Lettsomian Lectures

ON

AMŒBIC LIVER ABSCESS:

ITS PATHOLOGY, PREVENTION, AND CURE.

BY SIR LEONARD ROGERS, C.I.E., M.D.,
F.R.C.P. LOND., F.R.C.S. ENG., F.R.S.,

LIEUT.-COLONEL, I.M.S. (RET.)

LECTURE I.*—ÆTIOLOGY AND PATHOLOGY OF AMŒBIC LIVER ABSCESS.

*Delivered before the Medical Society of London on
Jan. 30th, 1922.*

I THOUGHT that amœbic disease would be a suitable problem to deal with in the Lettsomian lectures, especially as such great advances, in which I have been fortunate enough to have had a share, have been made with regard to it during the last two decades. As the late Dr. Sandwith ably dealt with dysentery in the Lettsomian lectures¹ delivered before this Society in 1914, I have chosen amœbic hepatitis, on which he had no time to speak, so that my lectures will be complementary to his, and at the same time will deal with that portion of amœbic disease which I had most exceptional opportunities of investigating during 20 years as pathologist to the large Calcutta Medical College Hospital, with access to unlimited clinical material in that and the other large Calcutta hospitals. In this period our great advance of knowledge of the pathology, prophylaxis, and treatment of both presuppurative and suppurative hepatitis have resulted in a remarkable saving of life. The story of these advances is unsurpassed in interest by any other recent discoveries in tropical medicine, although less dramatic than some of them on account of its more gradual development.

RELATION OF TROPICAL (AMŒBIC) LIVER ABSCESS TO DYSENTERY: HISTORICAL.²

At the beginning of the present century there was much confusion and difference of opinion regarding the relationship, if any, between dysentery and the large single tropical liver abscess, which it is essential to make clear before we can consider the recent advances in our knowledge. Nor was that difference of opinion surprising; by 1900 only one variety of the causative organisms of bacillary dysentery had been discovered, and that recently; and although amœbæ had been found in dysentery as early as 1875 by Lösch in Russia and in 1883 by Kartulis in Egypt, not until 1903 did Schaudinn describe and name the pathogenic *Entamoeba histolytica* and the harmless *E. coli*, and not till as late as 1913 did Walker and Sellards in the Philippines conclusively prove the pathogenicity of the former and the harmlessness of the latter. Similarly, Kartulis found amœbæ in sections of the walls of liver abscesses in Egypt in 1887, but up to 1902 they had only been found in about half the cases, and were very far from being accepted as the true cause of that disease. In India, as far as I have been able to ascertain, amœbic dysentery does not appear to have been recognised until, in 1902,³ I showed it to be common in Bengal, and that the so-called tropical liver abscess was always secondary to amœbic dysentery, usually of a latent nature, although as early as 1891 Councilman and Lafleur had come to similar conclusions in the United States. Now that these important facts are fully established it is easy to see that formerly the great stumbling-block was our ignorance of the fact that there are two great classes of dysenteries, considered as one definite disease until quite recently; so that those whose experience happened to be in countries where the bacillary form prevailed naturally—and, as far as their experience went, correctly—denied its relationship to liver abscess, while in countries such as Egypt and

India, where the amœbic variety is now known to be common, some noted the close relationship between dysentery and liver abscess, although others were misled by the frequent cessation of dysenteric symptoms for some time before a liver abscess appeared, into denying any such relationship. As I pointed out in 1913,² so definite is the relationship between liver abscess and amœbic dysentery that it is safe to assert that where numerous cases of dysentery without liver abscess complications were reported by older writers, the bowel disease must have been of the bacillary type and vice versa. Thus, neither Sir John Pringle in the terrible epidemic dysentery in the army in Flanders, in 1752, nor W. Baly in his 1847 Goulstonian lectures on dysentery in Millbank prison in London, met with liver abscess, and we now know that the prevailing type of dysentery in temperate climates, as well as in army and jail outbreaks, is bacillary. John Hunter, in his account of dysentery in the army in Jamaica in 1788, again does not mention liver abscess, and he considered the disease to be the same as that described by Sydenham as so prevalent in London in 1797–80.

