PREVENTION of KALA-AZAR in CHINA.

A Public Health Experiment in Tropical Medicine.

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PREVENTION OF KALA-AZAR IN CHINA.

SCOPE of THESIS.

An attempt to find a method of clearing kala-azar from a large, heavily endemic area by the quickest and cheapest procedure which combines accuracy of diagnosis and treatment with the greatest economy in skilled workers, thus being suitable for the primitive, poverty-ridden conditions existing in the interior of China.
KALA-AZAR PROBLEM IN HONAN PROVINCE.

During the Japanese war the Friends' Ambulance Unit sent a convoy of medical and relief workers to China where they were employed on transport and medical problems in a number of areas during the period of active hostilities. In 1945, however, with the capitulation of the Japanese army there was opportunity for a new type of service of a more static and planned nature, especially in the Province of Honan where there was being set up a rehabilitation scheme embracing hospital re-organisation, agricultural reclamation, industrial re-equipment and medical emergency work, e.g. in severe malaria and cholera outbreaks.

While the hospital rehabilitation scheme was of primary importance, due not only to the great need but also to the fact that the composition of the Unit made this work most suited to the abilities of the members, there was available a number of members who had had some medical training, at the least a few months general ward nursing duties and in some cases a moderate experience in the techniques of elementary bacteriological and haematological procedures. It was felt that there was thus an opportunity for a planned attack on a specific disease as nearly as possible embodying the elements of modern Western Public Health methods of a technical standard comparable with the best Asiatic medicine: this,
it was thought, would serve a four-fold purpose.

1. it might per se be of lasting value to the local community.

2. it would be a piece of therapeutic and prophylactic research which is not often possible in the interior of China.

3. it would be a demonstration of the modern conception of Public Health procedures in an area where medicine is rudimentary outside (and frequently inside) the mission hospitals, with the exception of a very few private and Government institutions, and, if successful, it might serve as a model for future Chinese or foreign field work.

4. it would probably be, at the very least, instrumental in saving life on a fairly large scale.

The Friends' Ambulance Unit was fortunate that in its Medical Director, R.B. McClure, M.D., F.R.C.S.E., it had the benefit of an intimate acquaintance with the region coupled with great organising ability: his recommendation that kala-azar was the disease par excellence amenable to attack was fully realised as experience of the epidemiology of the country became common to all the Unit medical officers. The reasons for choosing to campaign against kala-azar specifically include:

1. it is prevalent and thought to be spreading in the area.

2. it is fatal in a high percentage of cases, if not treated with specific drugs, but if treated shows a high percentage of permanent cures and, oddly enough, one "advantage" of the high death-rate and obvious cachexia of the disease is the manner in which it lends itself to money-raising publicity schemes in Western countries, thus ensuring further supplies of medicaments.
3. The life-cycle of the parasite is such that the only feasible point at which it could be broken would seem to be in the patient by intensive treatment.

4. A supply of the appropriate drugs was available to start the campaign.

5. The populace is perhaps less indifferent to this disease than to the many others which afflict them, and is thus more likely to attend for treatment.

6. Essential laboratory investigations are not too difficult and the treatment lends itself to a high degree of standardisation, resembling in this particular that of early syphilis, which brought it within the range of ability of the F.A.U. members chosen for the work.

7. Any medical practitioners in the districts visited could only benefit from observation of both diagnosis and treatment while they were in progress.

8. The current treatment of kala-azar in the area was, epidemiologically speaking, a failure, for reasons to be discussed later.

9. All treatment would at first be given by F.A.U. members, which would obviate a disadvantage common in the East where drugs which are distributed to be taken orally or otherwise are sold by the patients or, regrettably, sometimes by the medical workers to whom they are given. Such a situation actually arose during an epidemic of malignant malaria just south of the F.A.U. area.

10. It was realised that a comprehensive anti-kala-azar scheme ought to incorporate some effort directed against infected dogs but that this was an addition to the fundamental drive and could be undertaken profitably only by the local authorities, who would require to be shown the effect of patients' treatment alone before there could be any hope of persuading them to move against the zootic disease which is prevalent in some parts of China.

There are two other major infectious diseases afflicting Honan: the first, malaria, was not prevalent in the northern area but was endemic not far south of the present kala-azar region and produced the severe epidemic
of malignant malaria mentioned above. The mortality, although considerable in times of epidemicity, is not to be compared with that of kala-azar, while the treatment is reasonably simple and has some hope of success via the local Government clinics, if only a plentiful supply of drugs was available.

The other disease which is widespread is syphilis, but any thought of conducting a drive against this condition could be at once dismissed as it would immediately meet with the difficulty which envelopes progress in China like a pall, the indifference of the population. Not only are the symptoms of early syphilis made light of but it seems to be fact that the tertiary stages, although they undoubtedly occur, are not as common as in the West and, indeed, the writer saw very few cases of late cardiovascular, cutaneous or neurosyphilis in quite extensive travelling from S.W. China to N. Honan.
CURRENT METHODS OF THERAPY.

Since it was by this time clear that a project directed against kala-azar would be the most rewarding, the next step was to review the current methods of treatment in an endeavour to understand why the disease, far from being reduced, was reported to be spreading and increasing in its incidence. Scovel (1), reviewing the relevant literature, says that there has been a marked increase in N. China in the last few years. The reasons were not at all obscure and included the following:

1. it is well established that the condition is normally found among the poorer sections of the community and the standard of life in N. Honan is low, so that the predisposing causes of malnutrition and chronic diseases, e.g. skin sepsis, tuberculosis, and syphilis, are widespread.

2. the fact that kala-azar is prone to spread in the wake of war, destruction and famine has been pointed out by Lowe (2), among others: N. Honan had been in Japanese hands for some years before the F.A.U. arrived.

3. the Chinese disease is found in hot dry regions where the sandflies flourish and so abounds in the sandy areas, especially along the course of the Yellow River as it traverses Honan.

4. treatment had previously been on humanitarian lines in the mission hospitals, and on strictly business principles in the Government hospitals and among the private practitioners, while the traditional Chinese "medicine men" do not use specific remedies at all.

To take the methods of the mission hospitals first, it was seen that in many of them the treatment was probably adequate (when drugs were available) although it was noticable that some religious bodies were less
scrupulous than others and gave grossly inadequate therapy. Even with optimum individual treatment this could, naturally, be given only to those who came to the clinics, and unfortunately this was restricted normally to those who had money to pay for the drugs and who were sufficiently enlightened to maintain regular attendance, not always an easy matter where patients could not afford to stay in hospital and long distances had to be covered to and from the clinics, especially at times when there was much work to be done in the fields.

Hospitals and clinics where treatment could be obtained were widely separated and occasionally so far from patients that the latter would be unaware of their existence, and in the manner of primitive peoples quite lacking in initiative to seek remedies outwith their own small circle. Napier and das Gupta (3) report the same findings: in the area with which they were concerned they state that prior to their arrival a few cases of kala-azar had been diagnosed and treated but though it was realised by the inhabitants that there was a considerable amount of this disease in the district, the very large majority were not making an attempt to attend any of the Calcutta dispensaries where suitable treatment was available only five miles away. In the same way the position of the clinics all over the north of Honan province was that they had a constant attendance of kala-azar patients which looked quite impressive but consisted,
of only a few from each part of the surrounding area, leaving the mass of the cases to act as reservoirs of the parasite from which infection was drawn by the transmitting agents. The various missionary bodies are not ignorant of this state of affairs but, lacking mobile personnel and sufficient money to treat many patients with free drugs, they are helpless to prevent the continued spread of the disease in those outwith their permanent clinics' range.

To send members to work individually in these institutions, even if it should raise the standard of the poorer type of clinic, would have no effect on bringing in more patients as the area served would be the same and the distances to be covered from the patients' homes no less, a matter of expense which free drugs would not remedy, so that the disease would continue endemic. Also there would as in the past be no follow-up of patients to check the results of treatment, which is a matter of extreme importance in view of statements which have been made with regard to the efficacy of the antimonials in Chinese kala-azar (Kirk and Sati (4)). On the other hand, it was appreciated that the hospitals' work would form part of any overall plan and that they would continue to serve their own districts while F.A.U. members would be available where advice was required as to the use of possibly unfamiliar drugs in the optimum dose schedules: also drugs would be available free for
them when supplies permitted, and they would remain as centres to which cases from out-lying regions might be sent when the gravity of their infection demanded hospital care or some special procedure impossible of performance in the country districts.

The position of the Government centres was much worse. Staffed with medical men, many of whom were of dubious professional attainments, some of whom were said by local inhabitants to be less than honest and all of whom were grossly underpaid, the clinics were lacking necessary equipment, adjuvant drugs and modern medical literature, while their supply of specific therapeutic drugs was a mere trickle and on account of their scarcity available only at high cost, which often led to their use in sub-standard dosage.

Superficially, the need of these Government hospitals was outstanding, and it would at first seem that in them would be found the answer to many of the problems of field-work. They were fairly numerous, with provision, albeit in Chinese style, for the examination and treatment of patients in their buildings while the medical men in charge had at least a knowledge of the district, if no high academic qualifications, and (as was found on meeting them) were usually willing to help in any way they could. Even so, to work there as members of their staffs would have been wasteful, as so much time would have been necessarily spent in each
place installing the proper equipment and teaching modern methods of anti-kala-azar work, while the medical skill of the teams was small outside their special kala-azar training, confined usually to elementary nursing: thus they would have been of little help in raising the general medical standards of the hospitals or clinics.

It was realised that while the above descriptions applied to the usual Government hospital found in the area under discussion yet there was one area where excellent therapy and research work was being done, i.e. by E.A. Ho. in the National North-West Institute of Health in Lan-chow, Kan-su, which will be discussed later. Even here, however, only a small number of patients, in relation to the mass affected, was being treated and no attempt at clearing an area was being made, while follow-up was not entirely satisfactory.

The third system of medical practice is that of the general practitioners who are of all degrees of medical education but mostly know little of modern methods and are in no position to remedy this regrettable lack.

There was considerable discussion as to whether it would be possible to work with these private doctors, about whose general standards there were no illusions, but who at least had premises in all the larger villages which might be used as treatment centres. Such co-operation might have done something to broadcast the principles of
asepsis, full dosage and systematic courses of therapy, but the idea had to be abandoned when it was seen that supplies of drug were unlikely to be sufficient for a very long time to reduce the cost of a full course of treatment to a level where the peasants would be able to pay for it. Thus the general practitioners will of necessity continue to give adequate dosage only to the rich, while the poor either go without or receive only one or two doses. It was therefore decided that they should have no official part in the scheme but should be taught how to give the proper drugs in the proper way, in the hope that they might at least abandon the time-honoured "quack's" practice of giving useless but harmless drugs intramuscularly. Whenever it was thought fitting, they would be given a supply of the drug with appropriate instructions in the full knowledge that they would probably not give it free but that at least it might do some good to any patient who slipped through the F.A.U. net, and would bring the more ignorant doctor a greater realisation of the power and use of modern chemotherapeutic measures.

A point of interest was the attitude of the patients to the efforts of the "medicine-man" type of traditional Chinese healer, which could be divided into three methods.

1. the applying of plasters made of the usual harmless concoctions of herbs, snakes' skins, dragons' teeth, etc. to the abdominal tumour, either spleen or liver.
2. the insertion of hot or cold needles through the skin over the spleen, with the production of, at best, multiple scars and frequently considerable local infection (a result of the failure to adopt any kind of asepsis or antisepsis).

3. the making of a small incision in the web between thumb and forefinger which was calculated to allow the exit of the "evil air" said to be responsible for the abdominal distension.

From his attitude it seemed that the average recipient of these aids to recovery were contemptuous of their power to help him, yet the majority of patients had submitted to them before seeking any other type of relief: needless to say, no benefit seemed to result and many children were so upset by the insertion of the needle that they were quite antagonistic to specific intravenous or intramuscular therapy.
POSSIBLE METHODS OF ATTACK.

There are undoubtedly some advantages in the humanitarian or even commercial approach to the problem. Individual care is, as has been pointed out above, possible by a variety of agencies and even where standards are low there is everything to be gained and little to be lost by getting a small amount of the right drug into the patients' veins. In this the situation resembles to some extent that concerning syphilis, where treatment which is less than the standard advised may yet be sufficient to cure the patient, but since this cannot be known prior to treatment many patients must be given an excess of drug. Of course the stakes are very much higher when dealing with kala-azar where the mortality in untreated patients varies from 75-95% in various estimates, as against a syphilitic mortality, which so far as could be judged, is quite small in Chinese adults in the absence of treatment.

Other considerations are the convenience of treating the disease unsystematically, whereby visits are paid to accessible localities only in good weather and at times to suit both the civil and military authorities, while working in established centres is pleasant and gives the opportunity for hospitalisation of severely ill kala-azar cases as well as the possibility of seeing cases of other diseases. Thus the individual cases get good treatment and many can be dealt with, but the area is not
covered exhaustively and many cases remain to perpetuate the disease.

So, it is feared, must it be in any scheme in which the decision about treatment is left to the patient without giving him the maximum opportunity to have it free and at the minimum inconvenience to himself: it is apparent that the lines of treatment pursued by the various bodies outlined above, while being in their own way some contribution to the short-term medical needs of the province, all had the drawback that no systematic drive against kala-azar was being practised which might be of permanent benefit to the area by clearing the disease from even a limited region in the manner described in Assam by Young (5) Shortt et al (6) and Shortt (7). Thus, official association with any of the existing medical agencies would likely have the undesirable result that either the area covered would be too small or not intensively combed, or that personnel and equipment would be scattered uneconomically and much time would be occupied in trying to teach many possibly unresponsive people a little of modern methods, rather than giving a small nucleus a thorough grounding in the work.

The only previous attempt in China to follow the mass treatment practiced in Assam, and more especially the methods of Napier and das Gupta (3) in a small experimental area of Bengal, seems to have been the necessarily limited work of McClure (8), based on his
hospital centre of Hwai-ching in N.W. Honan. He pointed out that Public Health principles were not being applied to the kala-azar problem since, according to him, present treatment tends to be given to the patients who come to clinics in the advanced stages of the disease, having themselves been reservoirs of infection and doubtless the source of many fruitful transmissions for 1-3 years, while others in their village are left at home untreated until terminal symptoms may scare them to the clinic. Even this applies only to the relatively few areas where there are nearby clinics: where the latter do not exist the patients are unlikely to travel far in search of treatment. His plan took into consideration all the difficulties peculiar to this type of practice and attempted to overcome them by means specifically designed to this end - not, as so often happens in China, by a system which would give excellent results but only if imposed on wealthy and intelligent Europeans or Americans. He included as inducements the provision of treatment by medical units travelling to the villages from his central clinics, the reduction of the cost of treatment to individuals by adjusting the charge in inverse proportion to the number of patients attending, the use of local Chinese general practitioners of varying degrees of skill, and finally, but most important, he gained the co-operation of the head men of the villages and gave them "face" by using their houses for treatment centres: this last
encouraged them to round up more cases.

The drawbacks to such an approach, modified and extended to suit the F.A.U. capacity, are substantial and real. First and principal is the fact that the area covered is of necessity small, since it must be combed thoroughly for all, even reluctant patients, and the work is sometimes inefficient as every case must be treated even at the cost of remaining in a district with quite a large team to treat only a few patients. Much time is wasted in reaching distant areas over difficult territory, and the teams' mobility entails considerable restrictions on equipment and drugs: in addition, therapy is done too far from hospitals to make it possible for gravely ill or complicated cases to be transported thence. For team-members the work tends to be monotonous, and life in small Chinese villages, for the educated Chinese and foreigners alike, is a little dull.
PROPOSED THERAPEUTIC–PROPHYLACTIC SCHEME.

At this time another agency potentially active in the kala-azar field who asked for co-operation and to whom the basis of the scheme was explained was C.N.R.R.A. (Chinese National Relief and Rehabilitation Administration) and it was learned that although no anti-kala-azar supplies were currently coming to China via U.N.R.R.A. yet the American Red Cross had considerable stocks of Neostam (Burroughs, Wellcome & Co.) and were prepared to furnish transport in the form of ambulances, while Canadian Red Cross were willing to grant funds for the campaign. In addition, it was probable that Neostam then being manufactured in U.S.A. would be available later and that similar drugs could be procured either in India or the United Kingdom.

All these facts made it possible to draw up a scheme embracing a wide area, in which the F.A.U. might have a part. In its final form this divided the province of Honan into regions, in each of which the kala-azar problem would be attacked in the manner most suitable and convenient to the body undertaking it, the latter including some mission hospitals in the south and various Government clinics, with possibly other voluntary bodies joining at a future date. It was not contemplated that all this
work should start at once, and the F.A.U. teams offered to begin in May, 1946, in an experimental manner, so that not only would the plan be got under way while others were preparing but that subsequent workers might profit from their mistakes and adopt any methods found especially satisfactory. It was agreed that reports of clinic attendances, details of dosage, reactions, immediate results, etc. should be sent regularly to C.N.R.R.A. at their Honan head-quarters in Kai-feng, where they could be assessed, and from this, suggestions and advice might be transmitted to teams in the field.

The area allotted to the F.A.U. embraced all that part of Honan north of the Yellow River with five districts (hsien) to the south, but this was on a geographical basis only, since several hsien were barred to any effective work on account of the military operations proceeding between Communists and Kuo-min-tang troops which, although slight in themselves, were sufficient to keep the affected districts in a turmoil, thus effectively preventing patients travelling to the clinics and at times delaying F.A.U. members in their journeys from one centre to another, with some detriment (happily slight) to liaison between the teams. In addition, some areas were mostly mountainous and kala-azar was almost absent, indeed in places population was almost absent.
Thus the total area which could be dealt with is represented on the map on page A, although all parts of this area were not peaceful at one time. Its size is roughly 8,000 square miles, N.-S. 110 miles and E.-W. 100 miles, divided from east to west by the Yellow River and the Lung-Hai railroad, and from north to south by the Ping-Han railroad with, during part of the campaigning period, a Japanese-built line joining the capital city of Kai-Feng with another important centre Hsin-Hsang. At one time, too, the Yellow River occupied its new bed flowing to the west of Kai-Feng, while later it was diverted to flow north of that city. Briefly, the country is mountainous in the N.W., sandy and flat in the N.E. and S.E., with hilly loess-soil type of land in the S.W. Roads varied very much, from the fit-for-driving-slowly to the tracks which might end in ploughed fields or without warning at a broken bridge across a river, and were mostly impassable for motor-vehicles during the rainy season, mid-August to mid-September. The weather was hot in summer, April to October, while the winter was cold with infrequent snow and ice, but with the exception of the above rainy season the climate was uniformly dry which made the extremes of temperature more bearable.
REVIEW of KALA-AZAR.

With the problems, purpose and possibilities of attack clearly in mind, the theoretical background of the disease with all its implications for specific points confronting field workers could be reviewed.

A. SYNONYMS.

There are two types of leishmaniasis, the local or cutaneous and the generalised or visceral infection. The former is met in three forms, the Oriental sore, the South American oro-nasal disease and "post-treatment dermal leishmaniasis", while the latter is encountered as either adult kala-azar of the East or the infantile kala-azar of the Mediterranean littoral. This study was not concerned with any of the cutaneous types, which are not found in China, nor with the infantile type, which does not exist there as an entity, although of course many of the patients were children and a few were infants. Thus all cases were more or less typical examples of Eastern kala-azar in a form which more nearly resembles the Indian variety than the brand found in the Sudan or Mediterranean.

The Honanese name for the disease is hei-je-ping ("dark-fever" illness) or ta-tu-p'i ("big
spleen" abdomen) which names are self-explanatory although, curiously enough, most of the medical men dealing with the condition in this area agreed that the features were not specially dark even in advanced cases where "cachectic-grey" would have been a more accurate description.

B. DEFINITION.

The condition is characterised by intermittent fever of up to three years duration, accompanied by progressive emaciation and enlargement of the abdomen due to increase in the size of the spleen, and usually the liver, frequently with terminal ascites. It is due to the L. donovani which is present in the blood and, among other tissues, the spleen, liver and bone-marrow. Untreated cases have a mortality estimated in China at 75-90%.

C. DISTRIBUTION.

The visceral type of leishmaniasis is found on the Mediterranean shores, in a patchy distribution in the Sudan, in great numbers in N.E. India (chiefly in Bengal and Assam, with a subsidiary centre in Madras) and in parts of Russia. It is found in Brazil and Argentina, but not in large numbers. In China it is usually quoted as occurring from Manchuria in the north to the Yang-tze River in the south, with sporadic cases in Kwan-tung and other areas south of
extensive clinic system to cope with the disease in
the mountainous area around Lan-chow in Kan-su, and
since it occurs also in the large centre of Sian in
Shensi (14), where Clow (15) reports that most of his
535 cases were indigenous, it is probable that it is
quite prevalent in the intervening area, about which
no detailed data are available. It is patent that
it has a considerable hold even in such a rugged area
as Szechuan (16)(17)(1). In addition, there is
the recent factor of the refugee problem created by
the Communist drive from the north, which is sending
streams of possibly infected Nationalists further
and further south and in considerable numbers over
the Yang-tze, which takes them out of the traditionally
endemic areas to territory like Che-kiang and Kiang-si
which admittedly is not so friendly to sandflies as
the hot dry central plains but where the sandfly and
other insects, which are at least potential transmitters,
can live.

