RECENT ADVANCES IN THE DIAGNOSIS AND TREATMENT OF HUMAN HELMINTHIASIS.*

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ADVANCE is not necessarily synonymous with progress. Recent work in these directions has concerned itself largely with ankylostomiasis.

DIAGNOSIS.

Recent advances in diagnosis have been *direct*, the recognition of a parasite, or of part of it, just as it is recovered from man; *subdirect*, implying its deliberate development to some further stage before diagnosis is attempted; *indirect*, the searching for evidence of man's reaction to the parasite, or of damage which it has inflicted on him.

DIRECT DIAGNOSIS.

Animals being nearly always classified on their adult structure, accurate identification of an adult helminth, usually macroscopic, involves accurate diagnosis. But the stage ordinarily available for this purpose is an immature one, and immature forms may be closely similar over large zoological groups. Moreover, too small a quantity of material may be examined. An accurate diagnosis by recognition of eggs in faeces can be made only if a female intestinal worm have a normal oviposition rate, if this rate be known, and if there be examined a fair faecal sample of sufficient size to display eggs with certainty when a single female is normally ovipositing. The normal oviposition rate can be ascertained by accurate determination of the number of eggs in the faeces and of the number of worms in the bowel contents. So reliable has worm detection been held that it has unhesitatingly been used to check—and to condemn—the accuracy of microscopic diagnosis by detection of eggs. The microscope has cruelly retaliated by finding fertile eggs when search of the bowel contents has revealed no male worms. The worm content of the bowel is no easy matter to determine; nor is the ovum content of the faeces.

Egg counts have been used since 1885 for determining the oviposition rate of hookworms, and recently for determining the accuracy of various counting and concentrative diagnostic techniques and for establishing the degree of infection of a community. These uses are correlated yet distinct, and merit further consideration.

The Accuracy of Concentrative Diagnostic Techniques.

These techniques, after complete disintegration of the faecal conglomerate into its constituent particles, lead eggs in one direction and faecal matter proper in another. Camouflage through overlying by faecal particles being largely removed, many eggs can be collected in a small area for ready examination. The efficiency of any such concentrative technique can be settled only by the use of controls which determine the number of eggs which the amount of faeces it uses contains and the number which it collects for diagnosis. Many concentrative techniques have been devised and advocated, almost none have been controlled. The first attempt to control a diagnostic technique by egg counts was my own ten years ago (1918). It was also, apparently, the first deliberately instituted egg-counting method used in determining the degree of infection of members of a community. Another egg-counting control was described by myself in December, 1922, a third by Stoll in January, 1923, designated by him "the egg-counting method," three others by myself (1924), and one by the Caldwells (1926). In testing the relative value of these I reasoned that the technique which, measured by egg counts, habitually delivered the largest number of eggs from the same evened material must be the most nearly accurate, and I showed that that position is held by a peculiar modification of the concentrative technique named direct centrifugal floatation† (D.C.F.), the

modification by which it is "pushed to finality." No criticism has shaken that proof.

Using carefully controlled conditions, D.C.F. pushed to finality has given me higher, more regular, and therefore more accurate counts than any other, and Stoll's technique the most erratic and undependable counts of all. The accuracy of D.C.F. pushed to finality has been questioned by Stoll and Hausheer and by Soper. I conclude from careful study of the papers that disintegration of the faeces was inadequate; the former, for instance, rejected pontifically (without evidence offered) the comminutor advised, an instrument which ovum counts have shown to be the most accurate at our present disposal, and obtained that type of ovum collection which is produced by inadequate disintegration of faeces. Any technique can be discredited by failure to disintegrate faeces completely. For the accuracy of Stoll's technique its author has offered no evidence, but maintains, against his own work, that it is accurate to within 10 per cent. It has been declared inaccurate by Hill, Maplestone, Sweet, Davis, Gordon, Chandler, and Soper—that is, by all who have reported on it independently, with the one exception contained in the report of Barnes and Russell from the Straits Settlements. They held it accurate for the inadequate reason that from it they obtained even results, yet their assistants could not do so. Evidence shows, then, conclusively that D.C.F. pushed to finality is the most nearly accurate counting or control method of which we have knowledge. It is, on present findings, obligatory where exact knowledge is required. In the grading of concentrative techniques such exact knowledge is completely essential.