On the other hand, all the great Anglo-Indian writers frequently met with liver abscess complicating dysentery, with the significant exception of Mackinnon, who dealt with jail dysentery in Northern India in 1848, while recent investigations show that to this day the bacillary type prevails in Indian jails, where the amœbic form is comparatively rare. Thus Annesley in 1828 records in his "Researches on the Diseases of India" liver abscess in 26 of 51 post-mortems on dysentery, while one of his beautiful coloured plates well illustrates amœbic dysentery as we now know it. It is also of great interest to note that Annesley divided dysenteries into uncomplicated and those showing hepatic symptoms, thus foreshadowing the present classification as bacillary and amœbic, although his descriptions and illustrations do not accurately correspond with the modern division. He also clearly stated that liver abscess was secondary to dysentery, and described the common post-mortem complications of sloughing amœbic dysentery—namely, peritonitis with or without perforation and post-colic abscess; hence it is quite certain that amœbic dysentery was common in Madras early in the nineteenth century. Twining in Bengal in 1835 also correctly described the post-mortem appearances and hepatic complications of amœbic dysentery, and pointed out that the bowel discharges may cease abruptly with the onset of liver symptoms, which were common in Europeans, but rare in natives of India, although the latter statement is at present far from true, probably on account of increased indulgence in alcohol among Indians. Parkes in 1846 found liver abscess in 21 per cent. of 61 post-mortems on fatal dysentery cases in British soldiers, but never found any in numerous post-mortems on Indians, being thus in agreement with Twining. He considered the abscesses were not pyæmic, as he never found inflammation or suppuration in the portal veins. Haspel in Algeria in 1847 and Bleker in Batavia in 1849 also found liver abscess a frequent complication of dysentery, the prevalent type in both countries being amœbic. Maclean in 1886 recorded liver abscess in no less than 60 per cent. of fatal dysentery cases in Madras, and Chevers, in his book published in the same year, supports the relationship, and quotes Waring as having found ulceration in the large intestine in 72 per cent. of a series of liver abscess cases, while Moore recorded figures of eight observers showing liver abscess in 18 per cent. or 1 to 8 of 1532 cases of dysentery, and Rankin in 150 fatal cases found dysentery without liver abscess in 66 per cent., dysentery with liver abscess in 28 per cent., and liver abscess without dysentery in 6 per cent. Fayrer, in his Lettsomian lectures before this society in 1881, quoted Sir Ranald Martin as having found liver abscess intimately related to disease of the cæcum, which is of great interest in relation to my own observations to be related presently.

* Lectures II. and III. will be published in coming issues of THE LANCET.

I may now pass on to the state of our knowledge in 1900, when I commenced my researches in Calcutta, and will begin with the opinions of the greatest modern authority, Sir Patrick Manson, as expressed in his classical work on Tropical Diseases. In the first three editions and reprints from 1898 to 1904 dysentery is treated as a single entity, although it was pointed out that the term probably included a group of diseases, and after discussing possible causative agencies, he summed up with the cautious wisdom of long experience, "Up to the present all or any of these claims, whether for bacteria or for protozoa, are still very far from being established," while he described the disease under the headings catarrhal, ulcerative, and gangrenous; bacillary and protozoal, including amœbic, dysenteries were not separately dealt with until the 1907 edition.

The confusion at the time I am speaking of is well illustrated by the completely contradictory statements in the articles on dysentery and liver abscess in the first edition of Allbutt's System of Medicine by Davidson and Lafleur respectively. Thus Davidson described the morbid anatomy of dysentery under the headings purulo-gangrenous and fibrinous or pseudodiphtheritic, which correspond roughly with amœbic and bacillary dysenteries as we now know them, while he did not admit that amœbæ might be a cause of dysentery. Further, one of his four classes of liver abscess was tropical or endemic hepatitis, occurring in tropical or sub-tropical countries associated with or independent of dysentery; and he concluded, "It is obvious from the facts before us that liver abscess occurs as an uncomplicated disease and that when complicated with dysentery it not infrequently precedes it," while he allowed no causative powers to the amœbæ, but held that tropical hepatitis was a primary hepatic insufficiency due to residence in a hot climate, "which favours the settlement and growth of pyrogenetic organisms in the liver, quite apart from any dysenteric complication," but he considered that an attack of dysentery might throw an additional strain on the liver and facilitate the entrance of bacteria by the portal vein. Lafleur, on the other hand, gave a clear account of amœbic dysentery, with amœbic liver abscess, both single and multiple, as its commonest complication, and attributed the suppurative action to the direct activities of the intestinal dysenteric amœbæ, as they were found in even small multiple liver abscesses without any accompanying bacteria, in which opinion he and Councilman were in advance of Kartulis, who held that the amœbæ produced liver abscess indirectly by carrying bacteria to the organ, the latter being less resistant than the amœba and dying in many cases—a view I have never been able to understand, as pyogenic bacteria do not so readily die out of abscesses in other parts of the body, although it may partly be explained by the inconstant results of the findings as regards bacteria and amœbæ in the small number of liver abscesses dealt with in the earlier papers on this aspect of the question. Thus, Kartulis found bacteria in 5, while 8 were sterile; Kruse and Pasquale found amœbæ in 6 and bacteria in 11 of 15 cases examined; and Councilman and Lafleur found bacteria in addition to amœbæ in 1 of 2 cases—cocci having been found 10 times and bacilli 6 times. Thus it is not surprising that the amœba was not accepted as the cause of the disease, although Manson in his earlier editions stated that they were present in over half his cases, which fact, however, did not convince him of their causative powers.

