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THE EPIDEMIOLOGY OF SOME SKIN INFECTIONS*

BY

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Malcolm Morris was appointed as the first dermatologist to St. Mary's Hospital in 1881. It was an important year for microbiology, for in 1881 Koch described his methods for obtaining pure cultures of bacteria, Pasteur demonstrated the protective action of anthrax vaccines, Alexander Ogston, in Aberdeen, isolated and described the pyogenic cocci, while Raymond Crocker, in London, first saw "chains of micrococci" in the vesicle fluid of impetigo contagiosa. Malcolm Morris was the last child of a family of fifteen. He came from Bristol to St. Mary's at the age of 17, his interest in medicine having been stirred by an experience in hospital with a broken leg after falling into the docks. His early postgraduate life was spent in general practice in Yorkshire and later in London, but after four rather dissatisfying years he decided to be a specialist and set up his plate in Montagu Square as a dermatologist. Later he moved to Harley Street, where he practised until he retired at the age of 69 in 1918. He died in 1924.

Like many of the older dermatologists, and some of the younger ones, Malcolm Morris was a good general physician, and he loved to play the medical detective in dealing with rather obscure skin diseases. He was among the first to recognize the skin sensitivities to plants like poison ivy and the primula. In this Memorial Lecture, therefore, I make no apology for taking as my subject "The Epidemiology of Some Skin Infections," for I am sure Sir Malcolm Morris would have approved the use of the modern detective devices in tracing the sources and modes of spread of skin infections and so leading to better methods for their prevention and control.

From a large and fascinating field the four diseases with which I shall deal—pemphigus of the newborn, impetigo contagiosa, ringworm of the scalp and skin, and plantar warts—represent infections with a variety of parasites which range from the infinitely small and host-dependent viruses to the much larger and semi-independent fungi. Here is the first advantage of studying the epidemiology of skin infections, for not only does the skin act as host to a wide range of parasites but we can easily watch and study the development of the host-parasite relationship and not simply conjecture what is happening in some hidden corner of kidneys or lungs. The factors concerned in the initiation of infec-

tion are still largely unknown, and I believe there is a fruitful field for the observer who is prepared to study carefully the early stages of skin lesions in communities where infections like impetigo, pemphigus, and ringworm are spreading.

Pemphigus in the Newborn

The first skin infection I wish to discuss is pemphigus in the newborn, or bullous impetigo. An infection of the first month of life, this condition develops as a small red area in the centre of which a bleb containing clear fluid rapidly forms. Within two to three days this fluid becomes turbid, and the bleb bursts, leaving a small red area surrounded by a frill of shreds of dead skin. The blebs occur most often where two skin surfaces rub together—for example, the groins, axillae, the inner surfaces of the thighs—and also on exposed surfaces which are liable to irritation, but never on the palms of the hands or soles of the feet. The condition to-day is usually mild, but there may develop a generalized exfoliative dermatitis or a secondary staphylococcal or streptococcal septicaemia, or the child who is puny and premature may succumb to other secondary infections. Outbreaks were not uncommon during the late war years for a variety of reasons—for example, emergency maternity homes with inadequately trained staff, poor quality soap, or lack of olive oil, which was replacing soap for cleaning the skin.

When we try to trace the source of infection we are immediately up against the real difficulty that the staphylococcus which causes this infection is the most ubiquitous of germs. It is present in the noses of half the adult population and on the skin of about a quarter; it is found in dust, in the air, and on blankets and various other inanimate objects that may come in contact with the baby's skin. Thus, while we might look for the source of infection in a septic sore on the finger of an attendant or in a breast abscess in one of the nursing mothers, we are often completely nonplussed regarding its origin. Fortunately, in recent years two technical advances have helped to trace the source of the epidemic strain. First, we can readily recognize the potentially dangerous staphylococci by the fact that they produce an enzyme, coagulase, which causes clotting of plasma. Secondly, we have been able to subdivide a high proportion of the pathogenic staphylococci into many different types by utilizing the activities of the bacterial parasite, bacteriophage, which selectively destroys the staphylococcus. (The techniques for demonstrating coagulase activity and phage-typing were shown in extracts from the film, "Tracing the Spread of Infection.") Using this phage-typing technique or the serological method developed by Cowan (1938, 1939), various workers have shown that the cases in any outbreak of pemphigus are usually

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due to one epidemic strain of staphylococcus, but that in different outbreaks the epidemic strain may belong to different staphylococcal types.