The same investigation has shown that every concentrative technique has its limit of effective concentration, that if it be used in too great concentration it becomes inefficient, first relatively, then absolutely. With due regard to this reservation and to the proper disintegration of the faeces, D.C.F. in the first adequate spin or centrifuging and with rapid lift, using faeces from a lightly infected case not on a milk diet, has delivered over a considerable series of cases 80 per cent. of the ovum content as shown by the same method pushed to finality. The minima and maxima were 61 and 95.

The Oviposition Rate of Hookworms.

The minimum ovum content normal for hookworms is the oviposition rate of the female hookworm expressed as the number of eggs present in a unit of faeces. I have not found that this number habitually drops below about 30 per c.cm. when tested by D.C.F. pushed to finality, and have concluded that this is the number produced by a single female in normal oviposition. The estimates of others, obtained by comparing egg counts with worm counts, are: Lutz (1885) 42; Leichtenstern (1885) 47; Darling (1922) 22; Stoll (1923) 40. Now D.C.F. uses 1 c.cm. of faeces, and 1 c.cm. of faeces contains 30 eggs if a single female be normally ovipositing. Used diagnostically, D.C.F. will deliver of these normally 24 and perhaps 18. If these conditions are fulfilled and these facts are correct, only gross carelessness can avoid a certain diagnosis by D.C.F. The acceptance of a higher rate for ancylostome infection may or may not prove correct. It is, I believe, based at present on undependable considerations.

The Degree of Infection of a Community.

Knowledge on this point is usually required as a preliminary to a treatment campaign. To its individual ascertainment strong exception has been and is being expressed on the score of uncertainty and cost. Since D.C.F. recognizes the presence of a single healthy female hookworm, the first objection fails. Expense consists largely of pay of personnel, which itself depends on the time taken to prepare and to examine specimens. The time of preparation for a single specimen, mainly taken up with that complete disintegration which is absolutely and fundamentally essential, varies comparatively little with different methods; but no concentrative technique, other than D.C.F., permits of mass methods; in it twelve specimens can be disintegrated and centrifuged as rapidly as one. The time of microscopic examination varies roughly with the area to be covered; in Willis's technique, so commonly employed, this

* Read in opening a discussion in the Section of Tropical Medicine of the Annual Meeting of the British Medical Association, Cardiff, 1928.
† The spelling implies the floating principle applied to diagnosis.

extends to 1,250 sq. mm. (2 sq. in.), in plain D.C.F. it is 150 sq. mm. (1/2 sq. in.), in D.C.F. with herding movements* it is 10 sq. mm. This small area can, in quite deliberate manner, be examined at the rate of sixty specimens an hour. Moreover, herding can be effected for twelve slides as rapidly as for one. Further, eggs in faeces covered with water and kept at a temperature not exceeding about 28° C. (80° F.) retain full capacity for floatation for several weeks. Accordingly a comfortable central laboratory (in which accurate and rapid work can be strictly exacted without hardship) can be fed from a wide collecting area, and reserves of specimens can be left for a time to accumulate until it is convenient to examine them. All this implies that a supervised laboratory party of four (in India two microscopists of the compounder class and two sweepers) supplied with a twelve-tube centrifuge, can report comfortably on a quarter of a million negative specimens a year, and on a greater number in proportion as the number of positives is greater than this. It seems to me, then, that no justification exists, moral or financial, for denying to "native" communities an individual mass diagnosis. That, at present, must be effected by D.C.F., seeing that it is not merely accurate, rapid, cheap, and reasonably fool-proof, but is the only technique to which mass methods are applicable. It marks the fulfilment of an aim which I set before myself over ten years ago, and have since then steadily pursued. Here at least advance and progress seem synonyms.

But if, in investigating the degree of infection of a community, individual diagnosis be not the aim and accuracy be not desired, any of the other counting techniques will suffice, as will an estimate of the numbers contained in the herd of a first D.C.F. preparation, or even the examination of a simple smear. The means should fit the end. I cannot picture Solomon trying either to extract a cataract with a shovel or to behead an elephant with a v. Graefe knife.