Lastly, in a discussion on dysentery at the 1902 meeting of the British Medical Association, our knowledge of the subject at that time was summarised in his opening address by the late Andrew Duncan,³ lecturer at the London School of Tropical Medicine and a very able and experienced retired I.M.S. officer, who had the misfortune to be a decade or two ahead of his time—with the result that his career in India was ruined by his having the audacity to criticise the antiquated views of his director-general on cholera;

that fate I was more fortunate in escaping, although certainly not through any want of outspokenness on my part. In opening the discussion on dysentery Duncan said: "India is a tropical country and I would advance the view that the amœba has nothing to do with dysentery in that country as a causative agent. The evidence brought forward in its favour to my mind is not at all conclusive." On the vexed question of the relationship, if any, of liver abscess to dysentery, he said: "My own view is that large tropical liver abscesses do not bear any special relation to antecedent dysentery, but that multiple abscesses do," and he correctly remarked that liver abscess was rare in the West Indies, in English asylums, and during the South African War, in the last two of which at least the prevalent type of dysentery is now known to have been bacillary. Very similar views were also expressed about this time in a short editorial note in the *Indian Medical Gazette*, in which the rarity of liver abscess cases in Indian jails was advanced as an argument against the disease being in any way related to dysentery.

Enough has been said to prove that, in spite of the valuable work, especially of Kartulis and Councilman and Lafleur, medical opinion in 1902, particularly in India, was against the recognition of amœbic dysentery as a distinct disease and also to a great extent contrary to its acceptance as the causative agent of tropical liver abscess, while there were still great differences of opinion as to whether such abscesses were in any way directly associated with dysentery. It was to the 1902 discussion on dysentery that I contributed my first paper on this subject, based on two years' researches in Calcutta, which may next be summarised.

CALCUTTA RESEARCHES OF 1900-02 ON AMŒBIC DYSENTERY AND ITS RELATIONSHIP TO TROPICAL LIVER ABSCESS.

Between April, 1900, and the end of 1902 I acted for the most part as professor of pathology at the Calcutta Medical College Hospital, and devoted much of my time to investigating amœbic disease; as early as July, 1900, I found numerous active amœbæ in both the wall of a liver abscess and in the dysenteric ulcers in the large bowel, which I believe was the first recognition of amœbic dysentery in India. As early as 1870 and 1871 Lewis and Cunningham had found amœbæ in cholera and other cases, but Cunningham certainly considered them to be non-pathogenic, while, according to Dobell, they were probably the harmless *E. coli* of present nomenclature. I am credibly informed that McConnell found living amœbæ in liver abscess pus in Calcutta soon after and independently of Kartulis, but as far as I can learn he never recorded his experience, while Lafleur, in his 1897 article on amœbic dysentery, makes no reference to its having been found in India. During the next two years I worked at the subject with abundant post-mortem and clinical material and recorded my results in 1902 and 1903 in two papers, the main points of which were as follows.

Constancy of Amœbæ in Tropical Liver Abscess.

The first point I set to work to elucidate was the frequency with which living amœbæ could be demonstrated in the large tropical liver abscesses so frequently met with in India and Calcutta. I soon found that at post-mortems it was always easy to detect them in large numbers in the walls of such abscesses by scraping the latter and searching the material under a low power of the microscope, but much more difficult to find them in the thick pus in the centre of such abscesses, which was in accordance with Kartulis's demonstration of amœbæ in sections of the walls of liver abscesses in Egypt. In order to get a larger number of cases than the post-mortems afforded, I next arranged with my surgical colleagues when they opened a liver abscess, as was almost invariably the procedure in those days, to place some of the thick pus in one sterile test-tube and in another a light scraping of the wall of the cavity taken with a Volkmann spoon, and in this way I accumulated the

data in the first two tables of my 1902 paper, including 17 cases examined post mortem and 20 at the time of opening. In the first place in 22 cases in which the thick pus was examined in only 4 were amoebæ found. On the other hand, with much less expenditure of time, the protozoal parasites were found in scrapings of the abscess walls in no less than 35 of the 37 cases, while of the two negative cases one was examined first on the twelfth day after being opened, and the other post-mortem 14 days after being incised and drained, by which time the amoebæ might have died out. Living amoebæ were, however, found in scrapings made on the third, fourth, and ninth days after being opened, others having found them in the discharge several days after operation. Active amoebæ were thus found by my method of scraping the abscess walls in 35 consecutive cases examined at the time of operation, dressing or post mortem within nine days of being opened and drained. I therefore concluded that they are practically invariably present, as I have since verified in scores of later cases, the only exceptions being the rare small encysted abscesses from which the amoebæ have died out.

Sterility of Great Majority of Amoebic Liver Abscesses when First Opened.

The next point to decide was the frequency of pus-forming bacteria in large tropical liver abscesses, which are so different clinically from pyæmic, pylophlebitic, and cholangitic multiple liver abscesses due to septic organisms. Out of 24 cases in which cultures were made from the pus taken in sterile test-tubes at the time of operation, 15, or 62 per cent., were sterile, as were 3 out of 5 unopened abscesses found post mortem, or nearly two-thirds of the total cases. In a later series of observations I found 86 per cent. of 87 cases sterile on first being opened, so it is clear that the very great majority of such amoebic abscesses are free from culturable bacteria, while none could be found microscopically. Unfortunately, few remained sterile for long in a tropical climate after opening and drainage in the ordinary way into dressings; this point I shall return to in my next lecture.