In searching for the source of infection, Allison and Hobbs (1947) showed that the epidemic strain does not come from the mother's nose, but that a high incidence of nose-carriers of the epidemic strain among the nursing staff may precede the outbreak among babies. When it is known that a large proportion of nose-carriers also harbour the same staphylococcus on the hands, it is easy to see how the organism may become transferred to the baby. Outbreaks are not confined to maternity institutions, for in domiciliary midwifery we have been able to trace cases of infection to one individual midwife who was a nose-carrier of the epidemic strain.

We must be careful, however, not to be too ready to incriminate the nurse, even if she may seem to be the most likely source of infection. Parker and Kennedy (1949), in an outbreak at Carmarthen, failed to find a significant number of nose-carriers of the infecting strain among the nurses, whereas this strain was commonly present in the noses of healthy contact babies, which suggested an infant-to-infant spread as the most likely mode of transmission. Their findings may explain the difficulty in controlling pemphigus by merely isolating the clinically infected cases, but even more drastic measures, such as ward closure, may fail to eradicate the infection. We must remember to deal with contaminated dust, blankets, napkins, and the like before reopening an infected maternity unit, and in this connexion there is much to be said for the small four- to six-bed unit in which mother and child are kept together. I should like to deprecate the indiscriminate use of penicillin cream for dealing with skin infections in the infant nursery. Its main effect is to lead to a sharp increase in penicillin-resistant strains, and we have had recent experience of severe penicillin-resistant staphylococcal infections among patients and staff in maternity departments.

Investigations in the Far East

While pemphigus in its typical bullous and infectious form is confined to infants in the first month or so of life in this country, it occurs as an adult infection in more tropical regions, and was a source of much trouble among our troops in the Far East during and after the late war. An M.R.C. dermatological research team went out to Singapore to investigate these prevalent skin infections, and I am indebted to Dr. J. R. May for permission to mention some of the findings embodied in his M.D. thesis. Among British troops in Singapore and Hong Kong bullous impetigo was found in 9%, whereas non-bullous impetigo was present in only 2% of the cases. Tropical bullous impetigo is characterized by superficial blebs of 0.3–0.8 cm. diameter with a turbid vesicle fluid and very little surrounding inflammation or local adenitis. These lesions are found most often in the axillae, and, in contrast to impetigo in temperate climates, the face is usually spared. May isolated coagulase-positive staphylococci from all of 101 unruptured blebs in 68 cases and haemolytic streptococci from only two atypical cases. Streptococci were, however, isolated more often from late ruptured lesions.

The main predisposing factor to bullous impetigo in the Tropics is obviously the moist, sodden condition of the skin in the axillae resulting from continual sweating and lack of ventilation in the hot, humid climate. It has, indeed, been shown that persistent moisture of the skin lowers its natural germ-killing powers, but, in addition to this locally lowered resistance of the host, May's bacteriological studies indicated that certain specific strains of the staphylococcus, different from those found in the nose or other skin lesions, were associated with bullous impetigo. There was, in addition, some evidence in favour of case-to-case spread. Thus the condition is similar in many ways to pemphigus in the newborn, and it seems that the occurrence of this distinctive skin lesion depends on a low resistance of the host skin associated with a staphylococcus endowed with epidemic propensities.

Impetigo Contagiosa

We turn now to the controversial subject of impetigo contagiosa, seen in its most typical form among children, but occurring also in adults. The controversy, which has gone on for half a century or more, concerns the primary aetiological agent, some believing it to be the haemolytic streptococcus and some the staphylococcus, while a specific impetigococcus has also been postulated (Hope Simpson, 1941). Good epidemiology depends, among other things, on careful clinical observation, and it is perhaps clinical confusion that has led to different views about the aetiology of impetigo. There is, I believe, good clinical and epidemiological evidence for the existence of two types of impetigo, due respectively to the haemolytic streptococcus and to the staphylococcus. The clinical differentiation was probably first made in Jadassohn's clinic in Breslau (see Epstein, 1940), where each new case of impetigo was carefully studied by more than one member of the staff, and each dermatologist stated, from his clinical observations, whether he regarded the case as streptococcal or staphylococcal impetigo. The clinical diagnosis was later compared with the bacteriological findings, and these trained observers were soon able to get reasonable agreement between clinical and laboratory conclusions.