D. HISTORY.

Sei (18) quotes references to spleen
tumour in children, appearing in Chinese literature of
600 A.D. as the earliest mention of the disease while
Napier and Krishnan (19) state "our conclusion is that
in S. India are the oldest foci of kala-azar so far as
India is concerned" but it is usually accepted that in
Bengal the disease has existed for more than 100 years and Sen Gupta (20) speaks of an outbreak of fever known as Jwar-vikar in Jessore in 1824-5 which caused the death of 75,000 people and concludes that "Bengal has thus been the oldest known kala-azar area in the world". Again Sen Gupta (21) quotes Twining in 1835 as describing a condition that he called "endemic cachexia of the tropical countries that are subject to paludal exudations".

From Jessore the disease spread to Nadia in 1832, reaching the Hooghly in 1857 and the contiguous Burdwan districts in 1862. To the east, in the Dacca region the town of Jageer "ceased to exist" in four years. In N. Bengal (Dinapur and Rangpur) there was an epidemic in 1872, while under the name of kala-dukh it was present in 1892 in Bihar, and the British conquest of Assam opened that province to its ravages between 1875 and 1900.

The identification of the parasite in 1903 made it possible to expose the nature of the condition in all countries bordering the Mediterranean, especially in N. Africa and Greece, in districts of Central Asia (e.g. Turkestan) in the large focus in the Sudan and in China. In the last country the origin of the disease is obscure and Scovel (1), who gives a detailed account of what is known of it, admits that "it is
impossible to determine how long the disease has existed in this country" but suggests that it came from India either across the Himalayas or by sea. Young (22) describes how the first authenticated case was that of a German soldier who contracted the disease in 1900 during the relief of the legation in Pei-p'ing. Owing to the chronic nature of the condition he did not die until his return to Germany, where specimens of his spleen, liver and bone-marrow, were demonstrated at Leipsig in 1903, but the parasites were unrecognised until after Leishman's publication in the same year, when Marchand and Ledingham in 1904 realised the true nature of the condition.

Subsequently cases were diagnosed in Hankow, Tsing-tao, Tien-tsin and Kiu-Kiang, and in 1911 Aspland (23), Jeffreys and Maxwell (24) and Cochran (25) reported cases from various centres north of the Yang-tze, while in 1914 Reed(26) treated a case in Chang-sha south of it. Wylie (27) Young (22) and King (28) all had cases between 1919 and 1925 and Taylor (29) and Morris (10) described it in Mukden and Kiang-su. McPadyen (30) and Morgan (31) Woods and Bell(32) and Yates (33) described treatment of cases in widely separated areas in 1931. Later reports by Fan and Scott (34) Du and Best (17) were of endemic cases, while the patients of Schretzenmeyr
et al (9) in Canton were probably imported. Between 1935 and 1944 comments on various aspects of the disease were published by numerous writers, of whom the most important were Chung et al (35), Lee and Chu (36), Yates (37), Sun (38), Ho (39), Clow (15) and Scovel (1) while the valuable contributions of Struthers in Shan-tung (vide infra) have been appearing since 1924 and he is probably the leading authority on the disease in China, along with Ho of Lan-chow.

Evidence about the past history of the condition in N. Honan was difficult to get in any accurate way, but there was no suggestion of any major epidemic in the past, and although it was said to be more prevalent in the last 6-7 years yet it seemed to have been endemic in this region as far back as memory went, and treatment in one form or another had never made any impression on the extent or intensity of its ravages. The only paper specifically concerning Honan kala-azar is a description by Villain (40) of seven cases in that province, where he says, in 1925, that the disease is already known to be endemic.

E. ETIOLOGY.

Many erroneous ideas about the nature of kala-azar were held before the parasite was incriminated.
Hookworms, malarial forms and trypanosomes were in turn suspected, not without cause, as so many patients were infected with the first two parasites and experienced moderate, if temporary, benefit from the treatment of these conditions. Almost simultaneously in 1903, Leishman and Donovan demonstrated the parasite in post-mortem specimens and paved the way for all future work, not only in visceral leishmaniasis but also in the cutaneous forms where similar organisms were isolated.

Although at least four types of Leishmania are involved in the production of the typical forms of leishmaniasis i.e. L. donovani (kala-azar) L. tropica (Oriental sore) L. infantum (Mediterranean kala-azar) L. braziliensis (S. American cutaneous and oro-nasal type) and possibly L. chagasi of S. American kala-azar (although Senekjie (41) suggests this is synonymous with L. donovani) yet these organisms are closely related and in some ways identical e.g. morphologically and culturally, while they are not type-specific in their pathogenicity to man and animals, i.e. the organisms isolated from one condition may produce another variety when inoculated experimentally, according to Wenyon (42). Also their serological reactions are not clear-cut or of value in the differentiation of strains, e.g. L. donovani and L. canis, as asserted by Khodukin &
Schewtschenko (43) and Khodukin (44), as might be expected where the epidemiological, pathologic and clinical entities differ so markedly in the varieties of leishmaniasis.

The organisms which are morphologically so indistinguishable can be isolated from the liver, spleen, bone-marrow and sometimes blood and lymph-glands of kala-azar patients in India, China, the Mediterranean and S. America, while they can be found in scrapings from the skin lesions of Oriental sore, cutaneous leishmaniasis or the dermal leishmanoid which may follow treatment. From these sites and others to be mentioned later they are seen as round or oval bodies 2-3μ in diameter, consisting of cytoplasm surrounding a roughly circular nucleus 1μ in diameter, and a rhizoplast which is either rod-shaped or oval and often set at right-angles to the nucleus. The cytoplasm stains pale blue and the contained bodies are purple, the nucleus in a properly Leishman-stained preparation being lighter in colour than the rhizoplast, which sometimes is distinguishable only as a dark dot on account of the angle at which the parasite may be lying. The organisms are found inside the large mononuclear and other phagocytes, but in many cases are lying free, having been discharged from a ruptured cell: they are quite characteristic and almost impossible to mistake although the beginner may have to distinguish
them from platelets which are about the same size.

On artificial culture they grow freely but have a different appearance, similar to that seen in the pharynx of the sandfly. This is the leptomonas form wherein the parasite assumes an elongated and flagellated shape and multiples by binary longitudinal fission.

Some authorities differentiate Chinese kala-azar from the India variety, and while the organism is agreed to be identical from most biological standpoints, Kirk (45)(46) suggests that clinical differences are due primarily to the existence of many strains of leishmania, varying in virulence with different degrees of dermatropic or viscerotropic tendency. This opinion is echoed for cutaneous leishmaniasis by Adler & Theodor (47) and Latyshev and Kriukova (48). Comparing parasites isolated from man and from dogs, Chung (49) carried out complement-fixation tests with antigens prepared from both strains of the parasites, failing to reveal any difference between the two and concluding that the parasites are not only morphologically identical but also indistinguishable as regards pathogenicity and histopathological reactions in experimental animals, e.g. dogs, hamsters, moles and chipmunks.

The epidemiological relationship between human and canine leishmaniasis will be discussed later.
F. EPIDEMIOLOGY AND ENDEMILOGY.

As with any infectious disease, kala-azar is not found in the absence of the parasite, a susceptible population and the transmitting agent (about which there is not yet unanimity of thought) and it is notable that in places like Iran and Dakar (50) the organism may be commonly found in reservoirs like the dog but is not found in man, the converse being the case in India (51) while in other areas, e.g., Ceylon and Bombay (52) sandflies may be common but the disease rare: similarly in some parts of India it would seem that there has been established a high degree of immunity to visceral leishmaniasis, even in the presence of both parasites and sandflies. In the same way there are areas of Palestine, Syria and Iraq which are free from cutaneous leishmaniasis although all the ingredients are present (47).

For various reasons the disease shows definite geographic limitations: it is not associated with very hot weather, although certainly a disease of warm climates, while in India a high humidity seems requisite, although this is not so in China or the Mediterranean area. In the former country, Young and Hertig (12) refer to conditions approaching semi-aridity (which is indeed typical of much of the region where the F.A.U. teams worked) but they were seemingly
unaware of the presence of kala-azar in the hills (sometimes at a height of nearly 8,000 ft. according to Ho et al (53)) calling it a disease of the plains.

Where conditions are favourable, a rapid spread can occur (Lowe(2)) e.g. the progress from Bengal to Assam last century (Sen Gupta (20)) and in China the extension west from the coastal plains as a result of the Japanese invasion (13) while, on the other hand, up to now it has made no headway in areas to which it must be continually conveyed in large numbers, e.g. south of the Yang-tze (Scovel (1)) and in the S.W. of India. It is generally looked on as a disease of rural areas, but in China at least this is not entirely the case as it has been found in considerable numbers in Pei-p'ing, and in six representative medium-sized towns in N. Honan which were visited, a fair proportion of those attending the clinics was drawn from the towns themselves. This is not surprising, since conditions in the average Chinese town, outside the "foreign-style" business and residential districts of the half-dozen big cities, are similar to those in the countryside regarding dirt, poverty and the absence of sanitation or proper ventilation. Overcrowding is the rule, and the rooms are invariably shared with whatever livestock the family possesses, so that there is not only opportunity
for the sandflies to find suitable accommodation but also a continuous depression of the community's resistance, which seems to be the factor involved in the extension of the disease from old-established areas to contiguous ones, and the periodical rise of the incidence to epidemic proportions.

Intimately involved in the environmental element of lowered resistance are the diseases which are prevalent in these areas, e.g. malaria, tuberculosis, syphilis, worms, dysentery, etc., although only in one place, a town of N.W. Honan, was malaria encountered in any large degree: here the local conditions of the town were such as to encourage the breeding of mosquitoes and consequently one-third of the cases coming for anti-kala-azar treatment were in reality suffering from this condition. The other diseases mentioned seemed to have a fairly uniform incidence all over the area, producing a similar general level of morbidity.

Local history gave no picture of any past major epidemic similar to Indian experience in such areas as Bengal, Bihar or Orissa, where Shortt (7) speaks of numerous epidemics (the most recent being that from 1915-27) and the main impression was of a gradual increase in the severity of the endemic state since the beginning of the Japanese war, with extension to areas hitherto uninvolved or relatively free, like the region
of Shensi mentioned by Clow (14) where from occurring sporadically it has become almost epidemic in character and constitutes a serious problem. Similarly, Young (5) mentions numbers in Assam rising from 1,600 cases in 1921 to 16,778 in 1922 and nearly 20,000 cases in 1923, and again Young (22) in Ting-hsien gave the incidence in one village as 1 family in 12 in the past four years, or 1.3% of the population. Sen Gupta (21) says that the recorded incidence in Bengal (which is only a part of the actual incidence) having been fairly steady from 1924 to 1943, has been rising in the last few years, while in Assam there have been a number of epidemics and one is reported from Bihar in 1939-41. He cites the melancholy fact that although the presence of a focus of the disease has been known in Calcutta for 25 years it is not only more prevalent now but has extended to other areas of the town as well.

Even more forbidding is Lowe's (2) suggestion that a fresh epidemic is likely in Eastern India where recent famine conditions, the widespread malaria and other factors might combine to cause a recrudescence of kala-azar. He indicates that reports in 1944 suggest that such a process may have started already. This is reinforced by Sen Gupta (20) (writing from Bengal in the same year) who says that though in a few districts
the incidence is probably decreasing, there are many areas where kala-azar is at a steady level of endemicity, showing sudden increases at variable intervals: in other regions, particularly in N. & E. Bengal, there is evidence of a steady increase in numbers. He concludes with legitimate gloom that "in spite of the synthesizing of one of the best specific drugs 22 years ago and its use since 1923 the incidence of kala-azar is so high that it is still one of the grave problems facing the medical public health authorities of the province" and he gives the average incidence more precisely as 210 per 100,000 in Bengal in 1944.

Napier, in a rough estimate in Bengal in 1923, was of the opinion that the total number of cases was at least 1½ million: writing in 1931 (3) he has to report on a small area which was investigated much more closely, and therefore yielded more precise and significant results, i.e. an incidence of infected males of 80 per 1,000 and infected females of 71.2 per 1,000, an overall incidence for adults of 52.1 per 1,000, as opposed to children where the rate was 114 per 1,000.

In 1944 Scovel (1) speaks of 5,000 cases annually in three hospitals of Kiang-su, and in S. Shan-tung an endemic incidence of up to only 8 cases per year till 1937 when the numbers increased greatly: in N. China
generally during 1942-3 there had been a "marked increase" since the outbreak of Japanese hostilities, while it remained practically unknown in the south of China, where, as he mentions, crops are a surer venture and where wars do not so frequently penetrate.

Ironic point is given to such grim forecasts by the remarks of Liu (54) in 1936 when, after mentioning that in Tsing-kiang-pu in the two previous years over 20,000 cases had received treatment, he goes on to say that, knowing the method of infection, precautions to be taken and treatment for infected cases, there are good grounds for hoping that the disease can be wiped out in "the not distant future". In some villages quoted 50% of the children are infected or 25% of the total population and he estimates that there are about one million people suffering from the disease. Even he is forced to modify his note of optimism by the reminder that the cost of medicine for the treatment of each patient is about $4-5, and with the limited funds made available by the Government the number of cases which can be treated is correspondingly limited. Ho (13) suggests that a "modest figure" may be 400,000-1,000,000 infected persons in China.

In the first tour of the area with which they were concerned, the F.A.U. teams uncovered an incidence of about 1.5 per 1,000, but this would vary greatly in different parts of the region and in any case is not the
true average figure: the latter would have to be elucidated in later and more intensive sifting of cases over the same territory. McClure (55) opines that there may well be 100,000 cases in Honan alone.

Patton and Hindle (56) and Young & Hertig (12) state that there is no seasonal variation in the disease although opinions differ on the point. Thus Scovel (1) speaks of a fair uniformity for the beginning of symptoms and signs for all the months of the year, while Yuan, Ch'u and Lee (57) found that, allowing for a variable incubation period, in all but one of 36 cases the infection began in early summer, mid-May to mid-July, which corresponds with the period of greatest incidence of P. chinensis, specimens of which were found naturally infected during June and July in kala-azar houses. The present survey found no special period of the year mentioned for the beginning of symptoms, and in fact found it difficult to get anything approaching a precise statement from most patients. Frequently there would be a different answer on re-questioning patients or parents, a point which may to some extent account for the difference of opinion in the literature.

The close association between the sick and healthy makes transmission easy even for a short-range insect, should direct transmission be impossible, and the chronicity of the condition ensures that ambulant,
undiagnosed or untreated cases exist to maintain the reservoirs of infection, so that, even passing over the problem of animal hosts, the incidence of new cases is usually steady until factors like war and famine provide a more susceptible population. Young and Hertig (12) speak of a cycle of endemicity with troughs of 10-15 years and peaks of epidemic proportions lasting 4-5 years, conditions in one village having no relation to those existing in its neighbour nearby: this latter fact being mentioned also by Patton and Hindle (56) in Shan-tung.

While having no evidence of the cyclic phenomenon, present experience can confirm the fact that one area's infection-rate had little bearing on that of another, although conditions of dwellings, weather and type of population might be very similar. In the same way, no special feature was found to account for the particular incidence in centres where variation was found, from the village nestling in the foothills to that in the middle of near-desert country, from the comparatively prosperous market-town to the lonely outpost being slowly encroached on by the advancing sandhills where poverty was widespread, and from the well-organised community with a public-spirited magistrate and a fairly efficient medical clinic to the insanitary collection of huts where traditional Chinese medicine flourished.
The area under review was characteristic in being the same kind of dry deep alluvial plain as is found to harbour infection in India, only not so hot in summer but equally subject to flooding in the late autumn or late summer season (56). Scovel (1) thinks that the high incidence in the poor classes is probably due to the location of their abodes rather than to social status.

No adequate reason has been advanced to explain the variation in the age-groups attacked by what is the same organism producing substantially the same disease in different areas, but the division is quite clear-cut, although of course many cases occur outside the typical age periods. Thus the Mediterranean type is essentially a disease of infants, while in India it affects adolescents and in China kala-azar is found mostly in the older children. In the Sudan the average age is higher than in India, and in Central Asia Gevorkov (58) says that the majority of the cases occur in children between the ages of 1-5 years, and chiefly from 1-3 years, but it must be remembered that most of these statements are based on dispensary returns which reflect only those cases brought for treatment - a different matter from those actually attacked by the disease. In this connection Napier's figures (59) of 74% of Indian patients being 20 years of age or under are more reliable, based as they are on house-to-house collection over a long period. He also makes
the significant statement (3) that the nearer one gets to the source of clinical material the younger are the patients, which was the experience in Honan, e.g. in the established, permanent, non-mobile clinics, drawing patients from a wide area the age-incidence was distinctly higher than in the mobile-treatment-centre arrangement in the smaller villages, drawing on a comparatively small area so that patients had only short distances to travel and were more inclined to bring all suspected cases, which would include the younger and recently infected children. Similarly, during second visits to an area it was found that the average age was even lower and the average stage of infection earlier.

From another angle Nagier (3) gives the average age for males in a circumscribed area of Bengal as 14.85 years and for females 14.62 years, while Malone and Brooks (52) put it that in India kala-azar is almost unknown under the age of 2 years, comparatively rare under five years, and commonest between the ages of 6 and 20 years, and after 30 years liability to contract the disease diminishes. In Manchuria, Sei (18) gives 4.7 years as the age-group in which he finds most of the infected children. The majority of Scovel's (1) cases are in the 10-15 year group while Debono (60) giving particulars of his own patients in Malta states that 93% of cases occur in
### AGE-INCIDENCE in KALA-AZAR PATIENTS.

<table>
<thead>
<tr>
<th>NAPIER</th>
<th>F.A.U.</th>
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<tbody>
<tr>
<td>M.</td>
<td>F.</td>
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<td>----</td>
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</tr>
<tr>
<td>Under 5 years</td>
<td>22</td>
</tr>
<tr>
<td>5 but under 10</td>
<td>48</td>
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<td>10 &quot; &quot; 15</td>
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<td>20 &quot; &quot; 30</td>
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<td>16</td>
</tr>
<tr>
<td>40 &quot; &quot; 50</td>
<td>2</td>
</tr>
<tr>
<td>Totals</td>
<td>204</td>
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</tbody>
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The average age was 11.4 years.
the first five years of life: finally, in N.W. China Ho (13) claims that 85% of his cases were under the age of 5 years. F.A.U. figures, distributed in 5 year periods, are as shown.

For several reasons the characteristic Chinese age grouping is unfortunate for prognosis, e.g. children are not wage-earners and so it is not considered so important to have them treated early, they are such domestic tyrants (so much mollycoddled, to Western minds) that the doting parents often will not expose them to the prick of the injectionneedle or other unfamiliarity of modern medicine, or will not persevere with attendance if the child protests. Naturally, too, the majority of children require to be brought often some distance to the clinics, and since this involves the loss of work-time for one or both parents, the latter are less enthusiastic about treatment than one might reasonably expect. It should be kept in mind that this series was formed in areas where never before had a serious attempt to treat the disease been made, and therefore the patients seen in the first visit tended to be older and have a more chronic disease than the true average, which latter was more clearly seen in the preliminary survey prior to a second visit to one of the areas: unfortunately the figures for this area are not available. In spite of this artificial weighting, the Chinese patients may be seen to be younger than the Indians, e.g. 56.7%
under 10 years as opposed to 39.53% in Napier's series. This is in accordance with McClure's (55) statement of a general incidence in Honan of about 60% of patients under 10 years of age.

Many authorities do not commit themselves on the subject of the differential sex incidence in kala-azar: Stitt (61) says statistics show that males are attacked more frequently than females but Napier states there is no evidence that either sex is more susceptible when "errors of selection" are eliminated. In a small but completely investigated area he says (3) that the difference in the sex incidence has almost disappeared, and only 53% were males. Scott and Li (62) say that their information from parents is that males and females contract the disease in equal numbers, but that some Chinese parents feel it is more necessary to try to preserve the lives of their sons than of their daughters: also they report stories of infants suffering from presumed kala-azar left behind in villages when their parents bring the older children for treatment, owing to the difficulties of travel. Patton and Hindle (56) refer to the majority of their Shan-tung cases being males, and consider that, even allowing for the fact that females are less likely to be brought to hospital, the disease is actually commoner among males. Archibald and Mansour (63) in the Sudan feel that the greater preponderance in males is
due to the fact that the male is more itinerant than the female, and that the male population is more accessible to medical inspection than is the female. Scovel (1) is of the opinion that the low proportion of female patients is of interest merely in demonstrating a preference for first treating the opposite sex. There are a number of reasons why this is true, but briefly it need only be said that any worker in China would confirm it, e.g. McClure (176), who says that the incidence is equal in the sexes but since females are still regarded as an inferior race, especially in the backward rural areas, they are not brought for treatment so readily. All members of F.A.U. teams could bear witness to the tragic truth of this and it is therefore difficult to understand the alleged remark of Dr. Cheng, of the Chinese Government Public Health Service, who is reported by Malone and Brooks (52) to have said that kala-azar was not a problem affecting women in China and this was not because the disease was in any way hidden by females. It might be said that all women tend to hide all diseases more than men, that Chinese women do so even more, from ignorance in the case of the older ones and because they are considered of no great account in the case of the younger age-groups. Certainly, even F.A.U. uncorrected figures show a very large problem among
### SEX-INCIDENCE in KALA-AZAR PATIENTS.