I therefore concluded that not only were the amoebæ constantly present in active large tropical liver abscesses, but that other causative bacterial organisms were completely absent in the great majority of them, thus confirming by the examination of a large amount of material the opinion of Councilman and Lafleur that the amoeba, since identified as the *Entamoeba histolytica* of amoebic dysentery, was the causative organism of this class of liver abscess.

Frequency of Association of Dysentery with Liver Abscess

Very early in my investigations I became convinced that the large tropical amoeba-containing liver abscesses in Calcutta were very frequently accompanied by dysenteric lesions post mortem, and that they were always associated with the amoebic and never with the bacillary type of that disease, and now that I had discovered the prevalence of amoebic dysentery in India, the key was furnished to the remarkable variations in the proportion of liver abscess cases to dysentery recorded by various observers, which it was of great importance to follow up. The striking fact that the proportion of liver abscess to dysentery cases in the British Army in India was 1 to 5 to 1 to 7, while in the Indian jails it was only one to several hundred, had never received any satisfactory explanation, as early and efficient treatment by the European medical officers might be expected in both cases. If, however, the prevailing type of dysentery was amoebic in the first case and bacillary in the second the problem would be solved, and this is now known to be the case. Moreover, the then recent discovery of the dysentery bacillus by Shiga and Kruse, and a little later of another type by Flexner, with the aid of which serum reactions could be obtained in the more chronic cases, opened up a new field of research in clinical

differentiation of the dysenteries, of which I early availed myself, as reported in my second paper of 1903.

The first point to be determined was the frequency of the association of any form of dysentery with liver abscess in view of the widely divergent data recorded regarding it, as already pointed out. On turning again to the cases in which both the clinical records of antecedent dysentery and the post-mortem appearances in fatal liver abscess cases were noted, it appears that in four cases there was no clinical history of dysentery, yet amoebic ulcers were found post mortem, proving that an absence of clinical signs of dysentery does not exclude the presence of amoebic ulcers in the large bowel. Again, in the clinical and post-mortem records of 14 further cases in three there was a previous history of dysentery 18 days, 3 months, and 1 year respectively before admission for liver abscess, yet no ulceration of the large bowel was found post mortem, so it is also possible for antecedent dysentery to clear up without necessarily leaving any ulceration by the time the patient dies of liver abscess. It is clear from these facts that in order to get accurate data of the relative frequency of antecedent dysentery in liver abscess cases it is essential to obtain both clinical and post-mortem records, and even then it is possible that a mild attack of bowel trouble of amoebic origin, which often gives rise to only slight diarrhoea, may be overlooked clinically and leave no evident post-mortem appearances, so that even with such complete records a few negative cases will not exclude antecedent latent amoebic ulceration of the large bowel, as I shall presently show. On adding together the two series we have 24 cases in which the clinical and post-mortem records were complete, in 23, or 95·83 per cent., of which there was either a clinical or post-mortem evidence of dysentery, while in 58·33 there were both.

On examining the post-mortem records before my time I found that abstracts of the clinical records had also been entered in many of them, especially in the time of McConnell, who would have been a much greater pathologist if he had not also had to do the work of resident physician and to vacate the pathology professorship under the rules on completing 12 years' service, when he soon became the leading physician in Calcutta. On adding these older and clinically less complete records to the foregoing cases we have clinical and post-mortem data regarding 63 liver abscess cases with evidence of dysentery in 90·48 per cent., including 55·5 with both clinical and post-mortem evidence, 20·63 per cent. with only post-mortem, and 14·3 per cent. with only clinical evidence of that disease. The remaining 9·52 per cent. of negative cases are easily explained by incompleteness of the records and the healing of slight latent ulceration of the colon before death from subsequent liver abscess. I therefore concluded that dysenteric ulceration of the large bowel is an almost, if not invariable, accompaniment of large tropical liver abscesses.

Lastly, in all my own cases the dysenteric lesions found post mortem in liver abscess cases were of the amoebic variety, and as far as I could judge from the older records the same was largely true, while an analysis of clinical records showed that in 80 per cent. there was clear evidence that the amoebic bowel disease preceded the fever and hepatic pain, which I took to indicate the commencement of the liver complication, in 7·5 per cent. the dysenteric and liver symptoms commenced about the same time, and in another 7·5 per cent. the symptoms of dysentery set in after the hepatitis, but in both these last classes the post-mortems showed older as well as recent lesions, while in the remaining 5 per cent. no bowel lesions were found post mortem, although there was a history of more recent dysentery than hepatitis, so still earlier slight dysentery may have been unrecorded. I therefore concluded that amoebic dysenteric ulceration of the large bowel, often of a latent nature not giving rise to any very evident clinical symptoms, always preceded the formation of

a large tropical liver abscess, to which the liver complication was secondary.

Value of Early Results.