If all eggs of a nematode species have about the same specific gravity all will float in a non-absorbed watery solution of sufficient heaviness; and addition to its specific gravity will not float more. Conversely, one concludes that, if further addition to the weight of a watery fluid does not float more eggs, all have been collected. D.C.F. pushed to finality in a saturated solution of common salt (sp. gr. 1200) does not deliver more hookworm eggs than does the same process carried out in a solution with a specific gravity of 1150. It is reasonably concluded that with the latter solution D.C.F. indicates the content accurately. The same apparently holds for trichostrongylus and enterobius eggs. To float all ascaris and trichuris eggs a specific gravity of 1300 is required. As a counting technique this has great practical disadvantages, yet the figures hitherto obtained show that, used diagnostically with a saturated common salt solution, the first spin displayed on the average 40 per cent. of the ascaris and 25 per cent. of the trichuris eggs indicated as present. The minimum ovum content of both species is probably such that, used thus, D.C.F. will detect a single fertilized normally ovipositing female of either species. Chandler reports D.C.F. as floating hymenolepis onchospheres, but the percentage of success is unknown. For trematode eggs, onchospheres of taenia, unfertile ascaris eggs, and strongyloides larvae all floatation methods are undependable.

For the collection of those ova which it floats D.C.F. should be used selectively, employing a solution whose specific gravity is no higher than necessary. The usual practice of stating, both in original papers and in uncritical abstracts of them, that the local percentage of worm infections reaches a certain figure, without stating the diagnostic procedure used, is valueless. Such reports and abstracts do not register progress.

SUBDIRECT DIAGNOSIS.

For hookworm infection this method has recently been allotted primary value. Faeces containing hookworm eggs are "cultured" and extracted in water. The principle, that of Looss, is effective only if larvae are infective in

stage and active in movement. Its details have been altered needlessly. Baermann's modification is convenient and well known; my own has the advantage of compactness in that several dozen cultures can be set or extracted simultaneously in a single incubator of ordinary size.

This method of diagnosis has constantly failed for two opposite reasons—the first that the worms (eggs or larvae) have died before extraction, the second that their activity has carried them out of the culture before its extraction. A hookworm larva is obligatorily aquatic, living normally within the water films which enclose particles of a moist soil. It passes from one particle of soil to another—readily if both lie within the same film, laboriously if the film has to be lifted until contact and fusion with another film are established. A larva may burst through the surface of a film and travel on, clothed with a minute and steadily lessening film of its own. If it does not enter another before its own is lost it must surely die.

To combat the diagnostic error introduced by larval death before extraction, our knowledge is at present insufficient. To circumvent the error induced by escape, every culture must be surrounded by a water trap. Into this trap migrating larvae tumble, and out of it they rarely escape. Indirect diagnosis not only is uncertain, but has introduced a completely unnecessary risk for those who have used it. It has been employed in a series of well-watered and untrapped soil samples to determine the duration of infection of the soil—that is, the longevity of hookworm larvae. Their disappearance from the sample may, however, be evidence, not of premature death, as is almost universally concluded, but, equally, of exuberant and vicious vitality.

For strongyloides infection culture with extraction or tracking in agar has been used successfully. Large cultures are advised, but the method's efficiency is really unknown, seeing that no satisfactory controls have hitherto been devised. It is, then, questionable to what extent there has here been advance; conclusions should be drawn with caution.

In infection with *Schistosoma japonicum*, subdirect diagnosis has a possible concentrative place. As Faust and Meleney point out, miracidia hatching out in clean water congregate in its upper few millimetres and, if melaninae have left a slime-track there, hover excitedly about that particular portion.

To sum up, apart possibly from infections elucidated by faecal examination, subdirect methods seem to offer little opening.

INDIRECT DIAGNOSIS.

1. Evidences of Reaction to Helminthic Parasites.

Eosinophilia in the blood was shown twenty-five years ago to be absent in the worst cases of hookworm infection. On the other hand, in Boycott's two deliberate infections it appeared about three weeks before eggs were found. Local eosinophilia in the tissues may be a marked feature of local infection. Local fibrosis may follow the local leucocytosis of which the local eosinophilia is an evidence, and of fibrosis onchocerca nodules are perhaps the most striking clinical evidence. Yet recent investigation has shown that these may commonly be undetectable when the corresponding microfilaria is present abundantly in the lymph of the lumbar region. In the same direction points Dyce Sharp's observation of a female onchocerca escaping from an ulcerated and non-nodular surface. A fibrous reaction seems no more a necessary part of the diagnostic picture of an onchocerca than of a loa infection.