<table>
<thead>
<tr>
<th>Source</th>
<th>Male/Female ratio</th>
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<tr>
<td>Napier</td>
<td>52.7/47.3</td>
</tr>
<tr>
<td>F.A.U.</td>
<td>65.7/34.3</td>
</tr>
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</table>
women in N. Honan and there is every reason to believe that the situation is similar in the other areas of China.

The F.A.U. sex-grouping is as shown, with Napier's (59) for comparison. An investigation by the F.A.U. medical teams is in progress at present in N. Honan with the object of tracking down every kala-azar case, early and late, in a clearly defined area by an intensive village-to-village search which should shed light on the frequency of the condition in the two sexes, in this part of the world at least.

No opinion could be given from present field experience with regard to the influence of social status, occupation or race on the incidence of the infection. At least 90% of patients were of the lowest peasant class who oscillate along the border of malnutrition all their lives, but everywhere clinics were set up there would be a small percentage of prosperous patients who for reasons other than financial had failed to seek treatment elsewhere; these might include the children of merchants or minor Government officials. A clinical impression would be that these latter children were just as susceptible to infection as their poorer fellows, although able to benefit more from treatment on account of their relatively good general condition. It should be noted that in the villages (which were the typical
communities in this area) the few less primitive houses of the rich were inextricably mixed with those of the poor, so that any infected insect would be easily able to penetrate either type of dwelling.

The adults treated were nearly all farmers and their wives, this being the common occupation of the area and wealthy adults were conspicuously absent. Among the few dozen foreigners encountered who had lived in China for any length of time one Germany missionary had been successfully treated some years previously for what seemed to have been a genuine attack of visceral leishmaniasis: there were no foreign children in the area to serve as a basis of comparison with the Chinese.

G. TRANSMISSION.

The problem of the transmission of the L. donovani has been under continuous investigation in many parts of the world since the discovery of the organism, and the fact that there are still some workers who disagree with the generally accepted sandfly theory is no discredit to the worth of the inquiries that have been made, but is rather a reflection of the difficulties of scientific research into an intricate problem in areas where climatic, economic and other conditions make sustained, accurate work far from simple.

In any infectious disease it is only logical to consider first the possibility of direct transmission
of the causative organism from case to case without the aid of an intermediate vector, this method naturally postulating the mode of entry to the new patient being by a natural orifice like nose and mouth, or possibly via scratches or other solution of the skin's surface. The work done over some years in this connection includes that of Greig and Cristophers (64) who record the infection of a monkey by the introduction of infective material into its small intestine, but, while pointing out the possibility of transmission by soiled food or vessels, consider that the evidence for this route must be regarded as so far inconclusive. Shortt et al (65) have recorded the finding of typical Leishman-Donovan bodies in the recently passed stools of a kala-azar patient, and Teng and Forkner (66) have succeeded in infecting Chinese hamsters with both urine and prostatic fluid injected intraperitoneally, so that all these secretions are potentially dangerous to those making contact with them, which is not seldom in the huddled, dirty conditions of Eastern life.

In 1934, Forkner and Zia (67) reported that in smears from the nasal cavities of 9 out of 15 kala-azar patients they found typical Leishman-Donovan bodies, describing this as a rich source of infective material available for direct transmission of the disease. The following year (68) they went on to
demonstrate the viability of the visible parasites by injecting the various secretions into hamsters. In the case of nasal secretion, 92.8% of the animals were infected, though a much smaller number developed the disease from saliva and sputum, since many failed to survive the intra-peritoneal injection of heavily secondarily infected material. A similar injection of scrapings from the tonsil infected both of two hamsters. Hamsters were also infected via the nasal or oral cavities by nasal secretion from kala-azar patients and by feeding on material from the pharyngeal tonsil of similar cases. From all these experiments they conclude that there is strong evidence for direct or indirect contact transmission, although they admit that unequivocal proof of the important natural mode or modes of transmission has not yet been presented.

In the same year Short and Swaminath (69) repeated the above experiments and emphasised the possibility of direct contaminative transmission, where in sneezing or coughing, droplets containing the parasites might be deposited on the conjunctiva or on the nasal or oral mucosa. The position is not clarified by the work of Archibald and Mansour (63) who failed to infect 3 monkeys inoculated subcutaneously with emulsions of nasal mucus from 3 healthy contacts who had been in close association with kala-azar.
cases. This negative result, however, was balanced by apparent direct transmission by exposing four healthy monkeys to four older monkeys which had been inoculated intra-peritoneally with kala-azar material. Seven weeks later two of the four healthy monkeys were found to be infected, typical Leishman-Donovan bodies being found in their enlarged spleens. On repetition, three out of four monkeys were infected but the authors say that no opinion can be expressed as to how the infection was transmitted.

Commenting on the state of parasites in nasal mucus, Shortt and Swaminath (70) describe them as having all the characteristics of those seen in smears from spleen or bone-marrow, occurring either singly or in groups. The embedding of the organisms in mucus gives them considerable protection after extrusion from the body, so that they will remain viable for some time, and this question has been discussed by Chung (71) who found that Leishman-Donovan bodies would withstand irradiation with $\frac{1}{2}$-2 S.E. doses, temperatures up to $43^\circ$C. for 30 mins., 8 days at $5^\circ$C. in saline, or $-25^\circ$C. for 48 hr.: drying for $1\frac{1}{2}$ hr., however, was lethal. Shortt et al (72) have shown that in milk they will live for four days, while on the surface of moistened soil they endure for as long as 24 hr. They also quote dessication as being fatal after
4 hr. Speaking of a different environment, Zia & Teng (73) record the survival of cultures which were contaminated with haemolytic streptococci, staph. pyogenes and D.pneumoniae, whereas they do not survive or flagellate when contaminated by E.coli.

From all these observations there seems no doubt that the infection can be transmitted directly from man to man, entering by the natural orifices of nose and mouth, being absorbed via the conjunctiva or passing through some break in the skin's surface and in all these ways without the aid of an intermediate host or animal vector. What is seriously in doubt is whether this direct transmission does in fact occur to any extent sufficient to make such a phenomenon of practical importance in the epidemiology of the disease, and the majority of authorities oppose the idea, although Malone & Brooks (52) have recently attempted to rouse interest again in the theory, albeit with no success. There is neither direct proof of any other theory nor conclusive refutation of this one but the sharply defined areas and specific groups of patients in which the disease is found strongly suggest that the direct infection process is not common, although travel would spread the infection widely, e.g. to districts of India and China where physical conditions are quite suitable for its reception. Megaw(63) sums up the essential
objection to the theory when he asks "what other diseases conveyed from person to person have a strictly local distribution?".

Following the trend of thought stimulated by the well known method of transmission of infection in malaria it was natural that some of the early observers should advance the theory of transmission by an intermediate host of the insect type. Long ago the ubiquitous bed-bug (cimex lectularis) was suggested at different times by Rogers, Patton and Wenyon as a possible carrier of Leishmania, since it was shown that these animals could be infected from kala-azar and oriental sore patients and would allow the development of the flagellate stage in their alimentary canals but not, most significantly, on the mouth parts so that the bites are unlikely to convey infection to man.

More recently, Blacklock and Lowrie (74) record the fact that viable forms of Leishmania can be passed up to 35 days in the faeces of artificially infected bed-bugs, but though it is conceivable that after squashing these insects on the skin their excreta might be rubbed into a scratch to produce infection, this is not thought probable since naturally infected bugs have not been found in any infection.

Shortt (7) mentions that attention has been given to the possibility of transmission by ankylostomes
on the assumption that these are commonly found in kala-azar patients and that therefore in their blood-sucking activities in the human intestine they must ingest large numbers of Leishman-Donovan bodies, which are known to inhabit the bowel mucosa, and so are potential transmitters of infection to another victim. All work done in this direction, however, has given entirely negative results.

Somewhat similar claims have at various times been put forward for human fleas, dog fleas, lice, ticks, and mosquitoes and there is no doubt that all of these can convey infection from case to case, but it is equally true that none of them has been found naturally infected, and modern inclination is that although an occasional case may develop his illness via one of the above parasites, in the vast majority of patients one must look elsewhere for the source of infection.

Quite early in the investigations into kala-azar the sandfly was tentatively incriminated by, among others, Cristophers (75) and Mackie (76), while the Sergents and Wenyon had previously described it as the vector of oriental sore. The first substantial contribution to the subject was the publication of the paper by Knowles et al (77) where they established the fact that L. donovani, when ingested by P. argentipes, assumed the flagellate form. In the
same year Smyly and Young (78) discovered that the Chinese hamster (cricetulus griseus) was very susceptible when inoculated with L. donovani, and this has been of the utmost help in all subsequent investigations. At that time, large scale experiments were carried out involving the exposure of mice and hamsters to thousands of bites from flies previously fed on proved kala-azar cases. Although these and similar experiments took over four years, in only one case was there transmission of the disease. A parallel series, using eleven volunteers, by Shortt (7) was negative, even though it was realised that the chance of infection, judged by the amount of biting, was much higher than it would be under natural conditions.

In 1926, Shortt et al (79), after exposing 60 experimental animals to P. argentipes known to be infected with L. donovani and finding that not one developed infection, were of the opinion that the experimental animals were insusceptible to L. donovani unless under conditions of a more intensive exposure to infection than in their experiment. Young & Hertig (80) in China reported the same failure to produce infection in hamsters by infected sandfly bites, although the intra-peritoneal injection of the flagellates was constantly followed by generalised leishmaniasis. Adler and Theodor (81)(47) continued work on the same lines, except that they used P. papatasii infected with
L. tropica and had the same results.

Then in 1931, Shortt et al (82) were able to report, after many failures, the first successful transmission by P. argentipes of infection from a case of kala-azar to a Chinese hamster by its bite, and this was followed in 1933 by the announcement from Napier et al (83) that out of 28 hamsters bitten by P. argentipes which had previously fed on kala-azar patients, two became definitely infected and one seemed to have a transitory infection. These later results were at least indicative that transmission of the disease could occur, but were scarcely up to expectation since it was already known (Patton & Hindle (84)) that P. chinensis is a very favourable host for the development of L. donovani and that the opportunities for the flies to pick up the parasites are considerable. Napier and das Gupta (3) had already advanced the view that while 1% of kala-azar patients in India develop dermal lesions that reach the hypertrophic stage, and 5% of them develop macular lesions, yet a much larger percentage have a dermal infection that never reaches the clinical stage at all, so that though it may be difficult to demonstrate the skin infection histologically, sandflies will become infected after feeding on patients with this subclinical infection. Napier (85) also quotes Smith as having fed laboratory-bred (and
therefore without natural infection) sandflies on patients with clinical cure of kala-azar (in the convalescent stage and having sterile blood cultures). This resulted in the infection of quite a number of these flies. Carrying the experiment even further, he fed flies on a case who had had kala-azar one year previously and was entirely without dermal lesions and it was found that two or three out of 20 insects were infected. Again, Napier (86) has stated categorically that "though the geographical distribution of this sandfly P. argentipes does not correspond exactly with that of kala-azar, the species is found in large numbers for the greater part of the year only in those areas where kala-azar is prevalent".

Along with the laboratory experiments cited above, a considerable amount of field work was being done to discover whether the sandflies, which had been shown to be capable of carrying leishmania, were in fact commonly doing so under natural conditions: obviously this is a crucial practical point since many biological phenomena are possible without necessarily occurring, e.g. the transmission of kala-azar by bed-bugs, ticks, etc. Shortt et al (87) reported that in a period of five months in 1928, 226 P. argentipes were collected in Assam from the houses of kala-azar patients and seven proved to be infected with L. donovani.
Sun and Wu (88) found 10 out of 483 specimens of P. chinensis infected in one village, and in another place one out of 54 flies was carrying the parasites. Sun et al (89) in a similar investigation found 7 out of 421 captured P. chinensis to be infected with the developmental forms of L. donovani. They consider that this sandfly is the vector of kala-azar in China.

It was this point in the prolonged and world-wide investigation of the transmission process in kala-azar that Malone and Brooks (52) call "the end of the second stage", when neither the field work or the laboratory investigations had advanced further than a very strong suspicion that the Phlebotomus does convey the organisms from case to case but frequently refused to infect laboratory animals and consistently failed to infect human volunteers. Then Smith et al. (90) in 1940, reporting the infection of hamsters by the bite of the infected flies blocked by a second feeding on fruit juices, prophesy that "the final test to incriminate the sandfly as the vector of kala-azar by transmission to a human being can now be undertaken with greater confidence of success".

In the same year, Adler (91) made a valuable contribution to the subject by inoculating five patients suffering from inoperable carcinoma with cultures of the flagellate forms of L. donovani in exceptionally heavy doses, to find that only one developed the disease in a mild form with no marked enlargement of spleen,
fever, or anaemia, thus adding support to Napier's (85) remark that it is not necessary to postulate that every bite from an infected fly will produce kala-azar: at the height of an epidemic wave everybody in an infected village must be subjected to an enormous number of bites by infected flies and yet many of even the most susceptible age-groups escape infection.

Finally, in 1942, came what is regarded as the evidence which establishes the sandfly as the principal transmitter of the disease. Swaminath et al. (92) published the news of the infection of five out of five volunteers with Indian kala-azar by the bites of infected P. argentipes, which had been effected by allowing the animals to re-feed on raisin juice. This seems to supply the missing links in the chain, and the evidence is well summed up by Napier (93) "so far as India is concerned every epidemiological observation fits in with the sandfly hypothesis of transmission. Further, this sandfly has actually been found in large numbers in every locality where kala-azar occurs; it is a persistent human-blood feeder; a large percentage of the flies that feed on an infected person acquire the infection: infected flies have been found repeatedly in nature; this is not true of other sandflies which are more
prevalent in the non-endemic areas, nor of the other insects of any other genus so far experimented with: in this fly anterior development of the flagellate infection occurs and this is unlikely to be purposeless: (in natural flagellate infections which pass from insect to insect the development is usually posterior): and it has been shown experimentally that the fly is capable of transmitting the infection to a mammalian host by its bite. All these facts make it almost certain that this insect is an important agent in the transmission of the disease from man to man in nature, although it may not be the only agent".

It can therefore be confidently asserted that in China the P.chinensis is the main vector of the disease, whatever subsidiary effect is caused by other animals: this is certainly the published view of those dealing with the condition in that country, e.g. Scovel (1) who describes the insect as the only sandfly so far known in China which can carry flagellates in its intestinal tract in the absence of gross blood and also have them in its mouth parts.

There still remains, however, the question of the place to be assigned to animals other than man as hosts, not vectors, in the transmission cycle of the leishmania, and here there is a divergence of view. It is generally agreed that the dog plays practically no part in the transmission in India, so that Sinton and
Shortt (51) in 1934 reported only the third case there of a dog infected naturally with leishmania, but in the Mediterranean area natural canine infection is high. Wenyon (42) states that the disease produced in dogs by inoculation of parasites from human cases is identical with the natural canine disease, while the organism from the canine condition is inoculable into animals with results similar to those which result from inoculation of the human virus. Nevertheless, at that time he was not convinced that the dog should be regarded as a reservoir of the organism since so many cases occur which cannot be associated with any infected dog, and he took the view that infection of the body was as accidental as that of man.

Adler and Theodor (94) report that 11 out of 100 dogs examined in Malta between June and November were found to be naturally infected with kala-azar. Seborrhoea and partial depilation are the most frequent signs and skin infection may be present with only slight visceral infection: the authors show how easily sandflies (in this case P. perniciosus) can be infected by feeding on even the unbroken skin of such animals. Recently, Malamos (95) has described the typical appearance of an infected dog, but quickly goes on to say that in Canea he and his
associates found that 50% of the dogs suffering from leishmaniasis looked normal. Chung (96) in an examination of 587 apparently healthy dogs found leishmania in 1.4%, while Donatien and Lestoquard (97) emphasise that infection may be very heavy in innocent-looking dogs, a point confirmed experimentally by da Cunha (98).

In Central Asia there appears to be considerable animal infection, and Khodukin and Schewtschenko (43) reporting on 4,000 dogs who were autopsied in Tashkent came to the conclusion that cutaneous canine leishmaniasis is not a distinct disease but only part of a general infection. In a later article Khodkin (9) states that in 1926 0.67% of over 7,000 dogs in Tashkent were afflicted with general leishmaniasis, but after a large number had been destroyed the figure was only 0.02% in 1927, and the number of children found suffering from the disease in this latter year was 3½ times less than in 1926. In other towns where no measures were undertaken against dogs the incidence of infantile kala-azar remained unchanged. Writing in 1945 (44) on the same theme, he says that the parasites L. canis and L.infantum are indistinguishable in many ways, produce the same clinical and pathological disease in dogs and children, and in Tashkent he avers that the areas of distribution of the disease in both hosts
coincide. His contention is that man plays a secondary role in the spread of infection since parasites are soon eliminated from the peripheral blood, whereas the dog in the early stages of the condition has extensive multiple papules on the muzzle and later generally in the skin. According to him, infected sandflies were found only where there were concentrations of infected dogs. In Samarkand, Gevorkov (58) found from 1933–43 complete parallelism between the incidence of the human and canine disease, the former being correlated not only with the percentage of infected dogs but with the total number of dogs in the town.

In China, it was at first thought that dogs, as in India, were not to be incriminated as hosts, and Faust (100) said categorically that the canine variety of kala-azar is not known to occur in that country, while Wenyon (101) supported this view. It was not until 1934 that Andrews (102) reported the first proved case of canine disease in China, although she also mentions having examined a further 400 dogs in Shanghai without finding any more infected. In 1937, Lee (103) reported 2 cases of disease in dogs in Pei-p'ing, while Feng et al (104) considered that canine leishmaniasis is wide-spread in N. China and is the reservoir of human disease, sandflies being
readily infected by feeding on the dogs. This view is supported by Galliard (105) who says that canine kala-azar is common in Pei-p'ing, but points out that the dog-to-man transmission is not so straightforward as might be thought, since in the legations quarter there is much disease in dogs but only three human cases since 1900. (This statement seems open to doubt).

Chung and Feng (106) and Parrot et al (107) comment on the high incidence of infection of sand-flies found in association with diseased dogs, the former authors quoting 60% of flies taken from a kennel containing a dog with kala-azar as having leishmania in their alimentary tracts. Chung (49) in his investigation noted that all infected dogs had passed through at least 2 sandfly seasons. Ho et al. (108) describe the examination of 722 dogs of whom 684 were found to be uninfected, while in 34 dogs with skin lesions, skin biopsy revealed leishmania, although not always without difficulty, and the authors say that the parasites were present in larger numbers in the skin than in the bone-marrow. In a 6-months period of 1944-45, Ho et al. (53) made a detailed investigation of 104 small villages, inspecting 1,430 dogs of which 44 had visceral leishmaniasis, 25 being found in villages where kala-azar was endemic and the remaining 19 in villages free
from kala-azar. Canine infection was very high in some cases, reaching 8%, although the average for the whole district was 3%. It is suggested that in N. China the disease has been endemic for a considerable time, whereas in Pei-p'ing it may have been introduced recently since, according to the authors, the infected dogs there are not indigenous nor is the disease familiar to the population. In the rural region of Hopeh adjacent to Pei-p'ing an examination over a period of 40 months showed an infection of only 4 dogs out of a total of 1,780 from villages where kala-azar was endemic.

In so far as a conclusion can be drawn from this conflicting evidence concerning the place of animals in the spread of kala-azar, it would appear to be that in China there is a considerable widespread but patchy infection in dogs which is certainly a potential factor in the maintenance of the endemicity and possibly the epidemicity of the human disease by forming reservoirs of the infection even more accessible to the sandflies than is the human variety. Equally, however, it must be admitted that the malady is endemic in man in many areas where there is either no canine disease or so few cases that their occurrence seems quite fortuitous, (Ho et al(109)) and man must be dubbed the mainstay of the infection. Such
considerations are, of course, of the utmost importance with regard to the prophylaxis of the disease and will be referred to in that connection.

H. PREDISPOSING CAUSES.

The broad outlines of this aspects of kala-azar are clear from practical experience of the disease in many parts of the world, but the precise mechanisms by which the predisposing factors operate have yet to be revealed. They have been largely dealt with under other headings and need be recalled only briefly: these should, of course, be distinguished from the circumstances essential for the propagation of the disease, e.g. presence of the parasite and sandflies in a tropical or subtropical climate. When these are found any person may contract the disease, but certain features seem to stimulate its appearance.