I have dealt at length with the results obtained in my first two years' investigations of amoebic disease, as they formed the basis of the advances I was able to make in the remaining 18 years' work in Calcutta, while it is clear that my conclusions were diametrically opposed to those of the distinguished tropical physician who opened the 1902 debate on dysentery; I think it will be of interest to add that when home on leave in the following year I met Duncan for the first time, and with the greatest candour he volunteered the statement that my paper upset nearly everything he had said in his opening address, so it is evident that the facts I then brought forward were of some value in clearing up much-debated points regarding the relation of dysentery to liver abscess and the true ætiology of the latter.

There was, however, one error in my 1902 paper which I corrected in that of the following year on amoebic dysentery in India. It will be noted that I have so far only spoken of large single tropical liver abscess and said nothing about small multiple ones, which I at first thought, with nearly all my predecessors, to be pylophlebitic in nature, and I at first came to the conclusion that 17 cases of multiple small abscesses of the liver in the former post-mortem records were septic portal infections secondary to dysentery usually "of the ordinary catarrhal as opposed to the amoebic variety." Further experience soon showed me that innumerable small liver abscesses were not rarely secondary to acute sloughing amoebic dysentery often without very evident clinical hepatic symptoms, and bacteriologically completely negative, although swarming with active amoebæ, as Lafleur had previously recorded. Throughout my long subsequent experience of post-mortems in Calcutta I examined many such cases, and, much to my surprise at first, I always found them to be amoebic in origin and generally sterile as regards bacteria, so that in some 200 dysentery post-mortems, many of them sloughing or gangrenous cases, I never met with a single pure bacterial portal pyæmia with absence of amoebæ, although double infections with both classes of organisms were not so very rare. This is very astonishing when we think of the large number of chronic dysenteric ulcerations, including numerous cases of bacillary dysentery seen in the Calcutta post-mortem room, through which septic infection of the portal system might be expected to occur not infrequently, and the rarity of pylophlebitis under such conditions is difficult to explain. I think it is largely due to the fact that the pathogenic lesions of bacillary dysentery are essentially a toxic necrosis of the epithelial layers of the mucous membrane not much affecting the more vascular submucous coat (as shown in Plate 9 of my "Bowel Diseases in the Tropics"), while in the more chronic forms of bacillary dysentery there is a good deal of fibrous tissue formation in the bases of the shallow ulcers, which protect the more vascular deeper layers from microbial invasion (illustrated in Plate 10 of the same work). On the other hand, the lesions of amoebic disease are essentially an affection of the submucous coat (Plates 5 and 6, of the above), often extending in the more acute cases through all the layers of the bowel wall to reach the peritoneal coat. Whatever the explanation may be, I am sure that the great majority of small multiple liver abscesses seen in Calcutta are amoebic in origin; an important fact I shall return to presently in considering the mode of formation of the large single liver abscess, after dealing with the further evidence I have accumulated regarding the relationship of amoebic liver abscesses as a whole to amoebic dysentery active and latent.

In 1913² I was able to supplement the data I recorded in 1902 of clinical or post-mortem evidence of dysentery in 90 per cent. of liver abscess cases by an analysis of 45 post-mortems I had performed in such cases in the previous ten years, with active

amoebic dysentery in 77·8 per cent. and scars of former dysenteric lesions in 20 per cent. more, or a total of 97·8 per cent., leaving only one case with no post-mortem evidence of dysentery; proving that by careful search for dysenteric lesions they can practically always be found in fatal amoebic liver abscess cases. I also recorded at the same time an analysis of careful clinical records of 50 liver abscess cases in patients in the Calcutta European hospital during nine years with a history of dysentery in 72 per cent. and of diarrhoea in another 14 per cent., leaving only 14 per cent. without history of any looseness of the bowels, thus confirming my earlier data on this point.

Distribution of the Lesions in the Bowel in Relation to the Type of Amoebic Liver Abscess.

In studying a series of fatal liver abscess cases in the post-mortem room nothing is more striking than the differences between the typical large fibrous walled chronic single amoebic abscess and the multiple small acute abscesses from the size of a walnut down to that of a large pin's head, all secondary to amoebic ulceration of the large bowel. A close examination, however, of the distribution and extent of the bowel lesions (see diagram) throws much light on the matter. The positions and extent of the lesions, from the lowest part of the ileum down to the rectum, are shown diagrammatically by shading in 96 consecutive post-mortems in which I carefully noted them. The first line shows 27 cases of bacillary dysentery divided into acute cases with a continuous series of lesions extending in most of them from the lowest few inches of the ileum down to the rectum, and chronic ones of over one month's duration in which, as a rule, only the lower half or two-thirds of the colon is affected, a point of importance in regard to treatment as I have elsewhere pointed out. As none of these bacillary cases were complicated by any form of liver abscess they do not concern us further in this connexion, except to point out how relatively few they are compared with the number of fatal cases of amoebic disease, including those due to liver abscess, as shown in the last three lines of the diagram. The second line shows 25 cases in which the direct cause of death was amoebic dysentery, also divided into acute and chronic cases. It will be observed that in 5 of the 15 acute cases liver abscesses were also found, in 4 of which they were multiple small ones, and in the remaining a single small abscess, while in 4 acute peritonitis was present. Among the 10 fatal chronic amoebic dysenteries perforation was the cause of death in 4 and abscess around the spleen in 1. The last two lines show the bowel lesions in 42 cases in which death was attributed to liver abscess, while in 2 the fatal issue was due to post-colic abscess, and in Case 44 to cirrhosis of the liver. The liver abscess cases have been classified in accordance with the number and sizes of the abscesses—namely, multiple small ones in 1 to 5 and 20, from two to four large chronic fibrous-walled abscesses in Cases 6 to 17a, and single large ones in Cases 21 to 43, the great majority of which had been diagnosed as such and opened during life. It will thus be seen that the number of deaths directly due to liver abscess were nearly twice as numerous as those directly due to amoebic dysentery, clearly proving the immense importance of this serious complication.