Streptococcal Impetigo

Streptococcal impetigo is characterized by lesions mostly of the face and scalp, with thick stuck-on crusts of yellowish honey-like or dirty colour. There is some surrounding inflammatory erythema and the regional glands are often swollen. The original bleb of streptococcal impetigo is so short-lived that usually it is not observed. On the limbs, streptococcal impetigo may penetrate into the true skin and produce crusted ulcerations which are called ecthyma.

Staphylococcal impetigo is primarily bullous in character and the blisters may persist for some days. After the blisters have ruptured, the lesions become covered with thin flat varnish-like crusts. Healing occurs centrally at the same time as the periphery extends centrifugally, giving a circinate appearance. There is, however, little surrounding erythema and regional adenitis is rare.

When we consider the epidemiological evidence there are again good grounds for believing in two distinct entities. Streptococcal impetigo is the classical type of impetigo contagiosa found among schoolchildren, and various workers have established its streptococcal aetiology by examination of the blister fluid in the early stages of the lesion. This infection has a sex, age, and seasonal distribution remarkably similar to that of scarlet fever. About three-quarters of the cases in schools occur among children aged 5–9 years. Its incidence is minimal in the summer months, rises sharply to a peak in the late autumn; after a temporary dip around Christmas, it rises still further in the early spring and then falls steeply from mid-April. It thus simulates closely and antedates by three to four weeks the seasonal curve of scarlet fever, and it is interesting to note that the epidemic wave has already begun well before the reopening of schools in September. It is not to-day a highly contagious disease, family spread being noted by Newman (1935) in only one-sixth of his cases, while classroom spread was quite rare, although there was a tendency for aggregation of cases in particular areas of the town of Southampton.

The late Dr. C. J. Thomas, for many years school medical officer for the London County Council, believed there was an association between impetigo contagiosa and scarlet fever in schools, and suggested that an antecedent attack of impetigo might protect against scarlet fever. Although there is evidence that the haemolytic streptococcus isolated from impetiginous lesions usually belongs to Lancefield Group A, I know of no investigation utilizing Griffith's typing to show whether or not an outbreak in a school is due to one epidemic strain. It may be noted here that patients with streptococcal skin lesions, particularly when

grafted on eczema, may shed very large numbers of haemolytic streptococci into the environment in a way similar to the heavy nose-carrier and may thus give rise to secondary cases of various types of streptococcal infection (Lemon *et al.*, 1948).

Impetigo contagiosa is a disappearing disease among schoolchildren. This statement is borne out by collected data supplied from the chief medical officer, Ministry of Education, and from figures kindly collected for me by the medical officer of health for London and by a number of medical officers of health throughout the country. Infection has in the past been associated more particularly with poor personal hygiene, although the disease also occurs in well-cared-for children. There is no doubt that a dirty skin is more friendly to the haemolytic streptococcus than a clean skin, and the marked reduction in incidence might therefore be attributed to the steady improvement in the health, nutrition, and cleanliness of our children. There has been a change in the severity of the infection. Impetigo contagiosa, as Tilbury Fox first described it in 1864, was a highly contagious disease characterized by fever, chills, and general malaise, and was sometimes followed by nephritis. Since then, like other streptococcal infections, there has been a steady decrease in the virulence of the infection, until to-day it is a mild as well as a disappearing disease.

Staphylococcal Impetigo

Staphylococcal impetigo was a prevalent skin infection among our troops during the war years and was the subject of several interesting studies during that period. Thus Bigger and Hodgson (1943) showed that the staphylococcus was present in pure culture in the early lesion, and that secondary streptococcal infection occurred increasingly with the age of the lesion. Sheehan and Fergusson (1943) confirmed the predominance of *Staphylococcus aureus* as the primary infecting agent, and were able to reproduce impetiginous lesions of varying degree with cultures of the isolated staphylococci and with blister fluid, but not with haemolytic streptococci recovered from the lesions. This infection, in contrast to streptococcal impetigo, has its greatest incidence in the summer months, and in civilian practice is more common in adults than in children. It occurs commonly in areas with hot dry summers, as in Central Europe and the Middle West of America. Irritation of the skin of the face is probably an important predisposing factor, for, besides its age and geographical distribution, its prevalence among unseasoned male Service personnel in the summer months indicates that unusual exposure to the sun plus shaving helped to initiate the infection. There is very little bacteriological or epidemiological evidence about its contagiousness. In a group of men whom I examined there was no history of case-to-case spread (Cruickshank, 1941), and I would suspect that most of the infections are autogenous from staphylococci harboured in the nose. There is need for detailed bacteriological study, including phage-typing, to determine the source of the infecting staphylococcus.