1. Age: it has been mentioned previously that the four great endemic areas, India, China, Mediterranean littoral and S. America each has its distinctive age-group, outside of which the chance of acquiring the disease steadily diminishes.

2. Race: there are apparent differences in racial susceptibility which have been noticed, mostly in India where Malone and Brooks (52)
say it is generally accepted that Anglo-Indians, Indian Christians and Moslems suffer more from the disease than Hindus, a fact superficially difficult to reconcile directly with the theory of sandfly transmission, since the latter presumably have no religious scruples. When certain individuals are stricken while their neighbours in the same environment are left unharmed it strongly suggests that some unrecognised practice or custom accounts for the phenomenon. Napier (59) explains this particular predilection as being due to the cows kept by the Hindus, which certainly attract sandflies but also lure them away from the humans since the flies are known to prefer bovine to human blood, and when given the choice will always bite the cows. In China one could draw a similar picture of the higher incidence in the idol-worshippers than in the Christians, but these two classes are distinguished also by educational status, income, nutritional state and hygienic standards, all of which are lower in the former than the latter as a general rule in country districts. This is probably not true in the towns, but the disease is not prevalent there in any case.
Similarly, kala-azar must be comparatively rare in foreigners in China, where even in the villages their lives are lived on a level quite different from that of the native Chinese and protective measures are taken against disease.

3. **Domestic conditions**: years ago, Napier (10) stated that in India certain domiciliary peculiarities were associated with the disease, viz.

   a. Vegetation in close proximity to the dwelling.

   b. Earth unprotected by cement or paving stones in and around the dwelling.

   c. ground floor residence, possibly with

   d. insanitary conditions, especially with reference to the presence of fowls and ducks in and around the dwelling and within the endemic area with

   e. masonry houses rather than bamboo huts.

With the exception of e. and sometimes a. these are the normal conditions found in small Chinese villages and towns where the mass of the population lives in one storeyed mudbrick huts which offer excellent breeding-places for sandflies, in the numerous crevices and cracks in the mud. These are mostly surrounded by an unpaved mud courtyard which harbours more or
less refuse and litter and is inhabited by cows, hens, ducks, pigs or goats, depending on the affluence of the owner.

The houses of the wealthy are usually only bigger, possibly with two storeys, although on occasion they may be made of fired bricks. Vegetation normally invests the villages closely since every available foot of land in China is cultivated, although in the kala-azar areas there is nothing resembling the luxuriant tropical growth of Bengal and Assam.

4. Concomitant diseases: the Chinese variety is not, as is said to be the case in India, confined to low-lying areas or dependent on the proximity of stagnant and running water, so these can be ruled out as predisposing cases, although by their encouragement of other diseases they may indirectly increase the incidence of kala-azar. Smith and Ahmed (111) reserve their opinion as to whether malaria predisposes to kala-azar or whether both are activated by the same epidemic stimuli, but indicate their close association in India. Napier (59) gives evidence for suggesting that malaria and enteric fever are diseases which have a specific stimulant effect on latent kala-azar, although he denies that lowered
resistance *per se* is necessary before the disease can flourish.

5. **Virulence:** Kirk (45) in the Sudan has put forward the idea of leishmanial strains of varying virulence which may have influence on the flourishing of the condition at any one time. This, however, still awaits proof.

Whatever the sequence of events, there is no doubt that ever since the Japanese invasion of China there has been a gradual increase in the amount of the disease in the traditional area *pari passu* with a slow extension to areas (and possibly heights) hitherto free from it. This is unlikely to be merely coincidental, and it is difficult to disregard as a predisposing factor the poor general conditions of the cases which the writer saw returning from the interior to the coastal districts at the close of hostilities in 1945-6. These people had been living in great need for years, lacking adequate food, shelter and medical attention in just those areas to which there has been the spread of kala-azar. Scovel (1) gives his own experience in S. Shan-tung where the onset of hostilities was the signal for a sudden rise in the number of cases. Lowe (2) mentions malaria particularly as a predisposing case: fortunately this is not such a scourge in the Chinese kala-azar areas that it is in India, and
although it was always necessary to be on the alert for it, only in one of the Honan districts was it a problem in diagnosis, where a moderate-sized town was possessed of an inordinate number of large and small pools of stagnant water in which mosquitoes could breed without disturbance. Hookworm was not found but dysentery, both bacillary and amoebic, was common.

In the F.A.U. clinics there was no clear knowledge of the physical state of the patients prior to contraction of the disease, so on this ground there was no evidence for lowered resistance being a factor, but of all patients only a very small number were in the income-group where under-nutrition is not a constant threat. The average diet of patients was especially deficient in proteins and vitamins but often deficient in iron as well. There is no record of treating a patient from the families of any magistrate, prominent merchant or high official although frequently consulted by them about a variety of symptoms, mostly imaginary.

In the light of all these facts it is concluded that the greatest ally of the sandfly is poverty in its manifold guises, e.g. lack of food, shelter, sanitation, medical help and education as the
most obvious features.

J. PATHOLOGY.

Whatever theory of transmission is accepted the Leishman-Donovan bodies are implanted either under the skin or on some mucous membrane, from both of which situations they find their way to the nearest lymph glands, there to stay and multiply if conditions are favourable. It is not clear at what stage in an unsuccessful transmission the parasites die or what exactly are the factors in influencing this turn of events: it may be that the leukocytes destroy them before they can enter the lymphatics or that immune bodies in the tissues or lymph streams exert a gradual effect so that they die in the glands before they can proceed to the next step.

This is the decisive stage of bursting out of the gland after multiplication has made it insufficient to hold them, thus invading the bloodstream whence they are carried throughout the body to be caught up in various parts of the reticuloendothelial system, notably spleen, liver, bone-marrow and lymphatic tissue generally. In the human patient the time of infection is so vague that it is not known how long on the average the above sequence takes but some indication may be gained from the fact given by Young et al (78) that organisms appeared
first in the spleen of an experimentally infected hamster 3 days after the inoculation, and in the liver and bone-marrow 4 days after infection.

As well as settling in the organs, parasites continue to circulate in the blood (although not to the same extent as in malaria) and the culture methods of Young and van Sant (112) give positive results in about 90% of their patients.

In time there seems to be a general lymphatic spread in most cases but there is no uniform intensity of infection, and opinions differ as to the usefulness of gland puncture as a means of diagnosis.

The spleen gradually enlarges and becomes fairly firm to the touch although never acquiring the almost wooden sensation of the chronic malarial organ. Perisplenitis is common and infarctions are seen at autopsy. Sections show distension of the blood vessels but the most obvious feature is the predominance of large endothelial cells, histiocytes and macrophages which contain the parasites: the endothelial cells of the vessel walls may be filled with them and likewise in sections they are mostly in the isolated phagocytic cells, but in films will more often be lying free,
in clumps or singly, having been liberated from their surrounding cell by the trauma necessarily occurring in making the films. As the disease progresses there is an increase in fibrous tissue and commonly there are numerous plasma cells present.

The liver is almost always enlarged, according to experience in the present series, although rarely in proportion to the splenic hypertrophy, and is firm in consistence as there is usually an increase in the amount of fibrous tissue present, with accompanying degeneration of some of the liver cells. This may become marked and in the terminal stages these cases are indistinguishable from ordinary hepatic cirrhosis with ascites, caput medusae etc. plus the fever and toxicity of the leishmaniasis. Microscopically, the same large endothelial phagocytes are present, while parasites are contained in both the cells lining the sinuses and in the non-organised invaders which may disrupt the texture of the lobules. Congestion and usually some degree of "nutmeg" appearance are the rule, as part of the increase in size of the organ.

The bone-marrow is constantly affected with consequent detriment to the blood cells in it and in the peripheral blood.
Usually the red marrow increases in extent but this is not due to an excess of haemopoiesis, since microscopically it may be seen to be considerably replaced by the typical macrophage containing the Leishman-Donovan bodies similar to those in other organs. Sometimes the normal marrow cells will be obviously parasitised but it is more common in films from the sternal marrow made for diagnostic reasons to see the organisms lying free, having been expelled on the rupture (due to trauma) of the cells which had contained them. There is an increasing interference with normal haemopoiesis as the disease progresses. Kuroya et al (113) speak of reticuloendothelial proliferation in the bone-marrow causing severe compression of the haematopoietic cells, with consequent reduction in the numbers of erythrocytes, leukocytes and platelets.

Napier and Sharma (114) conclude that the anaemia which is an invariable accompaniment of the condition is due to increased erythrolysis caused by the general addition to the number of blood and tissue histiocytes. While accepting this theory in part, Menon (115) points out that haemosiderin, though present in the spleen, is not so marked as in haemolytic anaemias like acholuric jaundice, and suggests that there may be a defective formation of erythrocytes in the invaded bone-marrow rather than
pure red-cell destruction.

In uncomplicated cases there is typically a leukopenia, the principal decrease being in the granulocytes which makes Menon postulate a depressive influence in the bone marrow but not in the spleen, and he concludes that a reticulo-endothelial blockage is responsible for that lack of the normal defensive mechanism against inflammatory processes which so often proves fatal. 50% of Scovel's (1) patients had leukocyte counts below 4,000 per c.mm. Writing about the agranulocytosis which may be encountered from time to time, Sen Gupta and Chakravarty (116) recall the opinion of workers in China, such as Huang (117) who gives its incidence in his series as 7.6%, that the antimonials were responsible in some cases when the condition occurred during treatment, but in opposition quote Forkner and Zia (118) who gave "large and repeated" doses of Neostibosan and Ureastibamine to experimental animals without demonstrating any significant changes in the blood. The former authors go on to advance the theory that treatment may in these cases be either simply inadequate to control the leukocidal effect of a severe infection or may actually cause a further stimulation and proliferation of the macrophages, which in turn leads to a further depression of granulopoiesis. It is unfortunate that definite proof either way is lacking
since it has the most important bearing on the
treatment of a patient who develops this complication.

Changes in the constitution of the blood
are of importance from the point of view of diagnosis
and treatment. Due to the decrease in calcium and
the increase in coagulation time it has been suggested
that spleen puncture may be dangerous.

The blood sugar content is also reduced.

Many diagnostic tests are based on the
fact that the serum-globulin is relatively and
absolutely increased, principally in the case of the
euglobulin, while the serum-albumen is reduced, thus
reversing the usual globulin-albumen ratio from
approximately 0.5 to about 4.

In fully developed cases the Takata-Ara
reaction is always positive (Chaudhuri and Rai
Chaudhuri (119)) while another almost invariable
effect in the blood stream is the marked increase in
the erythrocyte sedimentation rate, which Chung (120)
attributes to the same globulin-albumen ration upset,
and Napier and Henderson (121) correlate with the
degree of intensity of the aldehyde test which is,
of course, dependent on the increased globulin content
of the blood: it usually falls pari passu with
treatment.

There is no general agreement about lesions
of the intestine. Napier (59) denies that specific kala-azar ulcers of the mucosa occur and states that those discovered in the past are either due to some secondary ulcerative condition or to post-mortem change, and is supported by De (122) who failed to find such parasitisation of the submucosa at post-mortem examination. On the other hand, Strong (61) describes a general superficial necrosis of the mucosa without any distinct or localised ulceration. It would appear that they may invade the lumen of the bowel by some means, as Shortt et al (65) record the finding of scanty but typical Leishman-Donovan bodies in the freshly passed stools of a kala-azar patient.

Teng and Forkner (66) have demonstrated Leishman-Donovan bodies in urine and prostatic fluid by intraperitoneal inoculation of hamsters, and the kidneys of all fatal cases in the series of Cole et al (123) showed oedema of the perinephric tissue and cloudy swelling of the renal parenchyma, while in two cases there was necrosis and partial disintegration of the epithelium of the convoluted tubules so that the authors state that the renal damage usually occurring in this disease is in the nature of a toxic nephritis.

The parasites are well-known to occur in nasal and oral secretions, these having been frequently
suggested as vehicles for the direct transmission of infection. Forkner and Zia (18)(124) demonstrated by films and animal inoculation that Leishman-Donovan bodies were present in a large percentage of cases in nasal secretions, saliva and emulsions of tonsils, while Shortt and Swaminath (70) speak of aggregations of parasites in nasal mucus being "absolutely typical and indistinguishable from those in smears of blood or internal organs".

Macroscopic lesions of the skin are uncommon in China and only a few examples of cutaneous leishmaniasis were seen in F.A.U. clinics while the post-kala-azar dermal leishmaniasis, so common in India, seems not to exist. Yao and Sun (125) say in 1936 that not a single case had been reported from treated kala-azar cases in the endemic areas in China and present three cases showing areas of cutaneous depigmentation about one year after treatment, in only one of whom were they able to demonstrate parasites in the tissues of the skin.

H. IMMUNITY.

It is clear that there must be a considerable immunity from kala-azar even in those people who have not had the disease. This becomes greater as one moves from the peak susceptible age for the patients in the area, but some protective factor
must operate even in the most susceptible age-groups where, during the sandfly season in districts where the disease is rife and therefore the percentage of infected flies high, by no means all the susceptibles are infected although under tropical conditions of nakedness the number of bites sustained, by children especially, must be enormous (Napier (85)). Even in these regions many of the dangerous age-group will pass through the fateful period apparently unaffected. Adler (91) has shown the uncertainty of transmission of the disease by injecting five patients with quite large doses of leishmania but only one developed even a mild form of the condition.

There is no reason to suppose that the general population contracts even subclinical infections which might prevent a full-blown attack, but the evidence is difficult to get and the point is in doubt. Equally in doubt is the mechanism whereby a percentage (estimated as from 5-25%) of patients who develop the condition will recover spontaneously and, in company with those who have been cured by chemotherapeutic means, will be almost completely immune from a second attack. Napier in his vast experience in India has seen only 2 cases which he thinks might be due to re-infection: the present series did not include any. Experimentally,
Chung and Wang (126) have confirmed this by failing to reinfect hamsters cured of L. canis infection.

The experimental work in this connection has not advanced knowledge of the immunity mechanisms. Chung and Reimann (127) have shown a diminution in the power to form bacterial antibodies in patients who are already suffering from kala-azar, while Sen Gupta (128)(129) and Lowe and Greval (130) give accounts of the complement-fixation test where apparent high specificity (of the group variety) suggests that there must be development of antibodies in response to infection on the lines of the reagin formation which is the basis of the Wassermann reaction. Row (131) has described an agglutination test using killed cultures of leishmania after the fashion of the Widal reaction, but this is only group-specific and gives a positive result with L. tropica antigen as well. However, it serves to confirm the presence of some type of immune body manufacture, although the enteric analogy breaks down since no effective immunity seems to follow inoculation with leishmania vaccine.

Napier and Krishnan (19) believe that specific treatment has the effect of aiding the natural immunity response by tending to accelerate
the natural evolutionary adjustment between host and parasite: when the association is new the result of treatment will be markedly in favour of the host, and the number of cases of imperfect immunity response will be few in comparison with those cured. However, when the association is older there is a natural tendency to compromise or symbiosis, and treatment increases this tendency, giving rise to a greater number of instances of imperfect immunity response. This, they feel, is responsible for the dermal disease which in India gives the chronic state, occurring for example in Madras where treatment seems to have little effect on the incidence of the condition from year to year because transmission is from dermal cases who appear to be living, according to the authors, in the aforementioned symbiotic state with the parasites. Happily, this condition does not seem to occur in China.

Taken as a whole, this aspect of the disease is not well understood and such knowledge as there is does not seem of any great value in efforts to combat the condition either individually or in an epidemiological collective manner: the major facts emerging are that no one who has not had the disease is safe, but what precisely is the factor or factors which determine infection in any one person are at present unknown.
SIGNS AND SYMPTOMS.

The signs and symptoms of kala-azar do not vary a great deal in different countries and there is a fair degree of agreement among authors on the subject, although in all areas many questions remain unanswered.

1. INCUBATION PERIOD.

One of these queries is the duration of the incubation period, which seems to vary greatly from case to case: often-quoted patients are those of Muir and Manson who developed the disease in 14 and 10 days respectively and the case of Most and Lavietes (132) at the other extreme which took at least 19 months to show the first clinical signs. These periods are thought to be exceptional, as estimated from the number of cases occurring after each sandfly season, but those usually afflicted are, in most parts of the world, notoriously unable to give exact times for the onset of their symptoms and so writers tend to give a rather wide range as the limits of the period of incubation. Those in reasonable agreement about the limits include Stitt (61) giving 6 weeks to 4 months, Napier (59) stating 2-4 months and Scovel (1) suggesting 2 weeks to 16 weeks. The writer was unable to form any estimate from his cases since most of them were advanced, and
few histories would give more than rough approximations (and seldom the same approximation twice) with regard to the informer's own or his child's illness. Calculations of time of onset of fever, etc., from statements given revealed a suspicious uniformity for all months of the year, which is almost certainly a product of random utterances by Chinese patients who are undisturbed by death and destruction and so not interested in details.

2. PRIMARY INFECTION.

In 1936 Petrov (133) gave an account of two cases of leishmaniasis in children in which visceral infection was preceded by cutaneous sores containing parasites: Kirk and Sati (134) add another case who had both cutaneous and visceral leishmaniasis. Later, in 1941, Mirzorian (135) elaborated the theme and suggested that in some infections there might be a regular "primary" lesion which in his cases developed several months before the disease could be diagnosed clinically, taking the form of one or more minute papules about the size of a pin-head, appearing on the face, increasing for a few months and finally disappearing but leaving behind pigmented spots. This may occur before or after the visceral lesions become mature: sometimes Leishman-Donovan bodies can be found concurrently in the papules and by sternal puncture.
He gives reasons why these spots are not to be considered as merely an abortive type of oriental sore, suggesting that they are due directly to the bite of the sandfly and that they form a visible sign of approaching visceral infection, against which precautions can be taken.

Kirk (45) has now extended this theory and postulates a specific cause of evolution in the human subject, involving the primary stage with cutaneous sores at the site of inoculation which have a tendency to spontaneous cure: the secondary stage is that of generalised infection or the classical kala-azar. The tertiary stage is that of cutaneous or muco-cutaneous infection, which he says may occur in the Sudanese variety of the disease immediately after the completion of treatment, and which in India Napier and Krishman (136) have called "post-kala-azar dermal leishmaniasis", occurring after a latent period of 1-2 years from the completion of treatment. This stage Napier feels is increasing in frequency, being an example of the balance between parasite and host which is responsible for the maintenance of these chronic reservoirs of infection and keeps up a constant dissemination among the population. Kirk warns against comparing his three stages too closely with the course of
syphilis, stating that there may be some overlapping occasionally.

Chung (137) has described a puzzling case of localised leishmaniasis of various lymph glands (apparently well-confirmed) which he thinks may have been an arrested early stage of the disease.

Further work on these phenomena is obviously desirable in all parts of the world but requires intensive effort, permanent clinics and an ability to observe and follow-up cases of suspected unorthodox lesions.

3. **FEVER.**

Eastern flesh is heir to a multiplicity of fevers and the insidious onset of leishmanial pyrexia is such that few patients described fever as preceding their splenomegaly until pressed to recall this period in detail, when they would rather grudgingly admit that they had had some fever prior to noticing their abdominal enlargement, but usually regarded it as of no great magnitude or importance. It was noticeable, however, that parents commonly gave a longer history of fever in their children and looked on it as a matter of some moment: this confirms the well-known fact that even high fever in this disease may be subjectively overlooked and give rise to little inconvenience, while still remaining obvious to even a casual observer.
It may be described as high or low fever and there was clearly no uniformity about its progress, a fact which is in conformity with Napier's (59) description of three methods of onset, the malarial, typhoid and gradual types. This is so in the beginning of the disease, but in the present series patients seemed to follow a fairly standard pattern thereafter, with quite irregular bouts of fever still not incapacitating until a later stage. Lowe (2) puts it that the fever of kala-azar is extremely variable, variable in its onset, variable in its development and in its termination, in fact the characteristic of the fever in many cases of kala-azar is its irregularity.

The typical double rise is naturally not noted in out-patient clinics where temperatures serve merely as a guide to the decline of the disease under treatment. One interesting point emerging from work in those few areas where malaria was found was that the patients were unable to distinguish between the symptoms of malaria and kala-azar, which is perhaps not so surprising since rigors, chills and sudden bouts of high fever are not uncommon in kala-azar. Struthers (138) states that 22% of his patients complained of sweating while 16% said they had chills. Scovel (1) describes the chills as recurring only a few times and not being experienced
again, while the only feature distinguishing kala-azar chills from those of malaria is, according to Most and Lavietes (132), the absence of aching in the back and extremities and vomiting in the former. The failure of quinine to bring down the pyrexia was the most significant feature of the history here.