Bowel Lesions in Small Multiple Liver Abscesses.

A cursory examination of the diagram will at once attract attention to the great differences in the extent and distribution of the large bowel ulcers in the multiple small and one or more large abscesses respectively, which is what I want particularly to direct your attention to. Thus in no less than 8 of the 9 cases of multiple small abscesses the colon showed large sloughing or gangrenous ulcers represented by the extensive darkly-shaded patches in the diagram, while in 7 of the 9 these extensive lesions were distributed over the great portion of the total length of the large intestine, although never invading the ileum, as acute bacillary dysentery usually does.

life were found post mortem to be accompanied by numerous small ones throughout the liver, and so belong to a class intermediate between multiple small and single large abscesses, while the bowel lesions were also intermediate in extent between the usual types of distribution in the main classes of suppurative hepatitis—namely, a few large ulcers not very widely distributed through the colon, while Case 14 in line 2,

[illegible]

The parts of the bowel in each case affected by the dysenteric process are in the diagram shaded *continuously* when the mucous membrane was uniformly involved over a large part of the intestine, as is usual in bacillary disease, and shaded in an *interrupted* manner when there were healthy portions of the mucous membrane remaining between the ulcers, as is almost invariably the case in the amœbic form. *Transverse dark lines* represent ulcers extending across the axis of the bowel with healthy mucous membrane between them; a *dot* stands for small round or oval separate ulcers on an otherwise normal mucous membrane of less advanced amœbic disease; the *separate square or oblong* shaded parts represent the large thickened patches of ulcerated bowel in acute amœbic dysentery. An *X* indicates scarring of healed ulcers, and a *dot within a small circle* represents perforation of the large bowel at the point indicated.

with a single small abscess, also shows similar moderate bowel lesions.

There remains the exceptional Case 5 of line 3 with multiple small abscesses and very limited small amoebic ulcers in the descending colon and scars in the sigmoid, the history of which is most instructive. The patient was a young boy—in such cases liver abscesses are very rare—admitted for a fractured femur for which tenotomy of the tendo Achillis was performed with subsequent septic infection of the small wound. He died very suddenly and unexpectedly, and post mortem I found four large and numerous small liver abscesses containing numerous amoebæ and streptococci, the latter also being recovered from the wound, so I attribute the numerous small liver abscesses with only slight bowel lesions to the combination of secondary streptococcal with a primary amoebic infection, and it is noteworthy that such extensive liver lesions again aroused no suspicion during life.

It will be clear from the foregoing analysis that small multiple amoebic liver abscesses are essentially an acute, and usually quite unsuspected, complication of extensive sloughing amoebic dysentery with well-marked bowel symptoms, and consequently form quite a distinct clinical condition from the insidiously developing large single abscess with very slight or completely latent bowel symptoms, such as are illustrated in the remainder of the diagram to which we may now turn. A glance at the distribution and extent of the bowel lesions in Cases 6 to 17a of line 3 in which from two to four large chronic abscesses were found, and of 21 to 43 in line 4 with a single abscess, reveals such a close similarity between the two series that it is clearly only an accident whether one or two to four collections of pus happened to form, so their causation may be considered together. It will be seen that in none of them were the bowel lesions so large or widely distributed as in the acute sloughing dysenteries accompanying multiple small liver abscesses. Still more striking is the fact that in no less than 13 of the 36 cases the ulcers were absolutely limited to the cæcum, while in four more they only extended to the ascending colon, so that only the uppermost fourth of the large bowel was involved in nearly half the cases, while in several more only a very limited part of the colon was involved. In all such cases dysenteric symptoms are nearly certain to be completely absent while the patient is under observation for liver abscess, and in many of them no history of previous dysentery will be obtainable. Moreover, in Cases 38 to 43 only scars of former dysentery were found, which are indicated by small crosses in the diagram, and if we add these six cases to those with very limited ulcers we get a total of no less than 23 out of 36 cases, or almost two-thirds, in which the dysenteric lesions were pretty certain to have been latent during life at the time the patients came under observation for liver abscess. We thus obtain from this study a complete explanation of the former great stumbling block against the recognition of tropical liver abscess as always secondary to dysentery—namely, the absence of clinical signs of that disease in the large majority of patients suffering from this serious liver affection, and conclusive confirmation of the position I took up in 1902—that large single liver amoeba containing liver abscesses are always secondary to amoebic ulceration of the bowel, usually of a latent nature.