Creeping Eruption.—Looss described this in connexion with penetration of the skin of his arm by a number of strongyloides and ancylostoma larvae. Kirby Smith was apparently the first to demonstrate a larval nematode in the epidermis in such cases—cases, that is, not due to fly larvae. Fülleborn has shown by serial sections that larvae of the dog uncinaria, applied to his own arm, produced tunnelling of the epidermis, the tunnels filling with lymph, breeding bacteria, and producing dermal inflammation. His observation suggests that, when creeping eruption is due to the larva of a nematode, that larva belongs to a species for which man is an unsuitable host. Failure to make the usual immediate entrance into the dermis is

* Herding is effected by to-and-fro and circular movements which collect ova about the centre of the hanging preparation obtained after D.C.F. with rapid lift.

explicable as abhorrence of the larvae for lymph with man's specific lymph character. The worms cannot, so to speak, bring themselves to enter as usual the dermis where that lymph is characteristic, but wander forlornly in the epidermis, where it is so disguised by excretions from epidermal cells and bacteria that it becomes, for those particular larvae, at least endurable.

Sensitization.—The principle of the Casoni reaction for the diagnosis of hydatid disease has recently been extended to other helminthic infections, particularly by Fülleborn. In strongyloides infection the "flames," consisting of masses of filariform larvae, are sterilized and dried. This vaccine, used within a year of production, is rubbed into the shallowest possible scratches in the skin, for the least bleeding is harmful. In a pronounced reaction urticarial swelling begins in a couple of minutes, reaches its full size of about 15 cm. in diameter in about fifteen minutes, and begins to disappear in about an hour. The reaction appears to be constant in infections having a duration of eighteen months or more, and was present once in eleven cases where all other evidence suggested absence of infection. With this reaction Fülleborn correlates like lesions constantly appearing perianally in chronic strongyloides infection, and that in spite of meticulous care in cleanliness. These he attributes to natural development to the filariform stage of larvae in tiny particles of faeces retained in minute perianal creases and their penetration of the perianal skin. Such repeated auto-inoculation would explain the long duration of some of Fülleborn's cases, one extending to over twenty-four years. For ascari infection Fülleborn makes his antigen from the body wall of *Ascaris lumbricoides*, recovered from the pig, after the cuticle has been rubbed off, while Ransom, Harrison, and Crouch use the body fluid of the worm. These last workers found four of twenty persons sensitive. None, apparently, had been or were infected, but their work had brought all four into contact with ascari for five to twenty-five years. Sensitiveness to ascari material seems to hold no necessary implication of infection. This reaction will have a practical diagnostic value only in so far as it is positive at least as frequently as is the appropriate direct examination.

Complement Fixation.—Here the recent work of Hamilton Fairley is important. In echinococcus infection he finds that scolices must form the antigen. The most suitable material is scolex-containing fluid from pulmonary or hepatic hydatid cysts of the sheep. Examination of nearly 1,000 cases showed that a positive reaction was clear evidence of hydatid infection; but absence of reaction did not necessarily exclude this. Age is important. Of infected persons under 20 years of age, about 40 per cent. gave no reaction; while of those over 60 years old all reacted. Failure is variously caused. Not all cysts contain scolices—that is, antigen. Not always is antigen absorbed, as appearance of complement fixation for the first time after rupture of a cyst shows. Very rarely is antibody not formed. Fairley concludes on very strong grounds that persistence of this reaction for more than twelve months after removal of a cyst implies persistent latent infection. In schistosomiasis Fairley's antigen is again a larval form—the cercaria in the snail's liver. This reaction is not zoologically specific, since, using livers of *Planorbis exustus* infected with cercariae of *S. spindalis*, he has obtained effective reactions not only in infections by this parasite in goats and buffaloes, but by *S. indicus* in goats and by *S. haematobium* in man. Although a generic reaction, it is sensitive and valuable, seeing that no effective direct concentrative technique has been devised for the extraction of trematode eggs from faeces.

2. Appraising the Damage done by Infection.

Stiles instituted two methods of approach to this problem.