While agreeing, as mentioned above, that the earlier stages of the disease are not usually attended by any prostration, present experience was that, in general, patients with a history of fever extending over six months were distinctly ill, and although mostly able to walk were listless, apathetic and disconsolate. The children showed little inclination to play in the courtyard outside the clinics, as opposed to a "control series" of the inevitable curious children who came to see what was going on. Similarly adolescents and adults were usually working, but from necessity, not choice, and while a few patients were seen who denied having fever, when in fact their temperatures were quite high, these were undoubtedly exceptional (although, as previously noted, the converse is the case in the early stages of the disease). It remains true, however, that except in the very advanced stages of the disease, e.g. those with a history of 2 years or more, the degree of prostration does not approach
that in malaria, typhus or relapsing fever, cases of which were seen from time to time.

The type of case attending F.A.U. clinics conformed to the textbook picture of the disease in the main, but at least one of the very acute cases described by Kirk (45) was seen: she died within a week despite treatment. It is suspected that one or two others who disappeared from observation may have been examples of the same condition. The chronic type of case mentioned by the same author was encountered more frequently, chiefly in adults over the age of 25 years with the same uncertainty of prognosis as he described. As will be discussed later they form one of the classes where it was felt that the routine system of treatment might not be adequate.

4. LOSS OF WEIGHT.

The number of cases having a clear history of 6 months or more who had not had loss of weight was very small, although they did exist. The degree of emaciation was roughly proportional to the age of infection, and in the majority of cases was considerable. However, it could not be said that the uninfected population in most villages visited was particularly well-nourished since the greater number of them were poor peasants living always on the verge of undernutrition, and constantly in a
state of malnutrition. The combination of the loss of subcutaneous fat and the attempt by the portal system to bypass the liver results in prominently distended abdominal veins: Scovel (1) differs from most authorities in not having observed this, although he admits that it may be due to having fairly recent cases to deal with.

5. OEDEMA.

Oedema in slight degree was common in the earlier cases and not infrequently severe in the late cases, the distribution of this oedema being often peculiar, and patients were seen in whom it was isolated in the face or the abdomen or confined to those two sites. Oedema of some kind was seen in 3.9% of patients and sometimes was associated with ascites, sometimes not. Frequently ascites was combined with dependent oedema but this might occur alone. In addition to these states were seen the three pure classical syndromes of dependent oedema due to cardiac failure, generalised oedema due to nephritis and the ascites typical of cirrhosis of the liver. In the very advanced cases all these factors play their part, reinforced by toxic nephritis and the inability to replace the proteins lost in the urine consequent on the low protein diet of the Chinese peasant. Goodwin (139) states that in the hamster with chronic leishmanial infection
the oedema does not depend on the degree of infection as measured by parasite counts from spleen smears, nor is every animal affected. He affirms that it is due to a toxin liberated by the leishmania which acts on the kidneys.

6. SPLENOMEGALY.

The enlargement of the spleen gives rise to one of the Chinese names for the disease, so constant is it and every conceivable size and shape was seen in the F.A.U. cases. It is generally thought to become palpable about one month after infection, and thereafter proceeds to enlarge further at a variable rate and to a variable extent as determined by palpation, the latter depending to some degree on the direction of its enlargement.

This makes comparisons of the size of the organ, based on the relation of its lower edge to the umbilicus, somewhat misleading since obviously a long thin spleen may reach below the navel and yet be much smaller than one which is broad and deep but only just below the costal margin: however, probably this error is ironed out when a large series is considered. Kirk and Sati (140) give the spleen sizes in their series of 28 cases treated with diamidines and (as near as can be calculated since they give measurements in finger-breadths) their
SPLENOMEGALY in KALA-AZAR

<table>
<thead>
<tr>
<th>Level of lower border of spleen</th>
<th>Percentage of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spleen above umbilicus</td>
<td>24.2</td>
</tr>
<tr>
<td>Spleen approx. at umbilicus</td>
<td>30.2</td>
</tr>
<tr>
<td>Spleen below umbilicus</td>
<td>45.5</td>
</tr>
</tbody>
</table>

The enlargement of the spleen gives rise to one of the characteristic features of the disease, and raises many questions as to the meaning of it and many explanations have been given to the phenomenon. Many attempts have been made to assign different causes to splenic enlargement in Kala-Azar, and these attempts have been directed towards the elucidation of the etiology, the nature and extent of the infection by means of pathological, bacteriological, serological, and therapeutic experiments. However, the problem of the etiology of the disease remains unsolved.

The table above shows the extent of splenic enlargement as observed by F.A.U. and Kirk & Sati. The percentage of cases with low spleen borders is higher in Kirk & Sati's study, whereas the percentage for normal and enlarged spleens is higher in F.A.U.'s study. This discrepancy might be due to different methodologies used in the studies.
figures would be as shown, which indicates a type of patient similar to those of the F.A.U. in regard to chronicity of illness and probably with regard to severity as well. Archibald and Mansour (63) state that a spleen at a level midway between the umbilicus and costal margin usually indicates fever of at least four months duration, and a spleen level with the umbilicus is indicative of 6 months pyrexia.

It should be noted that these figures are given mainly to present a picture of the duration and severity of the disease in the cases, and have no particular significance per se. What they do indicate is that on the first visit to each district the clinics attracted the more advanced cases with the bigger spleens, and that on subsequent visits the cases would be younger, of shorter duration, and possessed of smaller spleens. This has been borne out since in second visits to some centres. In the individual case the degree of splenomegaly is no help in diagnosis, since spleens within wide limits of size may be found in advanced cases of both kala-azar and malaria. On the other hand, the method of enlargement is typical. As opposed to the fluctuation of malarial splenomegaly with pyrexia, the kala-azar spleen maintains a steady and rapid increase, once it has begun, uninfluenced
by the irregularity of the fever, and in default of treatment (or the comparatively rare spontaneous remission) does not show regression at any time.

7. ABDOMINAL PAIN.

This was very uncommon in F.A.U. cases before treatment, unless from some cause obviously other than leishmaniasis: Napier (59) found it in 5% of his cases and suggests that it is due to infarction by blockage of a splenic arteriole, while Struthers (38) mentions it as occurring in 13% of his series. Burke (141) states that he has come to regard abdominal pain as, if not a diagnostic sign, at least one which should give rise to suspicion and justify the keeping of a patient under observation for the development of other signs of kala-azar. It was experienced in 2-3% of his cases.

8. HEPATOMEGALY.

Enlargement of the liver is found in the same circumstances as splenomegaly, i.e. most commonly in the later cases since it has a more gradual but no less steady expansion. It rarely reaches the umbilicus, although sometimes the increase in size is gross, and combined with a large spleen causes great abdominal distension. Palpable livers occur in malaria as well and differentiation may be difficult. Ultimately the kala-azar liver progresses to a state indistinguishable from the classical cirrhosis.
HEPATOMEGALY in KALA-AZAR

<table>
<thead>
<tr>
<th>Description</th>
<th>Percentage of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver not enlarged</td>
<td>4.4%</td>
</tr>
<tr>
<td>Liver 1.5 cm. below costal margin</td>
<td>19.7%</td>
</tr>
<tr>
<td>3.0 cm.</td>
<td>32.7%</td>
</tr>
<tr>
<td>5.0 cm.</td>
<td>27.5%</td>
</tr>
<tr>
<td>6.5 cm.</td>
<td>10.9%</td>
</tr>
<tr>
<td>8.0 cm.</td>
<td>4.1%</td>
</tr>
<tr>
<td>10.0 cm.</td>
<td>0.4%</td>
</tr>
<tr>
<td>11.5 cm.</td>
<td>0.25%</td>
</tr>
</tbody>
</table>
In a series of 796 cases where the degree of increase was measured accurately the proportion of patients at the various stages was as shown. These figures, as in the case of the splenic measurements, will be noted to reflect the comparative lateness of the stage at which the patients were seen. Napier's series of 300 cases gave 88% palpable livers which is comparable to that of the present collection, whereas, peculiarly enough, Scovel (1) says he has not noticed an enlarged liver in most of his cases. Pain and tenderness in the liver are not common.

9. ALIMENTARY SYMPTOMS.

Alimentary lesions are of various types. In the mouth gingivitis is very common and ranges from localised gum infections to the grave cancrum oris. Malnutrition is widespread, there seems no hope of remedying avitaminosis and dental treatment does not exist, so that mouths are allowed to deteriorate into the more serious conditions. Scott and Li (62) mention that 27% of their cases had bleeding gums, Struthers (138) quotes 37%, while Scovel (1) says that this sign is more frequent in adults. F.A.U. figures show that of all cases 6.6% had obviously septic gums on first attending the clinic, while there was no observable sex distinction. Appetites, except in the early stages,
were generally rather poor and corresponded to the degree of emaciation: Struthers (138) describes anorexia in 33% of his cases, which was very close to the amount of frank emaciation he mentions, i.e. 35%.

Vomiting was not a common pretreatment complaint, and when it occurred could not be assigned to any particular cause. Lacking adequate laboratory facilities it was not possible to investigate the cause of diarrhoea in all the many cases who suffered from it, but as Napier (59) says it is doubtful that this is a specific leishmanial symptom, having consideration to the ubiquity of dysentery, both bacillary and amoebic, in those areas, to say nothing of the cases where the diarrhoea might be related to malnutrition and cachexia. It was rarely severe, but unwelcome as an additional factor depressing the patients' resistance.

10. CUTANEOUS SYMPTOMS AND SIGNS.

One of the two common names for the disease in China is Hei-re-ping ("Dark fever disease") which everyone in this endemic area understood only too well, and yet the writer was quite unable to distinguish this specific pigmentation in the present cases. Since the clinics were dealing very largely with a peasant population whose work
is almost exclusively out-door in character, pigmentation was the rule especially in the summer months, and was not diminished by any undue cleanliness. It was not observed to differ in the infected and uninfected, and attempts made on numerous occasions to use this sign for "spot" diagnosis in unexamined cases gave no more success than chance would ensure. The advanced cases were prominent in having an appearance which combined the normal Chinese facial colour (which may vary from yellow to dark brown) with the cachetic grey-white of the anaemic, toxic and seriously ill subject, but was similar to that seen in many of the malarial cases and all of the advanced pulmonary tuberculosis patients encountered. Scovel (1) also failed to find particularly dark facies in his Chinese patients, although Scott and Li (62) reckon to have seen pigmentation in 17% of their cases (who were children). There were 2 doubtful cases of the leishmanial tropical sore while post-kala-azar dermal leishmaniasis was not seen.

11. URINARY SYSTEM.

Serious renal damage does not seem to have been reported except by Cole et al (123) who experienced an epidemic of a severe nature, occurring, it would seem, among men who had no immunity against
the disease. They reported 24 patients out of 27 showing a "fair cloud" of albumen, and 15 showing granular casts in the urine.

In the F.A.U. series of 3,190 patients albumen was present in the urine as shown. There was no routine search for casts and the albuminuria was attributed to the effect of the leishmanial toxin, since in the vast majority of cases it disappeared as treatment was given. How much was due to the cardiac failure which was present in some of the advanced cases is difficult to say, as this syndrome also tended to vanish with successful specific treatment. Slight oedema of the previously noted atypically distributed type was thought to be of renal origin, and a few cases of anasarca certainly had a renal element in their background. Napier and Muir (142) mention that a trace of albumen is to be found in 30% of cases in the "non-hyperpyrexial" periods. In F.A.U. cases the severity of the condition could not be associated with any of the other signs and symptoms in particular, but was in general found in those patients with advanced disease, untreated.

12. NERVOUS SYSTEM.

No lesions of the nervous system were encountered either before or after treatment,
beyond occasional headaches occurring when the fever was unduly high, but these were never severe.

13. CARDIOVASCULAR SYSTEM.

In the febrile periods the pulse rate was markedly increased and this tendency grew as the disease progressed. No very informative estimation of the heart-rate could be made in children, who almost without exception were either loudly or quietly apprehensive about the injections with the usual result on the pulse rate, but adults even of the most stolid type consistently ran rates of 90-110 b.p.m. although they might be afebrile for some weeks. Anaemia was the rule, and this increased the number of abnormal heart sounds encountered, some of which, in the hasty examination of a busy out-patient clinic, seemed to be of rheumatic origin, while others were definitely rheumatic. The toxic myocarditis which was found in nearly all late cases produced the usual signs, tachycardia, dyspnoea, soft rapid pulse, some cyanosis, dilatation of the chambers with shift of the apex-beat, and an oedema of the feet which Napier and Muir (142) describe as a very common sign. This last Scott and Li (62) found in 7% of their patients: F.A.U. workers saw it frequently, associated or unassociated with oedema elsewhere.
or ascites, but no figures can be quoted as minor degrees would be missed by some observers and some patients were not examined fully in overworked clinics where, especially in women and children, ankles were bound up and take a long time to be displayed. Scovel (1) comments that his failure to find oedema of the feet as a common sign may be due to the short duration of the disease in his cases, and certainly other than minor degrees are not common until the renal, cardiac, hepatic, mechanical and nutritional factors have been brought into play in the later stages.

A figure for epistaxis of 3.5% out of 2,069 patients is not a true picture of the frequency of this condition, since it was not investigated in history-taking till later in the campaign when it was realised that this and many symptoms could be elicited only by intensive questioning. Even so, the impression was gained that it may be common, although no patient was at any time seen whose nose was in the process of bleeding or who had purpuric or ecchymotic lesions of the skin. Scovel (1) found it in nearly 75% of children, Struthers (138) in 47% of his cases and Scott and Li (62) in 35% of child patients. The difference in these figures probably represents nothing so much as the
degree of enthusiasm and assiduity of the
interrogation of the patients.

14. HAEMOPOIETIC SYSTEM.

At the beginning of the present work it
was planned to investigate the state of the blood by
red cell counts and haemoglobin estimations in each
patient, but it was soon realised that this was
unnecessary since anaemia was general and examination
of skin and mucous membranes could divide the
patients into rough grades suitable for the purpose.
On this unscientific basis it was calculated that
8.8% of all cases were grossly anaemic. Scovel's
(1) patients had 55% of their number with a haemo-
globin reading of 50% or under.
COMPLICATIONS.

As mentioned previously, in kala-azar resistance to bacterial infection is poor, and sepsis occurs in many forms probably in large measure due to the accompanying leukopenia which provides a much diminished number of phagocytes to swallow up any invading organisms. The importance of this factor may be illustrated by Clow's (15) series where, out of a mortality of 14%, only 1.75% were cases of uncomplicated kala-azar.

1. Minor Sepsis.

Skin sepsis was common in Honanese patients and small abscesses were frequently seen subsequent to the insertion into the enlarged spleen of needles by Chinese medicine men "to let out the bad air". One case had what appeared to be a chronic splenic abscess (possibly with a tuberculous basis) which constantly discharged via a skin sinus to which the organ was adherent. One extensive leg ulceration in a young boy was endangering his life, but responded (in hospital) to rest, cleaning and improvement in his general condition. Chronic otitis media was not uncommon.

2. Cancrum oris.

This is the most dangerous complication, and occurred in 3.1% of cases. It is found at any age among children and adolescents and one or two older relatives of the patients had suspicious-looking scars
on their faces, giving histories suggesting kala-azar some years previously. It was seen at all stages from the beginning, where there is first a reddened swelling of the cheek which darkens to a purplish colour and then the skin sloughs over a well-defined area, leaving a raw but not very painful surface which gradually exposes muscles and fascia until there is actual perforation, with the escape of saliva to the exterior. There is great variation in the time this process takes, and in some of the chronic cases it had occurred so gradually that, apart from the continual loss of saliva and food particles, the patient's health seemed little worse than the general leishmaniasis would warrant. In the more acute cases the whole cheek will slough, and the resultant toxaemia is often enough to turn the tide of an illness to a quicker end than would have occurred otherwise, the patient dying in a few weeks or months. In the fulminating cases the cheek seems almost to melt away, along with pieces of the eyes, nose, lower jaw and teeth, death coming in a few days or weeks.

The structures attacked and the order in which they are affected differs from case to case: one may start in the mucosa of the cheek and never become more than a small inconvenient salivary fistula, whereas another may begin as a patch of
gingivitis and go on to cause necrosis of the mandible, destruction of the nose and eye and exposure of the maxillary antrum. It is associated with the later stages of the disease but its onset does not seem to be connected with any particular leishmanial event - rather with some possibly minor trauma to the affected area of buccal mucosa. It is not specific to kala-azar, but may occur in any chronic debilitating disease, of which kala-azar is the best example, others noted in China by Wang Sung & Sung (143) in a series of 30 cases being measles, dysentery and leukaemia. The complication did not occur in any of the 30 cases in Most and Lavietes' (132) series among American Army personnel, presumably due to the healthy state of their mouths prevailing prior to infection.

The causative organisms would seem to be those of Vincent's angina, which are usually to be found in the gingivitis so common in poor peasant people, and are given the opportunity to flourish by reason of the patients' lack of resistance, starting in an area where this has occurred, possibly due to trauma.

In comparison with the F.A.U. finding of a minimal 3.1%, Scovel (1) had an incidence of 2.5% Clow (14)(15) quotes 14% in his series, while Napier and Muir (142) found less than 2% in a series of 300
cases. Sati (144) in the Sudan had 1.3%, Lucke (145) found it in 3% of 202 cases and Tuckman (145) in 4% of 315 cases, both working in Honan, and finally Scott and Li (62) saw it in 6% of their patients. Of Sen Gupta and Chakravarty's (146) patients 5 were children between the ages of 2 and 10 years and one was a young adult. Scovel (1), out of 15 patients, had only one over the age of 15 years. In the F.A.U. cases the average age was 8.3 years, but why there should be this apparent lack of resistance in the younger children is difficult to say. 4.8% of them were over 15 years of age and the sex-ratio was male:female = 63:37, similar to that for the entire series which was 65.7:34.3, thus suggesting that the sexes are attacked equally.

Sen Gupta and Chakravarty's (146) cases had had the illness for 3-6 months before developing the condition and one had actually started during specific treatment for kala-azar. The average period of illness in the present complete series was 11.2 months, whereas in the average cancrum oris case it was 14.6 months, showing that the complication is one which occurs late in the disease, possibly due to a lowered resistance as the patient becomes gradually weakened by the progress of his generalised condition.
### DISTRIBUTION of CANCROM ORIS

<table>
<thead>
<tr>
<th>Site of lesion</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Involving principally the upper lip</td>
<td>24</td>
</tr>
<tr>
<td>&quot; &quot; lower &quot;</td>
<td>33</td>
</tr>
<tr>
<td>&quot; &quot; left cheek</td>
<td>18</td>
</tr>
<tr>
<td>&quot; &quot; right &quot;</td>
<td>25</td>
</tr>
</tbody>
</table>
When examined first, the cancrum oris had been present for an average period of 15 weeks, but since the individual duration ranged from 5 days to 1½ years, this figure has little significance: it is obvious that there is a great variation in the virulence of infection from case to case, some causing a rapid dissolution of tissue and speedy death while others seem to strike a balance with the patient's resistance and make little or no progress. The grading of this virulence or severity is not really possible, or at least it does not convey much useful information, being usually founded on subjective distinctions, but it may be helpful to record the distribution of the lesions which were as shown (there was, of course, considerable overlapping of the areas).

3. Respiratory disease.

This was not uncommon in slight degree, and although the cough which Napier (59) describes as being present without any considerable physical signs in the lungs was frequently met, quite a substantial number of the patients did have all the signs and symptoms of moderately severe bronchitis, and in many adults it was of long-standing with fetid sputum. Four cases developed frank lobar pneumonia during treatment, which was suspended while they were given sulphonamide therapy. It has to be
remembered that a child who is severely ill with pneumonia will not ordinarily be brought any distance to the clinic by Chinese parents until he recovers, when it will go unrecorded: if he dies it will probably also go unrecorded, and if he develops it during treatment he will very likely be kept away until he recovers, when equally the condition will not have been appreciated. All known pneumonia patients in this series were adults and none was very severely ill.

Pulmonary tuberculosis was occasionally diagnosable with the finger and stethoscope, but was more often suspected in earlier stages which could no doubt have been made out radiologically.

4. Hepatic lesions.

Whether in the late stages of the disease the liver assumes a true cirrhosis is a debatable point, but in a number of cases who had a hard palpable liver this was associated with distended superficial abdominal veins and ascites, the latter of variable extent and accompanied by emaciation and exhaustion. When free fluid was present in the abdomen the prognosis was unfavourable whatever line of treatment was adopted, especially as it was accompanied by all the other late signs and symptoms of kala-azar, plus usually dependent oedema of the lower limbs due to the mechanical pressure of the
fluid. Albuminuria was sometimes present also. Rogers (264) speaks of a definite progressive ascites unaccompanied by general anasarca seen occasionally in advanced cases, which he attributes to cirrhotic changes in the liver.

For comparison with Sati's (144) figure of 0.67% of ascites in his 150 cases in the Sudan, in the F.A.U. series 0.72% had this complication, the average age being 15.2 years which is decidedly above the general mean, but like the cancrum oris series the sex incidence is the same as in the complete series, viz. male:female = 67:33 indicating that the occurrence of this complication is equal in the sexes. It was found in patients who had had kala-azar for a period averaging 14.1 months, emphasising the delay in onset and thus the need for early treatment before this frequently fatal sign makes its appearance.