That a low tissue resistance may be a factor in impetigo is suggested by the relatively high incidence of seborrhoeic impetigo and dermatitis seen among the troops in the war years and also in civilian practice. In the group examined by Twiston Davies *et al.* (1945) 148 out of 200 cases of impetigo among troops were included in the seborrhoeic group. There is serological evidence that the closely related condition of sycosis barbae is an autogenous infection caused by the staphylococci carried in the patient's own nose, and that prevention of relapse in this infection may depend on elimination of the staphylococci from the nose (Hobbs *et al.*, 1947).

Summing up the evidence about impetigo, I suggest that there are two distinct entities—one streptococcal and the other staphylococcal—which can be differentiated on both clinical and epidemiological data. Streptococcal impetigo is a contagious infection of schoolchildren, with epidemiological features in common with scarlet fever and other

streptococcal infections. Staphylococcal impetigo is dependent on an antecedent and predisposing skin irritation which lowers resistance, and the infecting organism is probably autogenous rather than exogenous in origin.

Tinea Capitis

Although ringworm of the scalp has been gradually brought under some measure of control by improved methods of diagnosis and treatment, particularly the use of Wood's lamp and x-ray epilation, it is still an unpredictable and to some extent uncontrolled infection. During the late war there was a widespread recrudescence of the disease, associated, perhaps, with the mixing of town and country children and the general lowering of sanitary standards. But even in the more normal post-war years quite large epidemics have been occurring in different localities, and some attempts have been made to learn more about the epidemiology of this troublesome infection. Here, again, accurate diagnosis is essential; yet, despite the stimulus of Sabouraud's great work *Les Teignes*, published in 1910, little attention has been given in this country to the cultivation and precise identification of the species of fungi that cause ringworm. It was fortunate in some ways that Professor Topley had earmarked some of the highly specialized microbiologists for the Emergency Public Health Laboratory Service, for at the outbreak of the war it took Dr. J. T. Duncan from his "ivory tower" at the London School of Hygiene into the West Country, where he came in close contact with fungous infections. In 1945 he published the first comprehensive mycological survey of ringworm and identified 490 cultures of dermatophytes, of which 200 were *Microsporum audouini* and 156 *Microsporum canis*.

The high incidence of ringworm infections derived directly or indirectly from cats and dogs was impressive, but a large proportion of the specimens came from the south coastal counties, where, in certain areas, *M. canis* infection was apparently endemic, to the virtual exclusion of the more common *M. audouini* infections. Duncan's work was continued by his daughter, Mrs. Jacqueline Walker (1950), who published her findings in a three-year survey (June, 1946, to September, 1949) of ringworm infections in Great Britain and Ireland; among 2,473 cultures of dermatophytes she had identified 15 species in the genera *Microsporum*, *Trichophyton*, and *Epidermophyton*, and has confirmed Duncan's earlier recognition of two types of *M. audouini* and three types of *M. canis*, the two fungi which together were responsible for more than three-quarters of all her cases. This subdivision of the common skin fungi should allow us to trace more accurately the sources and modes of spread of ringworm infection, and local authorities should be encouraged to make use of these new precision tools.

Epidemics of scalp ringworm are practically always caused by *M. audouini*, which is a strictly human parasite. The fungus mostly attacks schoolchildren between the ages of 5 and 10 years and is six to eight times more common among boys than among girls, possibly because the girls' longer hair protects the scalp against infection. Transfer of the fungus probably occurs in a variety of ways, since the infected brittle hairs break off and contaminate clothing, caps, seats, dust, etc. Moreover, the fungus may remain viable in the environment for periods of a year or more. The high incidence of primary infection in the back of the head has led to suspicion of the barber's clippers, but it may be due in part to the easier access of the fungus to the scalp in that area, where the hair is usually cut short. Symptomless carriers, detected only by the use of Wood's lamp, are sometimes found, and search should always be made for carriers when the infection is spreading in a school. There is no evidence that the louse is a carrier of the fungus. Little is known about the development of immunity following infection.