Method of Formation of the Large Single Amoebic Liver Abscess.

It is generally agreed that the amoebæ pass from the bowel wall to the liver as a rule through the portal vein, but it is difficult to explain the formation in this way of the common large single fibrous-walled abscess. This, however, is the end-product of a somewhat chronic pathological process, and it is only by a study of all the stages of its production from the earliest beginnings that we can hope to elucidate the problem, a possible solution of which I put forward in my paper of 1903,⁴ in which the earliest stages are

illustrated, as seen in the acute rapidly forming multiple small abscesses of the liver accompanying sloughing amoebic dysentery, which I have mentioned is generally a pure primary amoebic infection. In Fig. 4 of that paper is depicted a minute pinhead-sized abscess with clotting in an interlobular branch of the portal vein and commencing cellular infiltration and softening of its walls from a case of mixed amoebic and staphylococcus infection, while the small hepatic arteries and bile-ducts are healthy. Fig. 5 of the same paper, from a case of pure amoebic infection, shows both well-stained apparently healthy and granular degenerating amoebæ entangled in blood-clot within a small branch of the portal vein. It is clear from these specimens that the earliest stage of the formation of small multiple amoebic liver abscesses is inflammation with clotting in the minute branches of the portal vein, where the amoebæ coming from the bowel ulcers lodge, which is followed by softening of the thin walls of the blood-vessels and extension of the inflammatory process to the liver parenchyma. I believe that the addition of a bacterial infection greatly facilitates the softening and breaking down of the vein walls, with the formation of numerous minute abscesses, especially when the virulent, but comparatively rare, streptococci are present; and that this accounts for the rapid formation of small abscesses, in addition to several large ones in the mixed amoebic and streptococcal infection in the tenotomy wound case already mentioned in the absence of any extensive amoebic bowel ulceration. On the other hand, when multiple small abscesses arise in the liver as a result of pure amoebic infection secondary to extensive sloughing dysentery, the protozoal organisms reach the liver in enormous numbers, as is evident from the number seen in a single field of an ordinary high power of the microscope in the blood-clot in a minute interlobular vein in the figure I have just shown you. In that, the usual case, I suggested that the clotting in the small veins is sufficiently extensive at various points to cut off the blood-supply from small areas and so produce focal necrosis leading in their turn to softening of the walls of the veins, enabling the amoebæ to escape into the soft-liver tissues and produce abscesses.

We have next to consider the more difficult problem of how one or more large abscesses can develop as the result of a portal infection, but first I must say a few words regarding other possible modes of infection of the liver. In my first paper I was inclined to think that the frequency with which large abscesses occurred in the upper part of the liver under the diaphragm, and the fact that in acute amoebic dysentery the protozoal organisms frequently penetrate the whole thickness of the bowel wall and are found in the lymph on its peritoneal coat without actual visible perforation, suggested the possibility of their passing in the lymph flow up to the under-surface of the diaphragm and there penetrating the liver substance or producing the so-called perihepatic abscess. It is possible for a liver abscess to be formed by direct extension of amoebic infection from the bowel to the liver, but I have met with only one case of this nature, so it is quite exceptional. The next coloured drawing shows the opposite condition of extension of an hepatic abscess to discharge into the colon, which also shows a very chronic form of amoebic dysentery, which, as a matter of fact, had not produced dysenteric symptoms while the patient was in hospital for the hepatic complication. Further studies by cutting sections of the walls of apparently suprahepatic abscesses convinced me that they are really formed within the organ, and not between it and the diaphragm, and what at first sight appears to be the capsule of the liver is really the deep fibrous wall of an abscess within the organ, the outer wall of which has merged with the diaphragm to which the liver had become adherent, the abscess having thus originally developed within the organ, as is quite clearly the case with the great majority of such collections of pus. Moreover, single liver abscesses

are rarely found in sloughing amoebic dysentery with penetration of the parasites to the peritoneal coat of the bowel, but only multiple small ones which are certainly portal infections, so it is evident that we cannot explain the development of the large single abscesses as a class except as infections from the bowel through the portal vein.

We have to look to another intermediate stage to explain the ultimate development of the fibrous-walled large abscesses, which is not very commonly met with, although I have seen several in my long experience of tropical pathology. I refer to large ragged cavities without well-defined walls, which are intermediate in acuteness, and in the extent of the primary bowel lesions, between the small multiple and the large chronic abscesses. In such cases there is no definite limiting membrane, but the tissues around the irregular cavity are infiltrated by pus and appear at first sight to be a number of minute abscesses immediately surrounding the central collection of pus. On making sections it can be demonstrated that the suppurative process is extending from the central cavity along the veins, in which clotting and softening is taking place accompanied by very numerous amoebæ, without any bacteria being present in at least some of the cases, the pathological process being thus but a more extensive development of that by which the small multiple abscesses are produced. We have only to imagine a somewhat less acute process in which the patient survives long enough to allow the active spread of the suppuration to come to an end, and organisation of the inflamed tissues around the cavity to take place and form a fibrous capsule and we can visualise the whole process of the development of the more chronic type of abscess. We have also seen that in cases in which one to four large chronic abscesses are found the amoebic ulceration of the bowel is comparatively slight and superficial, and usually limited to a very few ulcers in the upper part of the colon, so that the number of amoebæ likely to reach the liver through the portal vein within a limited time in such cases will be infinitely fewer than in the extensive sloughing dysentery accompanied by multiple small abscesses. I shall show in a later lecture that very many cases of acute amoebic hepatitis may clear up without going on to definite abscess formation, so it is clear that many amoebæ may reach the liver without suppuration in the organ necessarily taking place, in which respect the amoeba apparently differs from pyogenic bacteria producing pylephlebitis, I believe owing to the greater difficulty with which the protozoal parasite causes inflammation of and breaks down the walls of small veins.