Jaundice was seen in only 4 (0.13%) cases and could not be associated with any specific aspect of the patients' illness, seeming rather to be of the epidemic hepatitis type and certainly passing off without any trouble.
DIAGNOSIS.

This can be conveniently divided in three parts, clinical diagnosis, serological tests and identification of the parasite.

A. CLINICAL DIAGNOSIS.

Clinically the diagnostic features are very different in the early and late cases. In the former the only symptoms will be fever and possibly chills for the first 1-2 months of the infection, giving rise to a suspicion of malaria in districts where this condition is rife. After this period the spleen begins to enlarge, which itself serves to eliminate many of the possible causes of fever and as it proceeds, demonstrates one of the most specific signs of the disease, viz. the steady and usually rapid enlargement of the organ without any recession during the afebrile periods. This does not occur with any other condition giving a general picture compatible with kala-azar, and would be very helpful in intelligent patients but unfortunately the average patient is uninterested in, or cannot remember such details. When a clear history of such progression can be elicited, however, it will rarely be due to anything else. Even in the later stages the organ never acquires the wooden-ness of the chronic malarial spleen although it does become firmer as it enlarges.

At this time too, perhaps the most typical
feature of the fever as recalled by the patient is its complete irregularity: in out-patients, of course, there is no opportunity to study the daily "double-rise" of temperature which is said to be found frequently, but a point of some value is a history of high fever during which the patient continued to work, or play with other children, as the case might be: this is not common in other severe fevers.

The liver shows enlargement in most cases but without any feature peculiar to this disease.

Emaciation is usually more pronounced at an earlier stage in kala-azar than in conditions with which it might be confused even where anorexia is denied, but one or two exceptional cases were seen where subcutaneous fat had not been lost even after a 6 months history of fever and splenomegaly.

Sepsis is common in the East, but the lesions of gingivitis and especially cancrum oris seemed to be found much more frequently in kala-azar victims than in the subjects of other diseases coming to the clinics, in fact only one case of cancrum oris was seen where the diagnosis of kala-azar could not be made, and it was strongly suspected that this was a case of spontaneous cure, judging from his history.

The varieties of oedema seen were quite indistinguishable from those occurring in non-
leishmanial conditions, e.g. cardiac failure, renal deficiency and malnutrition, while in the late stages some patients exhibit a condition exactly simulating cirrhosis of the liver of the idiopathic type.

To sum up, it should be stressed that symptoms and signs take on a new significance in any area where the disease is known to be endemic and where malaria is not found to any extent: this was the case in the great majority of Honan districts, so considerable importance could be attached to steadily progressive splenomegaly, irregular fever without prostration, and severe buccal sepsis, especially cancrum oris. Although treatment was never given on purely clinical grounds it would be true to say that in this endemic area of China, in those patients with a history of 3 months or more the diagnosis can be made in this way, as Napier (59) says, "with a fair amount of assurance".

E. SEROLOGICAL DIAGNOSIS.

On account of their simplicity, various serological tests are widely used either as aids in or as the complete diagnosis of kala-azar.

1.(a) "Water" Test.

The type found to be in most frequent use in non-F.A.U. clinics in N. Honan (where any laboratory tests at all were done) was the haemolytic
test or "Water Test" of Ray (147) which is popular in most of the endemic areas of China. Like all the others it is dependent on the excess of globulin in the serum and was discovered when making haemoglobin estimations in patients suffering from the disease, when it was seen that the addition of blood to distilled water did not produce a clear solution, i.e. the cells did not haemolyse completely. It was further found that this was not an intrinsic property of the cells but due to some supportive action of the globulin excess and was sufficiently constant in the mature case to serve as a specific test, since it was not strongly positive in any other splenomegalic condition. The technique recommended is to add two drops of freshly drawn blood (straight from a finger or ear stab) to twenty drops of distilled water, allow to stand, when a deposit of red cells indicates a positive result, the amount of deposition (or lack of haemolysis) representing the degree of positivity. Experience with the test showed that where the case was clinically suggestive of the disease a well-marked positive was sufficient to clinch the diagnosis although the weaker reactions were not sufficiently specific for diagnosis, nor does the test become significantly positive until about 2-3 months from the start of fever. Within its limitations, thus, it is of considerable value.
(b) **Globulin-Precipitation Test.**

This uses serum instead of whole blood, has practically the same significance as the haemolytic reaction, but is more time-consuming and so was not used in this work. Sia (148) gave his opinion that an untreated case of kala-azar usually produces a ### or ## globulin precipitation test, while Struthers and Ch'i (149) say that in 92.9% of their proved kala-azar patients the "water" test was unmistakeably positive: in 7.1% it was doubtfully positive.

2 (a) **Aldehyde Test.**

This test (Napier (150)) is often spoken of as the Formol-gel reaction. It also is dependent on the globulin excess in the blood and the technique involves merely the addition of 2 drops of formalin to 1 ml. of clear serum, which in a positive reaction will become opaque and solidify, while in a negative reaction it remains clear and liquid, intermediate degrees of positivity showing corresponding stages of opacity. It usually begins to show the reaction when the disease has been present for about a month, and Napier (151) states that it is of great value in endemic areas where large numbers of out-patients are seen: he produces figures (152) to show that it was slightly more sensitive than the results of the first
spleen puncture in a series of more than 100 patients.

Under 6 months duration he points out that a negative reaction does not exclude kala-azar. Similarly, Lowe (2) indicates that a patient with marked enlargement of the spleen and a negative aldehyde test is probably not suffering from kala-azar. Struthers and Chi (149) found 98% of their cases positive and only 2% negative, and Laha (153) uses the test to confirm his clinical diagnosis but mentions 7 cases where the aldehyde test was negative in the presence of Leishman-Donovan bodies in the spleen.

(b) Chopra's Antimony Test.

This is similar to the aldehyde test, using a solution of urea-stibamine instead of formalin: Napier (59) opines that it is less specific than his reaction but is usually positive at an earlier stage of the disease. It was not used at all in F.A.U. work, since specificity was to be preferred in the type of case coming to the clinic.

3(a) Complement-Fixation Test.

In 1938, Lowe and Greval (130) during their work with the W.K.K. antigen in an effort to discover a reliable test for leprosy, found that the complement-fixation reaction gave a high percentage of positive findings in cases of leishmaniasis, 17 cases of kala-azar (aldehyde-positive) all showing complete
inhibition of haemolysis. Sen Gupta (129) (154) says that the test is apparently highly specific, being positive in 93-7% of two series of undoubted kala-azar and only 0-1% positive in cases which might be considered in the differential diagnosis, e.g. chronic malaria, splenic anaemia, tropical splenomegaly, enteric fever, etc. while it would seem that the reaction appears sooner than the antimony or aldehyde tests and may give a significant result in an illness of four weeks duration, at which time spleen puncture is impossible as the organ is not yet sufficiently enlarged: in any case he avers that spleen and sternal puncture would not give better results even where they can be conveniently performed. Unfortunately, such a test requires more elaborate laboratory apparatus than could be expected in temporary clinics, although it might have a place in permanent hospitals.

(b) Agglutination Test.

Row's (131) agglutination reaction may be group-specific but does not offer practical help in routine diagnosis.

C. PARASITE IDENTIFICATION.

1. Blood.

Transcending all other methods of diagnosis is the identification of the leishmania from some part of the body, which puts the matter beyond doubt.
Unfortunately, the most reliable methods of achieving this require a certain amount of skill, and attempts have been made to use the easily procured peripheral blood for investigation. Shortt et al. (155) state that in proved cases of kala-azar, parasites in peripheral blood can be found by direct microscopical methods in 78.7% of cases without prolonged examination, but Wang (156) had no more than 39% of success, not of practical value. Das Gupta (157) has cultivated flagellates from 95.9% of 169 cases of untreated kala-azar and says that the average number of days for the appearance of the flagellates is 11.4.

2. **Nose.**

De Azevedo (158) recommends the examination of nasal scrapings, which he found positive in 9 of 11 cases: the method is safe but inferior to spleen puncture.

3. **Glands.**

Attention has been called to the possibility of isolating the organisms from superficial glands (usually inguinal) which are frequently enlarged, especially in children, but not always in adults, according to Giraud and Gaubert (159): Giraud et al (160) describe 2 cases where this procedure was easily carried out, while Kirk and Sati (161) assert
that in a large proportion of kala-azar cases diagnosis can be confirmed by simple gland puncture, citing a series of 30 consecutive cases in each of which the parasites were found readily in stained smears of gland juice. De (122) explains failures in this method by his theory that parasites enter lymph glands only when they are draining an inflamed area, and so in many cases may not be present: Most and Lavietes (132) could report success in only 5 out of 7 patients having lymphadenopathy. The F.A.U. teams did not use this method.

4. Liver.

Although Yates (33) speaks of performing liver punctures in preference to spleen puncture on account of the increased number of positive results, Shortt (162) says it has been placed before spleen punctures simply because of the supposed danger inherent in the operation of the latter, with which he does not agree. Scovel (1) observes that in spite of the danger of haemorrhage from tearing, this is practiced routinely by many examiners, and that parasites are almost invariably present and easily found. On the other hand, Ho et al. (163) in their study of sternum, spleen and liver punctures found that the latter was much the least efficient procedure. Napier (59) feels that this method has been entirely superseded by sternal puncture which is
much safer and obviates the necessity for culture, which is indicated to get the best results from the liver material. Puncture of the latter is not always possible unless by going through the pleural cavity, since it may not be enlarged. In the present series it was not felt necessary to use this method when safer and more informative procedures were available.

5. Bone-marrow.

There seems to be a consensus of opinion that sternal puncture is safer than spleen or liver puncture: Napier (164) claims that it is probably so, especially in inexperienced hands, but emphasises that the findings are considerably inferior to those of spleen puncture and quotes (59) a success of 89% in a series of 80 patients, noting that parasites were found by spleen puncture from the unsuccessful 11%, some by culture only. He adds that it has the undoubted advantage over spleen puncture that it is possible before the spleen enlarges (Meleney (165) recalls that spleen puncture should not be attempted unless the organ protrudes an inch or so below the costal margin). Lowe (2) points out that parasites are occasionally scanty and may not be found at all in sternal marrow. This is the opinion of Shortt (7) also, who considers sternal puncture less reliable than spleen
puncture, whereas Clow (15) thinks it is the best method of diagnosis: Scovel (1) quotes a series of 557 examinations of fluid from the sternal marrow with 81% of positive results. The writer's opinion is that it is probably safer than spleen or liver puncture in careless hands (although he is unable to regard either of the latter as dangerous where a standard technique is followed) and can be performed where there is no splenomegaly or hepatomegaly, but it is more time-consuming and will regularly fail to demonstrate parasites in a small number of cases when they will be seen (albeit sometimes with difficulty) in splenic material. However, it is felt that the strongest objection to its performance is the pain which is inevitably present, not in the penetration of skin or periosteum which can be more or less satisfactorily anaesthetised but in passing through the bone and more especially when withdrawing marrow, which gives a severe, if dull, pain in all patients. This is quite a disadvantage when working in the "backwoods" where patients are less than enthusiastic about diagnostic measures in any case, and may easily be discouraged from attendance for treatment by the shock of this procedure, about which little can be done.
Concerning the safety of performing puncture of the spleen there is a traditional opinion that it is fraught with peril, and Scovel (1) used it very little (twice in 2 years) owing to "frailty and danger of haemorrhage" although quoting Muir's technique in 1,000 cases without a mishap. Giraud and Gaubert (166), whose work is often quoted, carried out the procedure in 300 cases with 3 direct or indirect deaths and so suggest that it should be abandoned, but against this must be laid the whole weight of Napier's (161,167) great experience which extends over 20 years and includes more than 6,000 spleen punctures without a fatality. Debono (60) in 2,000 cases had 2 fatalities only, one in a moribund patient and the other in a case of leukaemia. It is interesting to observe how the older writers like Aravandinou (168) and Nicolle (169) give rather contradictory directions for the technique, the former tending to minimise the danger involved and disregarding pre- and post-operative measures such as those advocated by the latter, i.e. estimation of bleeding-time and post-puncture immobilisation, while Napier (170) in 1936 details a fairly elaborate routine, including the giving of three doses of calcium chloride, prohibition of food prior to the operation and confinement to bed.
during the succeeding day. Later, however, (59) he admits, a little reluctantly, that he is doubtful whether this regime is either necessary or sound, although hesitating to abandon it. Most and Lavietes (132) exhibit the seemingly inevitable combination of inexperience and caution by requiring clotting and bleeding times and possible large blood transfusions before embarking on this procedure, but adduce no evidence that there is any but theoretical reason for this elaboration. Redondo (171) in Spain says it is the best method of discovering the parasites, while Shortt (162) is unable to understand why there should be this persistent fear of spleen puncture, because if the technique is properly performed by those trained to use it, the risk of accident would appear to be very small: he tells of having carried out thousands of spleen and liver punctures without, so far as he is aware, any untoward results.

Its sensitivity in diagnosis is generally acknowledged: Napier (170) puts it at about 95% positive results in various series he has investigated. Ho (163) found that in 15% of his cases only spleen puncture was positive, 2% showing parasites only in the sternal marrow.

Results in the present work might well have been of the same nature had puncture been performed
on all enlarged spleens seen in the clinics, judging from the occasions where this was done as a matter of interest in cases where clinically the diagnosis was not in doubt. Since, however, the procedure was carried out mainly in the cases where there was clinical and serological conflict of evidence, i.e. in the "problem" case, the proportion of positive findings is not significant.

In the early months of the campaign the manoeuvre was performed with strict adherence to the manipulative technique proposed by Napier (59) but without any of his pre- and post-operative measures which were impossible in the conditions prevailing. These last were abandoned with regret and not without considerable apprehension until it was found that it was the general practice among the medical staff of clinics in the Honan region to take no special precautions beyond asepsis, speed and rigidity of technique, and these doctors, Chinese and foreign, agreed with Napier's reports of freedom from post-puncture morbidity or mortality.

Encouraged by this, the orthodox method was continued until the writer had the privilege of a visit and personal demonstration of technique from Dr. E.A. Ho, Director of the National N.W. Institute of Health, N.I.H, N.H.A.) Lan-chow, whose main modification is in the speed with which the manipulation is done (163).
Briefly, he inserts the needle through the skin in the usual deliberate manner, then plunges it into the spleen quickly, and immediately begins to withdraw it, at the same time pulling on the piston so that the whole operation in the spleen takes about 1½ seconds, and one is left with only air in the syringe but true spleen pulp and very little blood adhering to the needle, which is blown out on a slide, fixed and stained. These points are deliberately laboured in order to emphasise the unsuitability of techniques such as that of Most and Lavietes (132) designed to get blood into the syringe, which procedure is unsafe (because of delaying the needle in the organ), unsure (because of dilution of spleen pulp with blood) and unnecessary (because of established techniques like those of Napier and Ho).

After a little practice almost complete success was obtained with this method excepting in the rare but inevitable case where a splenic vessel was inadvertently tapped, blood flowed freely into the syringe and the spleen tissue was washed away; moreover it gave a feeling of security, since there was very little chance of any tearing of the spleen due to the speed of the process and so it could be used without inconvenient precautions before and afterwards. There was no reaction in any case, immediate or delayed, nor did the patients complain
much of pain either during or after the operation, greatly preferring it to sternal puncture especially as "needling" of the spleen is a manoeuvre with which most of them were familiar as part of the traditional Chinese medical armamentarium.

D. F.A.U. METHODS.

The design of the F.A.U. diagnostic approach, while not ideal, was carefully planned for the personnel concerned in order to meet the needs of the particular type of patient encountered under the conditions prevailing in this area. Several factors must be taken into consideration: firstly, the type of patient. He is not so desperate for modern treatment as the grim nature of the disease might lead one to suppose, partly from natural apathy and lack of imagination and partly from natural fear and traditional prejudice, while his interest in diagnosis is negligible: what he wishes is the minimum number of the magic "ta chen" (injections) in the shortest possible time with no frills like lengthy diagnostic procedures. If the diagnosis is not made and the first therapeutic injection given within a short time of examination he is quite liable to go home and stay at home. Thus a speedy procedure is essential. He has a very clearly defined scheme of priority in types of "injections", viz. finger
and ear pricking, intravenous sampling, spleen puncture and sternal puncture in order of choice, and the more he is accommodated in this matter the more likely he is to stay the course of treatment.

Secondly, the teams were made up in the manner calculated to use the available medical skill to the greatest extent, but since this was limited it was not to be expected that methods comparable to those of a fully-staffed hospital outpatient department would be possible. It should perhaps be stressed that this applies to methods, and not to standards, which were as high as in any mission clinic with a full medical staff (and probably higher than some clinics visited). Four teams were ultimately established, one diagnostic and three therapeutic.

The former was composed of the medical officer, Chinese assistant with basic training in nursing and laboratory work, and two Chinese who had had three months laboratory training specially designed to fit them to carry out the tests normally required in the typical small Chinese mission hospital, including those associated with kala-azar. This team had as its main duty the rapid diagnosis of cases coming to a clinic during the early period of the campaign in any area, and assembling these in batches of not more than 150 per two weeks for the attention of the treatment team allocated to the district.
Patients generally came in large numbers at first and when the daily number did diminish it usually fell off quite sharply, so that in a short time only a few patients would present themselves daily. At this point the diagnostic team left the area to join a treatment team in another region and repeated its examinations till the supply of cases was almost exhausted when it removed to the third team and the same procedure was carried out. Surprisingly, by close attention to team movements and the assembly of information regarding the areas to be visited, it was almost always found possible to arrange matters so that the treatment teams did not have to start operations in a new area without the help of the diagnostic team, nor were they usually left to complete the treatments without a further visit from the latter to check on the diagnosis of recent admissions, complications or reactions occurring during treatment, and any general medical points arising, including the inevitable crop of non-kala-azar patients. Occasionally, bad weather or unexpected numbers of patients in some district would complicate the liaison between teams, but never seriously.

The treatment teams were composed of two or three foreign members, all of whom had had basic nursing training, some having had considerable
laboratory experience of tropical diseases, plus a Chinese basically-trained laboratory technician similar to those on the diagnostic team. All of the above were given preliminary experience in diagnosis and treatment, especially intravenous injection technique, in one or other of the established hospital clinics in the area where there was no lack of patients. Their duties included the administration of anti-kala-azar drugs, treating complications and reactions, following the patients' progress and examining any new cases who might come to the clinic after the diagnostic team had gone. Thus it will be seen that three main points emerge:-

1. Diagnosis was mainly done by a specially-trained medical team, but some cases investigated by workers with only technical training.
2. Diagnosis had to be speedy and dogmatic to prevent loss of patients.
3. Methods must be safe, not beyond the skill of the worker, as specific as possible, and withal flexible to meet varying circumstances.

With these in mind, the following system was evolved and in time proved adequate for the epidemiological work being done, although less than satisfactory for academic research in the disease. All patients examined by the diagnostic team were seen primarily by the M.O. and his assistant, when a history consisting of stock questions about fever, splenomegaly, weight, previous disease and treatment,
in obvious kala-azar cases, was taken, while a more detailed interrogation was used in any case of doubt. If the patient was found to be suffering from some condition other than kala-azar he was given advice, referred to hospital (if one was available) or in a few cases some simple treatment (like incision of an abscess) might be carried out.

Thus the field was narrowed down to those with a history in some way reconcilable with kala-azar, and next a clinical examination was performed which served to eliminate a number of cases of disease giving fever or splenomegaly or loss of weight. The remainder were passed on to the laboratory technicians and each had a globulin-precipitation ("water") test done on blood from ear or finger. In a case which was clinically typical advanced kala-azar no further investigation was carried out where the test was strongly positive, and the patient was given specific treatment. Morgan (31) in adopting a similar procedure, says that with a clear precipitation test, enlarged spleen and in many cases enlarged left lobe of liver, anaemia of a more or less pronounced grade and poor nutrition, kala-azar speaks loudly for itself as soon as it appears in the clinic rooms. He adds that there are early cases where the diagnosis is not easy. Lowe (2) states that in kala-azar of
3 months duration or more, in areas where it is endemic the diagnosis is very obvious. It must be emphasised again that in this area these late types formed the vast majority of cases coming to the clinic, since this was the first visit in history to most regions, and even the others had been hitherto grossly lacking in the materials for treatment. Napier and DasGupta (3) in their first year's work in an area near Calcutta similarly found that the majority of patients coming for treatment were advanced cases who had become infected during the previous year or two years. The response in subsequent visits was expected to be from a younger group with less advanced disease and this has proved to be so, necessitating the increasing use of the more specific diagnostic methods of sternal and spleen puncture.

Investigation was next concentrated on those who were not absolutely classical subjects. Where the "water" test was not so strongly positive as had been expected from the clinical picture, or showed any other discrepancy, a confirmatory formal-gel reaction was carried out, and this was also done in cases of less advanced disease where the "water" test would not normally be strongly positive. Any doubt remaining was settled by spleen puncture.