M. canis is a natural parasite of cats and dogs, and is most likely to produce infection, often clinically inapparent,

in kittens and puppies. Infection, once transferred to the child, can pass from child to child, but becomes attenuated in the process and dies out after four to six transfers. None the less, in endemic areas 70–80% of the cases are probably due to case-to-case spread. Although large epidemics like those due to *M. audouini* do not ordinarily occur, infection with *M. canis* is widely distributed throughout Great Britain in both town and country—for example, endemic foci occur in Coventry, Leeds, Leicester, Reading, and Portsmouth, while about half the cases of scalp ringworm in the London area are due to *M. canis*. In the epidemiological study of ringworm, recognition of the three types of *M. canis* is important, for the local distribution of these types remains undisturbed over a period of years, which suggests that the predominance of one type prevents the establishment of a new invader. Control of this type of ringworm obviously depends on the recognition and eradication of the animal reservoirs.

Other animal hosts of fungous infections are cattle (*T. discoides*) and horses (*T. equinum*); these cause infections of the skin rather than of the hair. Curiously enough, while the human cases derived from cattle ringworm occur mostly in farm workers, those from the horse have mostly been of urban origin. Mention should also be made of favus, which still occurs sporadically throughout the country. It is a disease of greater severity but much lower infectivity than ordinary ringworm, and is therefore a family rather than a community infection.

A most interesting feature of scalp ringworm is that it virtually disappears at puberty, and the most persistent infections will clear up spontaneously at the onset of puberty. The most rational explanation of this phenomenon is that given by Rothman *et al.* (1947), who showed that adult hair fat secreted by the sebaceous glands is much more fungicidal than the corresponding child sebum. It would seem, however, from later work by Kligman and Ginsberg (1950), that the differences in fungicidal action may be more quantitative than qualitative, since it is well known that there is a great increase in the secretion of sebum after puberty. This fungicidal activity is associated with certain saturated fatty acids contained in the hair fat, and this new knowledge has been utilized in the preparation of fungicidal preparations like undecylenic acid.

In attempts to control the spread of ringworm, a common procedure has been to exclude the affected children from school; this may lead to much educational loss to a child, in some cases up to 20% of its school life. In a recent study in Maryland, U.S.A., exclusion from school was not required provided the affected children wore close-fitting caps (Schwartz *et al.*, 1946). A systematic search for possible modes of transmission was made, and, while cinema seats were exonerated, the barber's tools, particularly the clippers, came under strong suspicion. Infected hairs were shown to persist in the clippers, and in most establishments there was no satisfactory attempt at sterilization of clippers, combs, and brushes. For this purpose I would suggest the use of formalin vapour liberated in an airtight chamber in the barber's shop, for it has remarkable properties in surface sterilization against all kinds of vegetative and sporing micro-organisms, fungi, and viruses.

Tinea Pedis

I want to deal briefly with tinea pedis, or athlete's foot. This is a fungous infection of varying prevalence among older schoolchildren and young adults, particularly those living a communal life—for example, school boarders, students, and troops. The main causative fungi are *Trichophyton interdigitale*, *T. rubrum*, and *Epidermophyton floccosum*. The infection usually begins in the plantar fold of the fifth metatarso-phalangeal joint, involves the interspaces and the plantar surfaces of the toes and the soles, and may extend to the sides of the feet, not quite to the ankles. This limited localization corresponds with the part of the foot where the skin is devoid of hair follicles and sebaceous glands. There is little tendency to secondary

infection elsewhere in the body, and the condition usually responds to the modern fatty-acid preparations. The localized distribution of athlete's foot in adult life is therefore not contradictory to the view that the ringworm fungi are particularly susceptible to the fatty acids associated with the increased production of hair fat after puberty. It has been noted that among students the incidence of infection increases to some extent with age, and it has been suggested that sensitization from previous attack is more likely to be manifested clinically.