(a) *In the same community infected were compared with the presumably uninfected.* He selected a group of school children containing individuals positive and negative to the smear, and to all of them applied certain physical and mental tests. Speaking generally, these were negative, but those children infected with necator were lighter and shorter than those in whom the smear failed to detect infection. In Queensland Waite and Nelson, examining

about 11 square inches of smear, partly centrifuged, concluded that they could demonstrate a retardation of mental development and of haemoglobin content corresponding to the degree of infection, and that the effect was cumulative. Gordon could find no connexion between helminthic infection and haemoglobin percentage, physique, general fitness, or mentality, except that an ankylostome infection of over 15,000 eggs per gram of faeces involved loss of energy.

Two drawbacks attend this method. First, factors other than helminthic infection may be influencing the subgroups. Neglect, ill feeding, and inherited mental weakness may well lie preponderatingly with the infected group. Secondly, the mode of diagnosis used has failed to differentiate the infected from the non-infected.

(b) *The same community was tested before and after treatment.* In an infected person the bodily state at any particular moment represents the balance between damage done and repair effected. This repair entails an unusual, often continuous, call which depletes bodily reserves even if immediate compensatory hypertrophy occur, since capacity for hypertrophy is always limited and has been encroached upon. This depletion of reserve must be measured if the damage done by an infection is to be appraised. Stiles's second group of tests noted the change in mortality, morbidity, and capacity for work which followed disinfestation. Under Wise, in British Guiana, disinfestation of those apparently in good health was followed by marked improvement in all these directions. Life became more comfortable, happier, healthier, longer. The same followed my own treatment of 20,000 infected persons in Darjeeling twelve years ago. This line of testing, dropped for some years, has happily just reappeared. For example, the *Transactions of the Royal Society of Tropical Medicine and Hygiene* (vol. xxi, No. 6, 1923) contains two instances. The first, by McKenzie (p. 461), records the gain in weight and working capacity following the disinfestation of a gang of "healthy" hard-working negroes; the second, by Rose (p. 486), stresses the striking rapidity with which lepers, who had failed to respond to treatment, did so when they were rid of their hookworms.

Exact inquiry on these lines seems to have greater scientific possibilities than any other. It is more likely to deal with single factors, and it investigates that side of the matter which calls out for clarification. Two requirements are essential: (1) the diagnostic technique used must detect at least the single female worm, for which purpose D.C.F. is at present essential in hookworm infection; (2) there must be evidence that the tests used do actually detect disability present. When Smillie and Spencer state with emphasis and confidence that, on the basis of the Stoll technique and of the physical and mental tests which they have used, "very light hookworm infestations produce no measurable harm," and conclude that these children are merely carriers whom it would be unjustifiable to treat to disinfestation, they assume, without evidence offered, unjustifiably, and as I believe incorrectly, that the tests they have arbitrarily selected are accurate and adequate. It is as useless to attempt to measure entamoebae with a foot rule, whether procured from Mr. Woolworth or from the Greenwich Observatory, as to record the hours of sunshine with the most delicate of barographs. There is no justification for the assumption that no individual harm is here measurable. That will be determined only when the two requirements just noted have been met. But whatever may be the final answer on this point the matter will not thereby be closed; for the harm a light infection does is not limited to its possessor, nor does his degree of infection constitute any measure of the risk which he is to the community. This will perhaps be startlingly clear from the conservative statement that, given ideal conditions of extracorporeal development and of establishing contact with man, a single pair of hookworms is mathematically capable of destroying the human race within a year. It must be, and is, these extracorporeal conditions which are all-important. It is almost true to say that the intensity of an individual's infection is hygienically immaterial; what is vital is the fact of infection and his particular, and often peculiar, fancy in defaecation. Unless that be rigidly

controlled in a primitive community, and generally it cannot, hope must lie in exact individual diagnosis and in treatment to disinfection.

TREATMENT.

The perfect anthelmintic, when we find it, will be, or will produce, a selective poison which in a single dose will kill all worms without injuring the host or risking his life. Pending the discovery of a drug with these properties, effective against even a single worm species, anthelmintic dosage must be so limited that the enthusiastic prescriber will not find himself killing man in order to kill his parasites. Since these parasites live in a fluid medium, it has been concluded that the greater the concentration of the drug in that medium the more helminthocidal will its action be. Hence has arisen the stereotyped routine for the expulsion of intestinal helminths—preliminary starvation and purgation to lessen the volume of the intestinal contents and to produce thereby the maximum perihelminthic concentration of a vermifugal drug, when this is administered in the largest dose safe for man, which must be less than its minimum lethal dose.