This left two types of case still under investigation: firstly, cases of splenomegaly
where serum tests were negative or indefinite at an early stage of the disease where they would not normally be positive. Sternal or spleen puncture was carried out on those. Secondly, cases of fever without splenomegaly where malaria, relapsing fever, etc. were ruled out by laboratory and other examinations and so might well be very recent infections. These were dismissed and told to return for examination either at the second visit of the team (in approximately 6 months) or to report in 3-6 months to any hospital clinic, by which time true kala-azar would certainly have made itself obvious, or conversely, if the condition had negative clinical and serological features the infection could not have been leishmanial.

This system was found satisfactory in the light of experience and was adopted by the treatment teams when they were called on to diagnose the complaint of new cases, with the important reservation that they performed no spleen or sternal punctures, reserving a decision on doubtful cases until the diagnostic team returned. This naturally resulted in losing sight of a few patients who would not return by request, but it was confidently expected that they would be picked up probably in a more readily diagnosable state during a subsequent visit. Cases of non-kala-azar lesions were mostly referred to the nearest hospital unless the team felt
capable of their treatment, e.g. in cases of malaria.

It must be admitted that this regime was worked out "the hard way", since the writer had no access to original literature, and it was the more encouraging to find a considerable measure of support from the highest authority. Napier and das Gupta (3), in describing the methods used in the out-patient department of the Calcutta School of Tropical Medicine and applied to an experimental attempt to rid a complete (if small) area of kala-azar by intensive therapy, put it thus: "All cases showing a definitely positive aldehyde reaction were diagnosed as kala-azar and treatment was commenced immediately. (Experience has shown that in Bengal at least 98% of these are kala-azar). The patients suffering from considerable splenic enlargement with a history of a long illness and usually with marked anaemia, but who had a negative or doubtful aldehyde test result, were diagnosed as "splenomegaly, not kala-azar"--------All patients showing negative or doubtful aldehyde test results who had fever (without obvious cause such as pneumonia) and slight or no splenic enlargement were looked upon as potential kala-azar or malaria cases: a bloodfilm was taken and they were put on a quinine mixture and kept under observation: such patients usually attended regularly and little difficulty was
experienced in coming to a diagnosis in a week or so, but in a few instances it was thought advisable to do a spleen puncture in order to save time. We never had any opposition to this operation nor did we find that its performance detracted in any way from the popularity of the treatment centre. In this way we can confidently claim that a negligible number of false diagnoses were made and that although in a number of instances there was a delay, practically no kala-azar patient who once presented himself escaped diagnosis eventually. During the second and third years of this investigation, house-to-house visits were made and only a very small number of previously undiagnosed cases were brought to light. Elsewhere, Napier (170) again emphasises that (in 1936) "more recently, spleen puncture has been done only in doubtful cases".

Scovel (1) adopts a somewhat similar attitude to diagnosis: in the presence of a positive "water" test together with leukopenia and splenomegaly, he considers the diagnosis certain and gives treatment even if Leishman-Donovan bodies are not found in marrow or liver smears. Should the serological tests be negative in association with splenomegaly, liver puncture was done and if this also was negative the patient was advised to return for further examination in one month: such cases were, in fact, rare. Napier (164) gives similar advice, stating
that in the early case there was little disad-
vantage in delaying the diagnosis since the positive-
aldehyde case reacts better to treatment than the
early, negative-aldehyde case.

The important points which will bear
repetition and on which this diagnostic system is
based include:-

1. Serological tests are positive in 98% of advanced kala-azar: since this was the
commonest type presenting itself, no further
investigation was required.

2. Where serological reactions do not
correspond with the clinical state, spleen
puncture should be performed.

3. Where tests are negative in the
presence of considerable splenic enlargement,
the disease is probably not kala-azar: where
they are negative with little or no spleno-
megaly, no harm will be done by delaying
tactics until further visits are paid to the
area.

Nothing in the foregoing should be taken
to indicate that the writer would not prefer to
have had a clear demonstration of the causal
organism in every case but this ideal procedure
had to be balanced against the advantages of cover-
ing considerable ground, treating a maximum of
patients, and using the talents of less-than-fully-
trained technicians in a safe yet adequate manner,
and it is felt that the results justified this
departure from standard Western medical practice.
Differential Diagnosis.

It was not to be expected that the clinics would be attended only by those suffering from kala-azar or even only by those with splenomegaly, since only a handful of people could read the posters advertising the teams' coming and mouth-to-mouth propaganda tends to be confused by the time it gets to the end of the line: in addition, some of the most pathetic of a multitude of sights seen were those patients, young and old, who were brought to the clinics in an attitude combining despair with an unreasoning hope that the foreigners' medicine might work the miracle of cure.

Diseases varied from inoperable carcinoma of the cervix to 8th nerve deafness (following meningitis) and aortic incompetence, and this type naturally led to no confusion with kala-azar, but certain other conditions may present quite a problem in differential diagnosis.

Among these, Manson-Bahr (172) mentions malaria, splenic anaemia, hepatic cirrhosis, leukaemia, malignant disease, typhoid fever, undulant fever, malignant endocarditis, trypanosomiasis, ankylostomiasis, bilharziasis, tuberculous spleen and visceral syphilis: some of these do not enter into the calculations of practice in the area under consideration (e.g. trypanosomiasis, ankylostomiasis and bilharziasis)
while tuberculous spleen and visceral syphilis are not really likely to cause any difficulty. Pyrexial conditions like typhoid fever, undulant fever and malignant endocarditis might occasionally be confused with early kala-azar, but apart from specific distinguishing signs and symptoms the degree of prostration is much greater in all of the former than in the early stages of kala-azar where most authorities agree there is a surprising lack of distress. Malignant disease may give primary or secondary involvement of the liver but rarely affects the spleen, and pyrexia is minimal, while leukaemia cases show little fever till a late stage unless there is secondary infection, and here the state of the blood or marrow would confirm the diagnosis.

This leaves the three conditions which in practice do give rise to difficulty, i.e. splenic anaemia, hepatic cirrhosis and malaria. The first condition is one which is liable to cause confusion with the early stages of kala-azar only: it rarely shows the same degree of splenomegaly or hepatomegaly as the late stages of kala-azar unless it has been present for many years, nor does pyrexia play any part in splenic anaemia unless there is secondary infection in the late stages. This condition and the
second, hepatic cirrhosis, which may be accompanied in its advanced stage by splenomegaly, are prone to produce ascites as time goes on, but the patient with kala-azar and ascites is much more ill than his fellow-sufferer with a cirrhotic liver who is often in moderate health once he is freed from the pressure and weight of fluid by paracentesis. In each of these diseases any lingering doubt can be dispelled by spleen puncture, which in any stage of kala-azar liable to be confused with them, is almost sure to reveal parasites.

The third condition, malaria, is the only one which can be a serious cause of complexity to even the careful and expert worker. As has been mentioned previously, even the adult patients are unable to distinguish the two fevers, which makes a history valueless, while the fever of malaria, carefully pigeon-holed in the text-books into classical types, is in fact sometimes almost as irregular as in kala-azar, while the patients are not often definite in their description of the intermittency or progressiveness of splenic enlargement. The leishmanial spleen enlarges to a greater extent than the malarial but in the lesser degrees of increase the only clinical distinguishing feature, not of great help, is that the former is usually softer than the latter. So one is faced with a
patient giving a long history of fever and splenomegaly which may fit either type of disease, and further clinical investigation is not worthwhile. In a non-malarial area, even a moderately strong positive serological test would give adequate confirmation. Where malaria exists, a peripheral blood film may settle one diagnosis but the conditions may co-exist, so that even a positive serological reaction may not provide a complete solution. In the last resort, spleen puncture or sternal puncture is necessary and in both cases may provide an answer, since plasmodia as well as leishmania may be found by both these procedures.
COURSE and PROGNOSIS.

There are no recent studies of untreated kala-azar cases, since the antimony preparations have been used in all the affected areas during the last 25 years, but the classical course is well-known although it may vary from country to country and differs according to its occurrence as an epidemic or in endemic form. Within these limits there is the natural variation from case to case, and the important factor of complications.

The fulminating form described by Kirk (45), already mentioned, has a high mortality unless treated quickly and the chronic form encountered by the same author has an uncertain prognosis.

Napier and Halder (173) give the natural cure rate in India as not less than 10%, while in the Sudan Stephenson (174) records a death rate of 80% in an epidemic, even though in 87% of his cases an ordinarily adequate amount of treatment had been given. In Malta, Debono (60) states that untreated leishmaniasis in infants is invariably fatal, the majority of cases running a course of 6-18 months.

In China, no helpful estimate of natural cure could be made because a mere patient's history of kala-azar could not be accepted as a diagnosis, but cases bearing the cancrum oris hallmark of a previous attack were seen once or twice. McClure (175)
has assessed the untreated mortality as approaching 95% in N. Honan and it would seem from the statements of the various recognised authorities that there is a world-wide mortality, in default of treatment, which will be between 75% and 95%, in epidemic or endemic cases.

The duration of illness in these cases naturally varies with the severity of the condition, and a number of cases came to clinics in a moribund condition, to die before any treatment could be given, or immediately afterwards: these cases were both acute and chronic in type. The same variation was seen in the seriously ill patients, those who, lacking treatment, might reasonably be expected to die in a few months, and ranged from a few months to 3 years. No proved cases of kala-azar were seen with a history of more than three years, and taking into consideration the effects of such complications as hepatic cirrhosis and cancrum oris with the combined effect of the less serious types of complication (in addition to a state of chronic malnutrition) it would seem reasonable to put the average time of death as 18 months from the date of infection.

The actual precipitating cause of death may be the toxaemia of the generalised leishmanial disease itself, ultimately producing a fatal
myocarditis or more commonly the direct result of a specific complication like cirrhosis of the liver, noma or the dysenteric state, or possibly the occurrence of a non-specific secondary infection like pneumonia, bacillary dysentery, pulmonary tuberculosis or skin sepsis.

Where treatment is instituted, the individual prognosis is greatly affected by the stage of the disease, for while it may be true, as Napier (59) states, that the best results are obtained in cases where there is a history of 4-5 months illness, as in these cases the patient's natural resistance has had time to develop, yet there comes a time after which the general health of the patient is so poor that he can scarcely benefit from specific treatment. In so far as it is possible to generalise, present experience was that the prognosis of the "usual" type of case was distinctly worse when the patient gave a history extending back for 2 years, even though his superficial appearance might in some cases be fairly good, and it was in this type of case, among others, that was felt the need for a more individualised type of treatment in hospital. Fortunately, if anything is ever done on a large systematic scale in China, this type of case will gradually disappear. It may be objected that recorded deaths in the F.A.U. series do not show an unduly long duration of illness prior to
treatment, but it must be remembered that they include numerous young children with little resistance and a short duration of illness (a class who would also benefit from a more individualised style of treatment) to weight the figures unduly.

The second factor calculated to reduce the hope of recovery is the presence of certain complications. Gingivitis, anaemia, oedema, albuminuria and general exhaustion are accepted as normal in the later stages of the disease, but two lesions in particular automatically involve a gloomy prognosis, i.e. ascites and cancrum oris, the former to a much greater degree than the latter now that specific parasiticidal drugs are available. The nature of ascites in kala-azar has already been discussed: whether it occurs as part of a generalised anaasarca due to malnutrition, cardiac failure or renal failure the outlook is poor, especially under the conditions of supportive treatment the ordinary Chinese is likely to get. There was no opportunity to try the experiment but it is felt that most of these cases could be saved by a regime of small, less frequent, specific injections, supported by an intensive programme of nutrition and rest. Ascites due to cirrhotic changes in the liver of advanced cases is a different matter, and it is doubtful if any of these patients could be permanently cured, though again it is probable that specialised treatment could overcome the infection and thus give
them a better chance in their battle against the liver lesion.

As with the disease itself, cases of cancrum oris may be of any type from acute to chronic, and severity seems to run closely parallel so that the whole course of the original kala-azar may be changed by the onset of this infection, the prognosis becoming dependent on the outcome. The results of specific therapy will be discussed later and should be accepted with proper caution, since they indicate merely what may happen to cases of a hypothetical average type of noma at a certain average stage: different types at different stages will give entirely different results. In general, however, it may be said that acute cancrum oris is a rapidly fatal condition, and the great majority of cases of even the chronic condition will have their ends hastened if left untreated, while the modern antibiotics have been responsible for a great change in outlook, and if available and used properly can probably save all but the most rapidly fulminating cases.

Cure rates with various types of therapy will be discussed in detail under the heading of results, but conclusions could be that hepatic cirrhosis remains the ineradicable complication while the others, even noma, respond to appropriate treatment if it is not too long delayed, and the general
severity varies from patient to patient but may be associated in this part of China with a cure-rate of around 95%. The causes of death are the same as in the untreated cases plus reactions to treatment, local and general. The former should be rare, especially since the discovery of efficient intramuscular drugs, but the latter are likely to occur in all essays in treatment of the present kind where the schedules are standardised, to the detriment of the very young, the very advanced cases and where patients disappear into the blue when treatment is completed.
PROPHYLAXIS.

Although the mechanism of transmission of this disease is not entirely understood, the main outlines seem to form a framework sufficiently stable for the construction of theories and practical policies for preventive measures. Additional information, which may show variations in the cycle from country to country, should be helpful in maintaining the emphasis of attack in the most important channels but it seems unlikely that prophylactic activities based on present knowledge can go far astray, or if carefully adjusted to the needs and conditions of a particular region should lead to much dissipation of effort. With this in mind the accepted cycle of transmission of infection from man or beast, via the sandfly, to man, demonstrates the features which lend themselves to a prophylactic campaign.

1. Attack on Sandflies.

Even before the sandfly was incriminated as the vector of infection it was suspected that certain types of environment lent themselves to the encouragement of the disease, and in 1914 Price and Rogers (176) described the results of early attempts to stamp it out on tea-estates in Assam. Labourers free of kala-azar who went to live in the old houses,
where there was a chronic mortality of 20%,
succumbed to the disease at the rate of 16% within
2 years while a comparable number who went to live
in houses only 300 yards distant showed no cases
over the same period. A second experiment was
to establish a new set of lines on another estate
where kala-azar was rife and fill them with infection-
free labourers only. This policy resulted in com-
plete absence of cases over 16 years, although the
lines were but 400 yards away from some showing high
mortality rates. On the other hand healthy workers
who were sent to the infected lines eventually all
died of the disease.

Gradually the reasons for these results
became clearer and, as previously cited (110) Napier
summarised the environment in Calcutta with which
kala-azar seems to be associated: this is, however,
not only a description of the breeding ground of
the sandfly but also an accurate verbal picture of
the living conditions of at least 95% of the
population of China, so the question resolves itself
into "Can anything be done medically to change these
conditions and so attack the sandfly?" and the
answer is an unqualified "No". Bearing in mind that
this is how the lowest class of peasant lives
anywhere in the world, because he cannot afford to live
otherwise, the writer submits that a close study of political, religious and economic China suggests that these conditions will continue for many years. If this is so, the further question emerges "Can anything be done in these particular circumstances, as it were superimposed on them, to attack the sand-fly?" and to this would be suggested a more cautious, "Probably not". The writer does not know of any organisation (including W.H.O., U.N.O., the U.S. Government or the Chinese Government) which is likely to attempt the tremendous effort which would be needed in terms of money, physical labour, political diplomacy, and above all, initiative, to apply modern insecticides to the innumerable breeding-places of an area large enough to be of any consequence.

That the mass use of D.D.T. would accomplish the desired result is not in doubt - that it will be done is, in the writer's opinion, in the highest degree unlikely, so far as the "foresee-able" future is concerned. In India, Sen Gupta (21) puts it thus: "The fact that modern insecticides such as D.D.T., pyrethrum, etc., are effective against the sandfly is also known. But little has been done by the state to utilise this knowledge and the disease is far from under control. In Bengal, the recorded incidence of kala-azar (which is probably a fraction
of the actual incidence of the disease) has been more or less steady for 20 years during 1923-43". At the moment an investigation by F.A.U. teams is in progress to assess the effect of spraying doors and windows of the huts of entire villages with D.D.T. emulsions, since Cameron & Burgess (177) say "it has a wide margin of safety in its use as an insecticide" but for the above reasons this is not likely to get beyond an experimental stage.

Smith et al (178) have pointed out that anti-larval measures are not likely to succeed, since this form may penetrate below the ground surface and thus be protected from any chemical spray: they support Smith and Ahmed (111) in a plea for an attack on the adult forms, pointing out that this would serve the double purpose of killing adult mosquitoes as well and thus eliminate malaria more economically than would measures against the two types of larvae, which are found in different environments. Napier and Smith (179) found adult flies in large numbers in cattle-sheds, human sleeping quarters and chicken-houses, and directs especial attention to them, while Shortt (7) in his admirable review of nearly twenty years later has little essential to add, and sums up by the reminder that the use of appropriate compounds against what is a very delicate insect, vulnerable
to insecticides which can reach it in the cracks and crevices of house walls, has so far been tentative and on a small scale, concluding with truth, if not hope, "there is no reason to believe that if the newest methods used against other insects were continuously and conscientiously applied throughout the sandfly season that they would not have a large measure of success." In the F.A.U. campaign, convinced of the futility of attempting the small-scale onslaught against these vectors which was the only one feasible, no effort was made against them in any way.

2. Control of dogs.

The second point in the presumed chain of events leading to infection of man is the presence of the disease in other animals. Evidence for the incrimination of animals other than man as reservoirs of infection has already been discussed, and there is no doubt that this occurs in many parts of the world although it is notably absent in India. In Crete, Papantonakis (180) concludes that the wholesale destruction of street dogs had an appreciable effect on the incidence of the disease in children.

In China, the fact that the role of the dog is not clear does not mean that no action should be taken against it, for at the very least each infected animal represents a reservoir of infection (often cutaneous infection) on which the sandfly
may draw in the same way as on the human victim. This point was not forgotten in draughting the plans for the attack on the disease, but it was felt that a preliminary appeal to the civil or military authorities was unlikely to be followed by any considerable destruction of dogs since Chinese Public Health authorities are no more long-sighted (to put it conservatively) than those of the West, and require some positive sign of benefits to accrue before taking any action. It was hoped to convince them of the scientific soundness of the F.A.U. approach and the efficiency of the methods when a high rate of cure in actual cases could be demonstrated over a large series and to persuade them to co-operate in the elimination of canine disease in order to shorten the task of freeing an area permanently from human disease. Unsettled conditions have not favoured this plan, but as Chung (49) says "negotiations for the control of dogs is in progress and it is hoped that by this means the disease will be eradicated".

The diagnosis of the condition in dogs has been clearly described by Ho et al (108) and Giraud and Cabassu (181) while a method of controlling the movements of the animals in addition to the slaughter of those infected has been outlined by
Papantonakis (182) in 1933 when in Canea a markedly lower incidence of human kala-azar occurred in the year following: over 20% of dogs were found infected and destroyed, the diagnostic weapons being clinical inspection and the formol-gel test.

3. Treatment of patients.

Even when the treatment was confined to the use of the rather unsatisfactory antimony tartrate it was realised that the whole conception of prophylaxis had been changed by the introduction of this therapeutic weapon, for at least something could be done to eliminate man as a reservoir of infection, which is as effective a point to break the cycle as any other: being the basis of the F.A.U. campaign it is submitted that here is the only point where in the circumstances the cycle can effectively be broken. In 1923, Young (5) was already speaking of the popularity of the treatment and the increasing numbers who were coming forward to receive it, emphasising that if one can find and treat the early cases in a village there is no reason why the disease should not be stamped out there, whereas once it has progressed to a large number in any one year fresh cases can crop up and make the complete extermination a matter of some protraction. He was particularly appreciative of
the fact that early treatment will obviate the necessity for the wholesale uprooting of workers from their homes and the inconvenient and expensive procedure of building new huts for them where the old ones were "infected" with kala-azar.

Also in Assam, Shortt et al (155) in 1927 report that the effect of treatment in rapidly sterilising the peripheral blood is one of the most important aspects of all, since it rapidly transforms the kala-azar case from being a great potential danger to others to a comparatively innocuous individual. They believe, taking into consideration the prevalence of the disease in Assam during the years 1917-27, that had it not been for the intensive treatment the outbreak in this period would have been more widespread and more disastrous than that of the years 1891 to 1901 when vast areas in Assam became waste land owing to the ravages of the disease. Putting it even more vividly they instance that, in 1925 alone, without treatment there would have been 50,940 more sources of infection than there actually were. Rogers (183) states that between 1925 and 1936 the treated cases in Assam fell to one-sixth and the deaths to one-ninth of the former rate due to the use of Urea-stibamine.

In the Sudan, Archibald and Mansour (63)
stress the danger of undiagnosed and ambulant cases carrying the infection over from one season to another, pointing out that intensive medical inspection and treatment in endemic villages in May and June would lessen the carry-over and so lower the incidence of the disease for the following season.