The epidemiological problem that creates controversy is whether the infection is exogenous or endogenous in origin; in other words, is it a contagious disease, or does the fungus live a saprophytic life on the skin and cause infection only when there is a lowered tissue resistance, rather like the pneumococcus in bronchopneumonia? In favour of the exogenous contagious view are the prevalence of the infection among those living a communal life in boarding schools, Army barracks, and student hostels; the isolation of different species of fungus at short intervals in the same individual (although mixed infections are not uncommon); and the predominance of one or other of the three common types in some surveys. On the other hand, the occurrence in different surveys of 1–3% of symptomless carriers, the frequency of the same type of fungus in recurrent attacks, and the remarkably constant ratio in which the three common types are found in groups of men at different periods suggest that the fungus may be present as a saprophyte until maceration of the skin from extensive sweating, warm humid climates, or frequent use of swimming-pools allows the fungus to produce clinical infection (Hopkins *et al.*, 1947). It is most important that this problem be resolved, for rational preventive measures will depend on satisfactory evidence in favour of one or the other view. The importance in the spread of this infection of bath-mats, showers, sandals, etc., in swimming-baths is still unproved, and the use of disinfectant foot-baths is probably of little value. Most benefit is likely to come from avoidance of the conditions that encourage excessive foot sweating or maceration of the skin, and the use of hygienic measures that will keep the skin of the feet in a healthy state.

There can be little doubt that fungous infections of the skin and hair are still unduly prevalent, and present many unsolved problems. Yet medical mycology is scantily taught and rarely practised in most medical schools in this country, in contrast to America, where departments of medical mycology are the rule rather than the exception. Although the systemic mycoses are not serious problems here, we should encourage the training of microbiologists in modern mycological techniques. I can assure you that we practise what we preach, for Dr. J. R. May, after some training in the Mycology Department of the London School of Hygiene, has been co-operating with our dermatology department in the identification by microscopical examination and culture of material from a variety of suspected fungous infections of skin, hair, and nail. The harvest after 21 months, if modest, is encouraging in that from 160 specimens a positive result was obtained by microscopical examination in 64 instances, while there have been 45 positive cultures representing seven different species of pathogenic fungi. I should add that good results will be obtained only when both the clinician and the bacteriologist are enthusiastic mycologists.

Plantar Warts

The plantar wart, or verruca plantaris, has become a troublesome skin infection among schoolchildren, for it is a chronic disease which may cause considerable pain and disability to the patient and has defied various efforts at prevention or control. It is caused by a virus, and characteristically consists of a single wart in the metatarsal area, where the flattened wart is often surrounded by thickened skin so that it may simulate a corn. The sex-and-age distribution is interesting, for plantar warts are found four to five times more often in girls than in boys; about two-

thirds of the cases occur in the age group 11-15 and a quarter in children aged 7-11, while the infection is rare in infant departments. When more detailed inquiry is made into the age distribution of cases attending foot clinics, as Dr. A. W. Forrest has done at Leyton (personal communication), it appears that the incidence rises to a peak in the 12-13 age group and thereafter falls sharply. Although there is evidence that the wart is a self-limited infection, this maximum incidence around puberty suggests that there may be a hormonal factor concerned in its pathogenesis.

The predominance of plantar warts among girls and the increasing incidence with school age has found various explanations—the more frequent attendance at the swimming-bath, increasing use of barefoot physical training and dancing, and the use of communal plimsolls. While contaminated floors and shoes are likely vehicles for the spread of what is undoubtedly an infectious disease, they do not seem to me to explain satisfactorily the peculiar age and sex distribution. There is need here for an inquiry into possible predisposing physiological factors and for more careful observation of the habits of schoolchildren and their relationship to the occurrence of what is a readily recognizable infection. Unfortunately, the wart virus has not yet been grown artificially, so that its distribution outside the body cannot be determined. Sometimes, however, the mode of spread of an infection can be demonstrated by blocking one or other of the possible channels, and some concerted study in this direction would probably lead to more knowledge about the spread and to more rational measures for the control of plantar warts.

Conclusion

I will conclude by reminding you that infections of the skin are still a major cause of absenteeism from school and from work. In a recent survey among schoolchildren skin diseases were responsible for an absence rate of 23 per 100 children, which was greater than the absence rate from any one of the specific fevers (D. D. Reid, personal communication). I have remarked on only a few of the common skin infections—we might have discussed scabies or acne, boils, wound infections or erysipelas, or some of the ill-defined conditions whose aetiology is still obscure. I hope the dermatologists and mycologists and medical officers of health will forgive a microbiologist for wandering into their fields, but I think they will agree with me that there are still some fascinating problems to be tackled. I am convinced that problems of this kind can be tackled and solved satisfactorily only by co-operative efforts between the clinician, the administrator, and the laboratory worker.