It is profitable to consider first the action of tartar emetic and emetine in the treatment of schistosomiasis. Recent work has firmly established their value. Their mode of action is illumined by Fairley's work. He showed that, as compared with solution in water, solution in serum increased the cercaricidal action of these drugs more than a hundredfold, while in plain normal serum, in that from a bilharzia case, in water, or in normal saline solution, cercariae live thrivingly. Clearly parasitic death in these cases is not due to direct poisoning by the drug. Quinine acts similarly on cercariae, which parallels its mode of action on the malaria plasmodia. These drugs themselves are not parasiticidal, they must be changed into something else before they become so. Does the same hold good for intestinal anthelmintics? Apparently it may. I have not been able to consult originals, even in translations, but it is stated that santonin and its derivatives are excreted into the lower part of the intestine when the drug is administered subcutaneously or by mouth after occluding the intestine; and that Takagame and Asada claim that santonin is not vermifugal, but after absorption it, by combination with bile and other substances, becomes so for certain intestinal worms. Accordingly certain anthelmintics are innocuous or nearly so, but poison worms indirectly.

Moreover, when a drug has to be altered by the body before it becomes vermifugal, an interval should elapse (in the case of santonin twelve hours) between its administration and the post-anthelmintic purge. For the use of this last, recent work has strengthened the triple reason: the man is well rid of such of the toxic drug as remains in his gut, of the toxins shed into his gut by dead worms, and of drunken but living worms (a condition marked with certain anthelmintics) which should be swept away before they recover their unpleasant instinct for attachment.

Apart from schistosomes, hookworms have attracted the greatest medicative interest of recent years. Thymol in 60-grain dosage has served well. More recently other drugs have been extensively used—for example, oil of chenopodium and its active principle ascaridole. Schüffner's advocated dosage for the oil was 1.2 c.cm., which is 48 drops delivered by the international drop-counter, not 48 minims. The use of this last and erroneous dosage has led to a number of deaths; the lower seems to be safe when the ascaridole content lies, as it usually does, between 50 and 70 per cent. In oils with a high ascaridole content, such as that issued by Burroughs Wellcome and Co. (90 per cent.), the dosage should be 0.8 c.cm. The usual dose of ascaridole is 0.5 c.cm.

Carbon Tetrachloride.

The most recently and enthusiastically advocated drug for the treatment of ankylostomiasis was introduced to medicine by that distinguished veterinarian Maurice C. Hall (who has done so much for the diagnosis and treatment of helminthic infection) in an advocated dose of 3 c.cm. equally for man and dog, the dosage being apparently

irrespective of weight even between dog and dog. The drug is held to have no minimum lethal dose, and of it Lamson and Wing write: "In the very extensive use of carbon tetrachloride in the treatment of hookworm disease, a few cases in each million have died." What are the facts? By shutting one eye or the other they can be made to suit any fancy. On the one side are such instances as Khalil's, with 150,000 cases treated with a partly redistilled drug, and one reported death, and he a poor creature—surely here, at last, is the perfect anthelmintic, which will destroy only "a few cases in each million," and those the ones we best can spare; Bishop's in Trinidad with 25,000 cases and no reported death; Lambert's 40,000 cases with no deaths, and yet three deaths in the next 8,000; Kehrer and Oudendal's, using 5 c.cm. with 1.5 c.cm. of oil of chenopodium, with no deaths in the first 9,000 and five in the last 6,000. On the other side lie Straub's two deaths in 1,400, one after a dose of 2 c.cm., and three deaths in hospital patients after doses of 1½, 2, and 2 c.cm.; Kouwenar's four deaths in 6,000, none getting more than 3 c.cm. and the drug passing chemical tests of purity; Neave Kingsbury's one in 143 with a dose of 5 c.cm.; Phelps and Wu's with two deaths, one in an adult taking 3 c.cm., the drug being pure; Bais's with three deaths. It is well to read the results with both eyes.

