervals from all the rheumatic patients, and from time to time from the orthopaedic patients. All group A streptococci were typed. From the results of the swabs, estimates were made, as described below, of the load of infection in the community—that is, the numbers who were carrying group A streptococci—and of the numbers of new infections which took place among the rheumatic children. Haemolytic streptococci of groups other than A were isolated occasionally, but were not considered further.

Twenty-two rheumatic children were given the specific treatment which was used for the first time on July 1. At first cases were chosen because they were persistent carriers of group A streptococci; later alternate admissions were treated. Fifteen of the treated children had been persistent carriers for from four to nine weeks before their first injection. The other seven had negative swabs for from two to seventeen weeks before the first injection. The treated children were distributed at random in the two wards. No child was treated until it had been in hospital for at least three weeks. Benzathene penicillin was given intramuscularly, into the buttock, in doses of 1.5 mega units contained in 5 ml. One child received five doses, seven children received four doses, six received three, five received two, and three received only one dose.

Serum penicillin levels were measured 4, 11, 18, and 25 days after the injection. The results are summarized in Table I. Most of the assays at 25 days showed less than

TABLE I.—Serum Penicillin Concentrations

	Days after Injection			
	4	11	18	25
Total No. of samples	66	62	58	56
No. with serum concentrations of				
0.02 u./ml. and over	66	54	33	15
Range (u./ml.)	0.24–0.025	0.14–0	0.10–0	0.07–0
Av. serum concentration (u./ml.)	0.08	0.043	0.029	0.012

0.02 unit per ml., but in many of these there were still detectable traces of penicillin in the serum. Absorption appeared to be irregular, even in the same child. Thus, after some injections serum levels remained above 0.03 unit per ml. for at least 25 days, while after others no penicillin was detected after shorter periods. The Chart shows the levels found in four children and how they varied in the same child from injection to injection. As noted by Stollerman and Rusoff, most of the injections gave rise to local soreness and tenderness for 24 to 48 hours. No urticarial or other skin rashes were seen. However, in 18 out of 67 injections slight fever was noted on the following day. This ranged from 99 to 100.5° F. (37.2 to 38.1° C.). It did not occur after every injection in the same child.

The "control" group of rheumatic children was made up of 43 children who received no treatment and the 22 "treated" children who were observed for from three to seventeen weeks before starting treatment. Seventeen of these were group A carriers on admission and yielded persistently positive swabs, without a change of type, throughout their period of observation, for from four to twenty weeks. Twenty-two had persistently negative swabs through-