REFERENCES

- Allison, V. D., and Hobbs, B. C. (1947). *Monthly Bull. Minist. Hlth Lond.*, 6, 109.
 Bigger, J. W., and Hodgson, G. A. (1943). *Lancet*, 1, 544.
 Cowan, S. T. (1938). *J. Path. Bact.*, 46, 31.
 — (1939). *Ibid.*, 48, 169.
 Cruickshank, R. (1941). *Lancet*, 2, 275.
 Davies, J. H. Twiston, Dixon, K., and Stuart-Harris, C. H. (1945). *Quart. J. Med.*, n.s. 14, 183.
 Duncan, J. T. (1945). *British Medical Journal*, 2, 715.
 Epstein, S. (1940). *Arch. Derm. Syph., Chicago*, 42, 840.
 Hobbs, B. C., Carruthers, H. L., and Gough, J. (1947). *Lancet*, 2, 572.
 Hopkins, J. G., Hillegas, A. B., Ledlin, R. B., Rebell, G. C., and Camp, E. (1947). *J. Invest. Derm.*, 8, 291.
 Kligman, A. M., and Ginsberg, D. (1950). *Ibid.*, 14, 345.
 Lemon, H. M., Loosli, C. G., and Hamburger, M., jun. (1948). *J. infect. Dis.*, 82, 72.
 Newman, J. L. (1935). *J. Hyg., Camb.*, 35, 150.
 Parker, M. T., and Kennedy, J. (1949). *Ibid.*, 47, 213.
 Rothman, S., Smiljanic, A., Shapiro, A. L., and Weitkamp, A. W. (1947). *J. invest. Derm.*, 8, 81.
 Schwartz, L., Peck, S. M., Botvinick, I., Leibovitz, A. L., and Frasier, E. S. (1946). *Publ. Hlth Bull., Wash.*, 294, 1.
 Sheehan, H. L., and Fergusson, A. G. (1943). *Lancet*, 1, 547.
 Simpson, R. E. Hope (1941). *Ibid.*, 1, 683.
 Walker, J. (1950). *Brit. J. Derm. Syph.*, 62, 239.

TRIETHYLENE MELAMINE IN HUMAN MALIGNANT DISEASE

RESULTS WITH ORAL ADMINISTRATION OF ENTERIC-COATED TABLETS

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Since 1950 reports have been published on the use of triethylene melamine (T.E.M.) as an alternative to nitrogen mustard in the palliative treatment of Hodgkin's disease, of the chronic leukaemias, and of various other neoplasms of the reticulo-endothelial system. The drug has been known as trisethyleneimino-s-triazine or 9500 in this country and as triethylene melamine or T.E.M. in the U.S.A.

In our first experiments with this compound it was shown to be a potent inhibitor of the growth of the Walker tumour in rats when given in aqueous solution by the intraperitoneal or intravenous route. When given by mouth, about 50 times the parenteral dose was needed to produce a comparable effect (Rose *et al.*, 1950). These results aroused our interest in the potentialities of the compound as an agent for the treatment of human malignant disease, and, with the possibility of clinical trial in mind, its pharmacology and toxicology were studied in animals of various species (Hendry *et al.*, 1951). In the course of these studies it was shown to produce a consistent temporary fall in the peripheral leucocyte count of the dog when given intravenously in appropriate dosage. On the other hand, when it was given to dogs by mouth—in gelatin capsules containing the dry crystalline product—the effect was very variable. Because of this it was decided to adopt the intravenous route in our first clinical trials of the drug, the results of which have already been reported (Paterson and Boland, 1951). Oral dosing, however, is simple and convenient, and the possibility of employing this route with T.E.M. was kept in mind.

While our early trials were still in progress we learned that this mode of administration had, in fact, been used in clinical trials in America (Karnofsky *et al.*, 1951), where the activity of the compound had been independently discovered (Lewis and Crossley, 1950; Burchenal *et al.*, 1950). It is clear from these reports, whether experimental or clinical, that a greater variation occurs in the response to the drug when orally administered than when given intravenously. Since T.E.M. is unstable to acids it seemed likely that the erratic response to oral dosing noted in the dog was due to variable inactivation of the drug in the stomach, and that this might also account in part for the variable response in man. The possibility of obtaining a more uniform response from enteric-coated tablets was therefore explored by comparing the effect of plain and enteric-coated tablets of T.E.M. given by mouth upon the peripheral leucocyte