Are such deaths entirely unforeseeable? Carbon tetrachloride produces fatty degeneration of the liver, and sometimes at least of kidneys and adrenals. In the former the change may be intense, and is ordinarily followed by phenomenally rapid regeneration. In single doses there may be produced a striking derangement of liver function, with increased bile pigment in the blood, reduced tolerance to levulose, a drop in the blood fibrin with production of haemorrhages, and a lowering of the phenoltetrachlorophthalein test for liver function. Yet if the drug be persisted in so that it actually produces "tremendous liver lesions of necrosis, scar tissue formation, and all the signs of an early cirrhosis of the liver," dogs so affected "give normal values for all these liver function tests." It is held that intoxication can probably be prevented by (a) avoiding administration of the drug without preliminary treatment for ascariasis, (b) refusing treatment to alcoholics; (c) having patients avoid alcohol and food before and after treatment; (d) ensuring an adequate calcium reserve. It may be said in comment that (a) in Neave Kingsbury's case this was effected and death followed, while the proposal renders absolutely obligatory microscopic examination of the stool before giving the drug; (b) alcoholics are little prone to announce the fact; (c) Davis has shown that a diet rich in carbohydrates lessens liver damage; (d) we are left wondering how attention to calcium deficiency can be effected on a mass scale. In other words, the recommendations do not enable the hygienist to foresee these tragedies. A dose of 1.5 c.cm. may kill and is less efficient than the older anthelmintics. I know, moreover, that all deaths from the drug are not being reported, and that such unreported fatalities have wrecked at least two hookworm campaigns. I believe that the general adoption of the drug is retrogressive, in that it obstructs investigation directed to the discovery of something far more nearly approaching the ideal anthelmintic than any we now possess.

The tests by which antiankylostome drugs have in the past been appraised are unsatisfactory. The work requires repetition, using as a basis, the enumeration, by accurate means, of the number of eggs present in a unit of faeces before and after treatment. Recent progress in diagnosis admits, at last, of this being effected with confidence of success.

Mass Treatment and Herd Treatment.

Finally, mention must be made of treatment of hookworm infection on an extensive scale. Of this there are two conceptions, surely morally incompatible. In the one, after a preliminary investigation of relatively few persons, to determine whether the community in question has a "sufficient" degree of infection, all are "persuaded" to accept treatment by a lethal drug without individual diagnosis. Euphemistically misnamed "mass treatment," this is, in fact, the drenching method which the veterinarian

applies to an infected herd of cattle. It is "herd treatment." I quote once more words by Major Church:

"To the native races," as Sir Frederick Lugard has said, "civilization must mean something more than the methods of the development syndicate or the assiduous cultivation of new wants." . . . The pursuit of wealth, if it is accompanied by the careless exploitation of native races, is neither an honourable nor in the long run a profitable policy for the representatives of a great nation."

Disinfested labour is more profitable labour; and it is easier to treat a whole heavily infected community herd fashion, at the risk of a few deaths in uninfected persons, than to determine who are infected and to treat them only.

The second and antithetic usage is an expression of the belief that every individual is entitled to an individual diagnosis of infection before he is treated with a possibly lethal drug. It is based on conviction of the extreme value of mass treatment, even to complete disinfestation; but admits of no justification in morality, science, or expediency for the infliction of herd treatment on backward races. Those advocating this second usage can now ask, "What possible justification is there for the herd treatment of hookworm infection when mass diagnosis has become so exact, and can be carried out at the rate of a quarter of a million specimens a year for every four persons employed in the actual preparation and examination of specimens?" Surely the answer is "None." We are further advised to adopt for herd treatment the use of a drug which has "no lethal dose" yet kills unforeseen in a smaller dose than that which is in habitual use in herd treatment. At the same time we are warned that the drug should be avoided in certain conditions whose presence, in the very nature of things, herd treatment precludes our discovering. If in these circumstances we elect to use herd treatment we shall, I am satisfied, not merely have disregarded our individual professional obligation to those we treat, but will have set our feet deliberately on a path which, for us at the present time, will be devoid alike of reason and humanity.

USE OF SUBCUTANEOUS INJECTIONS OF OXYGEN.

BY

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EARLY in January of this year Dr. Murphy of Lisburn told me that, as a last resource, he had treated one of his dogs, suffering from double pneumonia following distemper, with a subcutaneous injection of oxygen, and that this was followed by a rapid and dramatic recovery. This method of treating pneumonia in dogs was introduced and has been advocated for some time by Colonel Ryan, F.R.C.V.S., Cork. He treats such cases from the very start in this way and does not wait till the animal is seriously ill. I related this case to one of my colleagues, Dr. Rowland Hill, showed him how to give the oxygen, and he has had at least one wonderful recovery, which he has published.