Taking all these facts into consideration I suggest that in the slight or latent amoebic colitis from which large amoebic abscesses usually result, the comparatively few amoebæ reaching the liver become entangled in blood-clot in the small interlobular veins, producing congestion of the organ, but that the vast majority of them undergo degeneration within the vessels, not being able to escape through the vessel-walls without some previous damage to their coats, in which case only what I have called presuppurative amoebic hepatitis results. If septic organisms are also present softening of the vein walls and multiple small abscesses may occur with slight bowel lesions, as I have already shown, but these are exceptional cases. When, however, the amoebæ happen to reach some part of the liver in such numbers as to cause clotting of several contiguous small veins so as to interfere with the blood-supply sufficiently to produce a small focal necrosis with consequent softening of the walls of the veins allowing escape of the amoebæ into the soft-liver tissue, the commencement of an abscess results. The organisms then spread along the opened veins producing further clotting and softening, as I have shown occurs at the margin of an actively spreading ragged walled abscess, with further breaking down of the liver substance and extension of the cavity, and this process continues in concentric circles until, if the patient survives long

enough, a fibrous capsule develops, when the abscess only increases by distension of the cavity by continued formation of pus from its walls, but without further destruction of liver tissue—an important practical point I shall return to in my next lecture. Thus I conclude that almost all forms of amoebic liver abscess are due to pure amoebic infections from the bowel through the portal veins with variable numbers of amoebæ, while it is also easy to understand that whether an amoebic hepatitis goes on to suppuration or not may often be in the balance, so that certain predisposing causes, such as chills or alcohol, may easily turn the scale and bring about suppuration, which early diagnosis and suitable treatment may prevent.

CONCLUSIONS.

I have now completed my survey of the principal points in the ætiology and pathology of amoebic hepatitis, which I have dealt with at length because I hope to prove in the remaining lectures that amoebic liver abscess is both an easily preventable and a much more readily curable disease than it was only a few years ago, and that fatal cases have already so greatly decreased in India, and doubtless elsewhere, that future investigators will have little chance of obtaining the abundant material I had in my 20 years' work in Calcutta, that paradise of tropical pathologists.

My conclusions, which are now in agreement with those of more recent observers too numerous to mention, may be briefly summarised as follows. The serious affection formerly known as tropical liver abscess, both in the acute multiple, small, and chronic large single forms, is produced by infection through the portal vein with the *Entamoeba histolytica*, only very occasionally assisted by bacteria, and is always secondary to antecedent amoebic ulceration of the large bowel, which is clinically active and acute in the multiple variety, but usually completely latent clinically in the more chronic single variety, while such abscesses never occur in relation to bacillary dysentery—conclusions which are a great advance on the generally accepted knowledge two decades ago.

References.—1. THE LANCET, 1914, ii., 637, 683, 731, and 783.
2. Dysenteries, 1913, pp. 1-33. 3. Brit. Med. Jour., 1902, ii., 844. 4. Ibid., 1903, i., 1315.

The Advantages

OF THE

METRICAL SYSTEM FOR PRESCRIBING.

Introduction to a Discussion at the North British Branch of the Pharmaceutical Society of Great Britain, held in Edinburgh on Feb. 15th, 1922,

BY W. C. SILLAR, M.D., B.Sc. EDIN.,

LECTURER ON EXPERIMENTAL PHARMACOLOGY, EDINBURGH UNIVERSITY.

THIS subject has been forced on our attention by circumstances due to the war. The unusually large number of students attending the class of materia medica, the necessity of giving an adequate medical education to them without lowering the standard of knowledge and acquirement, the loss of time which many of them had experienced, and the difficulty encountered in resuming their studies, together rendered it necessary to lighten the curriculum or to make it more easily overtaken. Instead of teaching two systems, therefore, and letting the individual student exercise his preference, we weighed the relative advantages and disadvantages, made our choice, and adhered to that entirely. During the last two years we have learnt much, and desire to make known the results of our experience to the pharmaceutical as well as to the medical profession. The conclusions formed from this experience are that metrical prescribing will certainly displace the imperial method, that the process of changing from one to the other will probably begin at once, and that the numbers of those who prescribe according to the metric weights and measures will gradually, if not rapidly, increase.