On February 4th of this year Dr. Boyd Campbell asked me to give oxygen to a man in his ward. It was the ninth day of an attack of double pneumonia in a man aged 45. When I saw him both lungs were completely involved and his blood pressure had fallen. He appeared to be moribund. He was given a large dose of oxygen at 12 noon, and he died at 4 p.m. At 8.45 p.m. on the same day Professor Symmers performed a *post-mortem* examination that was rather interesting. There was absolutely no rigor mortis, the blood that issued from the anterior skin incision was bright arterial blood, the muscles were a brilliant red, the parietal pleura was also bright red, and the blood in the inferior vena cava was a distinct blue colour, not at all black and tarry. The lungs were to a great extent in the state of grey hepatization and there was not a half-inch of healthy lung.

Since then several cases of acute lobar pneumonia have been treated with subcutaneous injections of oxygen immediately on admission to hospital, and their charts show uniformly good results. The crisis comes on very rapidly. A case of pneumonia complicating glossitis, a post-anaesthetic pneumonia, and a case in a man with a bad fracture of the pelvis have all done well.

These results, taken in conjunction with Dr. Cannon's recent work, as published in the *British Medical Journal* of April 21st, on the inhalation of warmed oxygen as an early method of treating acute pneumonia, are very interesting and suggestive. Dr. Cannon claims that pneumococci give off oxygen and when the gas is sufficiently concentrated in the tissues the micro-organisms die.

If oxygen—say about 150 c.cm.—is injected subcutaneously into a rabbit and a few minutes later blood is drawn from a vein of its ear, the blood will be found to be arterial in character, and when shaken up with air its colour cannot be heightened. Also such a large dose does not produce any bad symptoms, such as apnoea. There is no doubt that oxygen is rapidly absorbed.

In pneumonia there are two things wrong with the patient—a general toxæmia and the local changes in the lung. Usually the toxæmia is the cause of death; and the oxygen seems to do good by neutralizing the effects of the toxæmia as well as possibly by its action on the micro-organisms. Toxæmia kills by producing anoxæmia, with reduction of the alkalinity of the blood, and the clinical condition of acidosis is produced. The acids in the urine, and in bad cases the glycosuria, indicate this state. The kidneys and liver, the organs apparently responsible for maintaining the proper alkalinity of the blood, may both be upset. It is possible, therefore, that oxygen given subcutaneously acts, as Dr. Cannon thinks, by helping to kill the pneumococcus and at the same time counteracts the toxæmia.

Given subcutaneously oxygen certainly does not produce any lung trouble or aggravate any existing lung trouble, as it may when inhaled, even if heated; and although I have given it in at least two hundred cases, not a single local or general bad effect has been seen, so that it may be considered a perfectly safe procedure.

Subcutaneous injections of oxygen, besides being of great use in cases of pneumonia, are of value in all cases of anoxæmia, and these are numerous and serious.

Chloroform or post-anaesthetic sickness is due to acidosis, and all my operation cases in the Royal Victoria Hospital before leaving the table are given a dose of oxygen; with the result that sickness is much diminished; since January only one case out of two hundred has developed any post-anaesthetic pneumonia.

A striking effect of subcutaneous oxygen is seen in connexion with extensive burns and scalds of the body. I have long been interested in these cases at the Children's Hospital, and have tried to solve the problem of the rise of temperature about the third day and the subsequent fatal result. For years I believed this toxæmia was due to microbial infection, but after trying all the known means to combat such infection, and not meeting with any success, I gave up that theory. Lately I found that scalds and burns that are going to do badly develop, before any symptoms are noticed, a severe acidosis, and apparently the toxæmia is due, not to a bacterial infection, but to the breaking down of the damaged tissue—that is, it is due to histamine poisoning, or to something akin to it. Later on, undoubtedly, microbes may cause complications.

During the last two months all the cases of burns and scalds of the trunk admitted to my beds have been treated with oxygen, and only one patient has died; but this case was not admitted till the third day, when the temperature was raised, the pulse rapid, and acidosis well established. Three similar cases were admitted a few hours after the accident, were given oxygen at once, and all did well; at most their urine showed a slight and temporary acidosis. The amount of oxygen given was largely determined by the amount of acid in the urine.

An interesting point in connexion with anoxæmia is that symptoms do not appear till late, and once they appear the patient goes downhill very rapidly—almost as if he had fallen over a precipice. So that in treating anoxæmia,