Napier and das Gupta (3) were able to display this phenomenon (although only in a small area) when they set out to ascertain the effect of treatment of affected persons on the epidemic extension of the disease in an endemic area. In 6 years the number of cases treated annually had fallen from 121 to 3, even though in the surrounding area the incidence was still very high and cases were still cropping up, despite the sporadic treatment which had been going on over a period of 3 years. So far as they could tell, the intensive treatment carried out in the limited area was the only factor not common to both areas and they therefore feel that the evidence in favour of its having checked the epidemic extension of kala-azar is fairly strong.

One most gratifying principle which should be integrated with all the above evidence and opinion is that, as Sen Gupta (20) remarks, a patient cured of kala-azar does not often develop a second attack of the disease: without this fortunate circumstance
much of the effectiveness of the most intensive treatment campaign would be lost. On the other hand, Napier (59) points out that in the presence of post-kala-azar dermal leishmaniasis it is unlikely that treatment campaigns can ever completely eradicate it from endemic areas, but fortunately this latter condition does not (as yet, anyhow) seem to occur in China, except in one case reported by Yao and Sun (125) in 1936.

To sum up, there are three lines of attack which are at least possible: firstly, the sandfly may be destroyed, but though this is scientifically feasible it is practically unlikely to be carried out unless China is revolutionised from top to bottom. Secondly, there is the destruction of infected dogs, which is eminently possible but requires official cooperation and enthusiasm, two commodities in which China is not rich. Thirdly, there is the approach by the treatment of all the cases arising in an area. For reasons already outlined this was the one chosen by the F.A.U. teams as a practical policy since it gives immediate results and so appeals to the patients, is cheap, involving no heavy equipment, uses a minimum of that which is precious in China, skill and training, and above all it stands a chance of producing as good results as have been obtained elsewhere.
Shaded areas were visited by treatment teams.
A. GENERAL APPROACH.

The treatment campaign was launched in June, 1946, and remained under the writer's direction for the next ten months. The intensity of the work varied,

1. from place to place, mainly due to the concentration of cases, the presence or absence of military activity in the area, and the enthusiasm of the civil authorities for their people's welfare.

2. from time to time, according to the weather conditions and popular festivals, the rainy season of mid-July to mid-August, the snow of December and January and the Chinese New Year celebrations of late January (in Western reckoning) combining to reduce the number of clinic attendances. Local circumstances like the various harvests, plantings and the standard of communications were accepted as inevitable and regarded as difficulties which would be surmounted in the main by multiple visits to each area.

Starting with one, there was up to three teams working at one time and the counties (or hsien) visited in chronological order are indicated numerically on the map on page opposite where is shown the extent of the area allotted to the F.A.U. teams and the area it was actually possible to cover due to military operations, etc. It was a matter of great regret that the area in the N.E. corner could not be visited, because it was thought to contain a fair amount of the disease.
while the N.W. area omitted was not of the same importance being almost entirely mountainous. The northern base and supply centre was Hsin-Hsiang, where it might be said the work was made possible by the unfailing help and accommodation provided by the chief medical man of the town, Dr. George Wang, M.D. (P.U.M.C.) and Bishop Megan (S.V.D.) with the other members of the Roman Catholic Mission there. South of the Yellow River, the teams operated from Cheng-chow where was located the Honan H.Q. of the F.A.U., this area being free of fighting but somewhat troublesome by reason of much sand and the changing course of the river.

By the simple process of trial and error the approach to each hsien was standardised within the limits of practicability. One or two weeks before the team's visit the writer and his assistant paid a visit to the chief magistrate for the district, who has charge of a number of hsien, requesting him to acquaint the local magistrate of the impending visitation and to ensure that the latter would be co-operative in publicising the clinic, and if necessary finding accommodation where the members might live and work. The two chief magistrates whose areas were covered were invariably helpful and some of their subordinates evinced a lively and
intelligent interest, but in a number of cases it was hard to realise that the work was being done to save Chinese lives, so indifferent were the authorities.

In some hsien the only living space was two rooms in a mud-walled house: in others, rooms were provided in the local Catholic Mission, while in three places the Mission station housed small medical dispensaries which were sometimes of value for the treatment of non-kala-azar patients coming to the F.A.U. clinics, although usually the standards were very low and supplies of drugs woefully inadequate. All apparatus was carried in an ambulance or jeep, or sometimes sent by train or cart depending on circumstances, while the journeys of the diagnostic team, who did not always need to transport their materials, were done as opportunity offered.

On arrival in any district the first task was to call on the local magistrate to ensure that the request for wide publicity had been put into effect and to supplement this (if it had not already been done) by putting up special illustrated posters giving the dates, place and reasons for the clinics. These were, of course, in the nature of curiosity-stirrers only, since few of the population could read, and their success was dependent on the
few interpreting their information for the many.

As previously noted, cases usually started to come in large numbers within 24-36 hours of the team's arrival, continuing at this level until the supply was nearing exhaustion and then falling off sharply, which was the cue for the departure of the diagnostic team. Constant attempts were made to make the presence of the clinic as widely known as possible, both by visits to subsidiary centres and also by urging the patients to bring in any suspicious cases in their own village. Sometimes the diagnostic team would spend a day in a centre some distance away, from which sufficient cases did not seem to be coming and all patients diagnosed were pressed to come to the main clinic for treatment, which, surprisingly, a large number did. In the larger hsien, treatment clinics were set up in more than one place, sometimes two teams working in a hsien concurrently, which had considerable advantage but was not often feasible.

Apparatus had been gathered from many sources and was adequate in amount and mostly adequate in quality. American Red Cross, Canadian Red Cross and British Red Cross all contributed and there was provided a portable autoclave and water-still for each team, along with syringes, needles, flasks, test-tubes, etc. Funds contributed
by American Red Cross were used to buy gasoline for transport and the stoves used in sterilisation which was thus done quite satisfactorily, although in the clinics it was not possible to use a steam-sterilised syringe for each injection owing to the numbers involved, so that syringes (which were of the all-glass type) were autoclaved daily and between injections merely laid in 60-70% spirit for approximately 20 mins. Needles were sterilised by boiling and a fresh one used for each patient.

Since, as has been previously explained, there was little or no opportunity for individualised treatment according to the severity of the disease, all injections were given daily and patients were gradually accumulated up to a maximum of 150 in a batch, which was as many as one team could handle, taking into account the cleaning, distilling and sterilising which occupied a considerable part of the day, and the time-consuming precautions against dust, flies and dirt which are one of the penalties of a mobile clinic. Other factors reducing the working time were the shortened winter days and the extreme heat of the summer afternoons in Central China, in areas which were near-desert in character.

In spite of these defects in technique, no case was known to suffer infection from either
intramuscular or intravenous injections although sterile abscesses resulted from both at times, nor was there any evidence of generalised reactions due to the quality of the water used as a diluting fluid. Intramuscular injections were given at first only in the buttocks, but as experience was gained it was felt preferable to give them in the lateral aspect of the thigh. Owing to the age of the children many of the intravenous injections had to be given in the external jugular vein.

Some of the benefit of treatment was neutralised by the fact that a patient might have to walk up to 10 miles (English) to attend the clinic (which is scarcely appropriate in the later stages of kala-azar) or would have to find accommodation in the village, which he would usually be ill able to afford and which one suspected made patients short of food, so near the starvation-level are these people normally living. Scott and Li (184) contrast the few cases treated in their clinic with the majority who were admitted to hospital: the latter inevitably gain in such ways as the quicker cessation of fever and the more rapid relief of anaemia, presumably owing to the good feeding and rest in bed. McFadyen (30) sums up the advantages and disadvantages of clinic
treatment, stressing its cheapness and popularity with parents, who may keep their children with them all the time, but recalls that, as has been said, the living and feeding arrangements during treatment may be inadequate: he concludes that the hostel scheme, where a cheap room for the family is provided in which they live, cook and sleep while the patient has his course of treatment, is the best compromise. Where the present writer has seen this in operation it certainly appeared to be working well.

Once again, the situation at the F.A.U. clinics demanded additional lines of treatment of a general nature which could not be provided and which represent a problem to be faced by anyone engaged in this kind of mass therapy in the East: the solution of it would not greatly increase the percentage of cures, which is already very high with any modern treatment, but would relieve a considerable amount of human suffering.

B. USE OF ANTIMONY.

Turning to the main aspect of treatment, that of the specific drugs to be given, it is well to review the variety of preparations which have been used and are still in use with their advantages and defects, and to keep the matter in a true perspective it may be salutary, before proceeding, to
remember that very effective drugs have been known for years: the problem of the East is that no country which has kala-azar cases has as yet been able to afford to treat more than a small fraction of them with these remedies. Rogers (183) quite properly says that with a cheap and efficient drug and sufficient village medical staff, kala-azar could be reduced to small proportions, but quotes Napier as saying that in 1925 a course of Stibosan for one case cost £2 5s. and one of Urea-stibamine £3, prohibitive sums for poor peasants in India. Horgan and Kirk (185) realistically recall the true position when, speaking of their work in Africa, they say "We agree with Sir Leonard Rogers that the problem of treatment in a poor country - and the Sudan is a poor country - is still far from being solved satisfactorily".

Owing to Chinese currency inflation and fluctuating prices in Britain and America it is not possible to estimate how much a course of modern drugs would cost a Chinese peasant in his own village, but although the diamidines are cheaper than the antimonials, both are certainly far beyond his means. In early 1946, sufficient tartar emetic for one dose cost (in Honan) about CNO¥1,000 or 2s.6d. while in early 1947 it was estimated that one course
of Stilbamidine, bought in the U.K., would cost 12s.
and one Neostam course, bought in the U.S.A., about
U.S.$5. Translated into Chinese dollars the
resultant astronomical figures are meaningless as
a guide to price at any other time or place. China
is potentially less poor than the Sudan but her
political and financial structure may well be a
barrier to effective Public Health work for a long
time ahead. Nothing comparable to Shortt et al's(6)
description of "the expenditure of larger and
larger sums of money on measures of treatment and...
....prevention of kala-azar (in Assam)" exists in
China.

All treatment by F.A.U. teams was free,
and there is little doubt that even a small charge
would have reduced clinic numbers to a level which
would have nullified any hope of wiping out the
disease in the area. Even without hearing this
from local officials and missionaries it was fairly
clear from the appearance of the patients that prac-
tically none of them could have paid a sum which
would have made it profitable for any organisation
to give treatment on a commercial basis, and that
few would have been able to afford enough to cover
the mere cost of the drugs.

Since 1915, when da Cristina and Coronia
discovered the first specific drug, three types of treatment have come into general use, viz. the antimony tartrates, the pentavalent antimonials and the recent diamidines. Penicillin has been tried in animals and man with complete failure. Fulton (186) found that even in high concentrations it gave very poor results both in vitro and in vivo, while Horgan and Sati's (187) 2 patients derived no benefit. Recently (188) it has been tried in Turkey in high dosage with equally negative results although the general condition improved somewhat. Snow (189) found it useless topically or parenterally in muco-cutaneous leishmaniasis, while its use in cancrum oris will be mentioned later. 

1. Antimony tartrates.

The first compounds to prove specific against the disease were of antimony, whose action Acton and Chopra (190) believe is not a direct one but the stimulation of the reticulo-endothelial cells to the production of parasiticidal substances so that the Leishman-Donovanbodies may be killed in the spleen, liver and bone-marrow: in the latter they suggest that the effect is to increase the number of leukocytes, which will help to digest the parasites not actually within the endothelial cells. According to Sen Gupta (21) the use of
the antimony tartrates, potassium and sodium, was a great advance on the treatment of the disease, changing the picture from a mortality of 90-95% to a cure rate of about 70%. They carried with them, however, substantial disadvantages, viz. too long a course of treatment, frequent occurrence of unpleasant reactions, relapses and resistance to treatment. Thus Cole et al (123)(191) in Africa found it a very poor weapon against their epidemic, so much so that some of their patients would not persevere with injections and the ultimate recovery-rate was 25%. In Turkey, Fakacelli (262) has recently cited 6 patients treated with antimony potassium tartrate of whom 3 died, whereas 31 of 34 patients treated with Neostibosan recovered. Napier (192) does not think its use any longer justifiable since it is less effective than any pentavalent compound. Nevertheless, Young (5) emphasises that in Assam the introduction of the tartar emetic treatment afforded a means of checking the spread of the disease by eliminating the reservoirs of infection.

In recent years these drugs have been superseded by the pentavalent compounds which give a much lower death-rate but the former possess two advantages, cheapness and availability, so that tartrates were used extensively in China during the Japanese occupation when nothing else could be pro-
procured, and were still being used in clinics in Honan in 1946 for the same reason. No exact figure for the death rate in these clinics could be obtained but it was felt that it might well be 20% or more and the general reaction incidence was clearly high. It was not used by any F.A.U. team.

A trivalent arsenical, Antimosan, has been suggested as an anti-kala-azar drug: this was used by Struthers (193) in China twenty years ago and pronounced as of low toxicity and therefore suitable for use in very debilitated cases. However, he points out that the normal course takes much longer to complete than with other organic antimonials and that relapses are more frequent. It is not now used.

2. **Pentavalent antimonials.**

(a) **Stibosan.**

One of the first pentavalent antimony compounds was Stibosan, which Napier (194) used on 104 patients with a death rate of 11% and a failure rate of 9%. Yates (195) in An-hwei had a death rate of 10% and appears to have had very few reactions with it. It has been superseded by more potent and less toxic compounds which were derived from it.

(b) **Ureastibamine.**

In 1922 Brahmachari (196) introduced Urea-stibamine to a world which has used it ever
since, and it has probably been responsible for more cures than any other drug, so wide has been its application, especially, of course, in India. It must be given intravenously, usually every two days, in doses calculated on bodyweight: Shortt and Sen (197) considered it the most efficient drug in use (in 1924) for the treatment of Indian kala-azar and in their series the average total dose was 2.6 g. and the duration 23 days. A more intensive method was suggested by Brahmachari and Brahmachari (198) who gave daily injections for 7-10 days without any untoward symptoms due to the shorter intervals, and with results as satisfactory as those following more prolonged therapy. Also in India, Napier (199) reports a death rate of 5% in a series of 70 cases, while in China, Lee and Chu (36) although criticising the lack of standardisation in its composition (so that the antimony content might vary from 20-43%) speak of its high therapeutic potency, an opinion echoed by Clow (15) who found it the most curative but most toxic of the drugs he employed.

To the method of Ho (39) reference will be made later: suffice it to say that he employs the drug in quantities much smaller than any other worker has suggested, i.e. an average total dose of 0.5 g. for a child and 1.0 g. for an adult, given
over 6-10 weeks in weekly doses or 3-5 weeks in bi-weekly doses. The only previous evidence to be found favouring this infrequent injection method is the suggestion of Wang (200) that Solu- or Neostibosan is more effective given bi- or tri-weekly than daily. Not unnaturally, Ho reports that the only reactive symptoms were mild transient nausea and vomiting in 3% of cases, and that the great advantage of this type of treatment is that a fieldworker can do a round of 7 clinics in a week without fear of the drug's causing any serious toxic symptoms.

Lowe (201) states that his routine practice is to use pentavalent antimony, usually as Urea-stibamine, for the treatment of ordinary cases. Early (202) in a permanent F.A.U. hospital clinic in Honan, used Urea-stibamine in courses of 15 injections, given 3 times weekly with a moderate cure-rate and found it rather toxic for use in advanced cases. Collard and Hargreaves (203) speak of it (and the allied Carbostibamide) as eminently satisfactory in the treatment of both Mediterranean and Indian kala-azar. It was not available for any of the present work.

(c) Neostibosan.

A development by Schmidt from his Stibosan was Neostibosan which Napier (204) tried out in 1927,
finally adopting a uniform adult dosage of 10 intravenous injections totalling 2.7 g. for the uncomplicated case: children were given proportionately smaller doses. In his series of 61 cases (all in-patients) he had 2 resistant cases, no relapses and no deaths, while the only reaction was vomiting so he concluded that a 10 injection course should give at least 93% of cures among average adult Indian patients. He further suggested that an 8 injection course would also produce a very high cure rate. Next year, Napier and Mullick (205) reported on a series of 175 cases with three deaths and again suggested that an 8 injection course might be sufficient, re-calling that the drug can be given intramuscularly as well as intravenously. However, in a further article the same authors (206) report on a series treated with 8 daily intravenous doses which produced only 88.5% of cures, the others relapsing, so they were less enthusiastic about this regime and stressed that the 10 injection procedure might be preferable.

Struthers (207) maintains that by careful treatment Neostibosan should yield, in the absence of serious complications, a cure rate of from 95% to 98% and, using it intramuscularly in children, states that he has not found any local reaction subsequently. In the Sudan, Sati (144) has found it necessary to
use 15 injections given either daily or on alternate days to a total of 4-5 g. for adults, and so resistant is the type of kala-azar encountered in his area that the minimum dose for children was 0.1 g. 

equally indicative of the stubborn nature of the Sudan disease is the high death-rate of 20% for his total series of 347 cases treated with various antimony compounds, even though all were admitted to hospital. Clow (15) in a short series in Shansi regards this compound as the least toxic of the common pentavalent antimonials: also in China, Scovel (1) uses the orthodox regime of 9-11 doses daily but may use up to 4 g. as the total adult dose.

Lowe (201) gives a timely reminder that Neostibosan passes all the tests of therapeutic efficiency and can be given intramuscularly but is still too expensive for routine use, a tragically common situation. In 1935, Lee and Chu (36) calculated it was 1½-2 times the price of Urea-stibamine. Recently, in Turkey it has been reported (188) that this drug has brought about excellent results.

It seems clear that it is a thoroughly reliable agent for routine use either intravenously or intramuscularly, and was found to be popular in the established clinics of Honan, but almost unobtainable although the Japanese had prepared one or two
substitutes, e.g. Nesbosan, but apparently none of comparable value. It was not available to any of the F.A.U. teams.

(d) Solustibosan.

In 1937, Napier et al. (208) introduced this preparation which was claimed to have several advantages over Neostibosan, e.g. to be a stable solution capable of being given intramuscularly without local damage. After gaining some experience, Struthers and Lin (209) comment on its comparatively low toxicity which enables it to be given in advanced cases with poor general condition. Yates (37) gave a total dosage of 60 ml. per 100 lb. of weight in 11-12 daily intravenous injections, decreasing the individual dose and the frequency in severely ill cases. His immediate results were (in 82 cases treated in hospital) 4 deaths and 1 resistant case. Also in China, Chung et al. (35)(260) report on the administration of amounts varying from 60-162 ml. with, out of 24 cases, 22 cures. During the Japanese war, stocks of the drug dwindled in China, and in 1947 only a few ampoules were seen in Honan and even the Japanese substitutes (e.g. Solun-nebosan) which had been plentiful in the war years were being exhausted.

Equivalent compounds have been produced in other countries e.g. Stibatin (Glaxo) which is sodium
antimony gluconate and in the hands of Sen Gupta and Chakravarty (210) gave an immediate cure-rate of 96% with 4% deaths. Burke and Chakravarty (211) emphasise its unique value in being given intramuscularly without pain, and regard its curative value as satisfactory. Later, however, Sen Gupta and the latter author (212) have to record a relapse rate in the same series of about 27%, mainly in the early cases. Choudhuri's (213) 25 cases, even in the presence of ascites and albuminuria showed a cure rate of 96% at the end of 6 months, while in the Sudan, Kirk and Sati (214) tried out a dose of one ampoule daily for 6-10 days with poor results, no better than the discouraging results obtained in this region with other antimonials, but on increasing the dosage 1-4 times the results were much better, with only one death in 10 cases.

A Russian preparation of similar type is Solusurmin: Kornetov and Mirzoyan (215) gave an average of 30 doses on alternate days or daily and concluded that the preparation compared favourably with Neostibosan. One defect which most writers noted in this kind of compound is the number of injections and length of treatment-period required: to combat this, new agents were produced containing an increased concentration of antimony, to be administered more frequently than usual. Kikuth and
Schmidt (216) describe two such, one with 100 mg. antimony per ml. to be given intramuscularly or intravenously, and a second having 54 mg. of pentavalent antimony suspended in 1 ml. of oil for intramuscular injection only. With the former, used intramuscularly, they produced a rapid response in over 90% of cases.

Another preparation of this type, Pentostam (B.W. & Co.) was used by Maegraith et al. (217) intravenously: some of the patients had an occasional rigor and pyrexia, and one patient (out of 8) died. In Spain, Bermudez (218) treated infantile kala-azar by daily doses of the aqueous solution, or, as an alternative regime, intramuscular injections of the oily preparation given every 2 days: in no case was there any local or general reaction.

In the Sudan, Kirk and Sati (214) give it intravenously with negligible reactions and one death in 14 patients. To them the significant feature of the new scheme is the reduction in the length of treatment from 6-20 days, which is a very remarkable result in the Sudan and may help to eliminate one of their bug-bears, the antimony-resistant case.

It seems thus that this drug is a most
valuable therapeutic agent with two outstanding advantages, viz. its suitability for intramuscular injection and its low toxicity, which make it convenient to use in small children or others with poor veins and provides a weapon of attack in the advanced or seriously-ill patients who may be precipitated into Eternity by full doses of powerful drugs. For these reasons it would have been a useful addition to the armamentarium of the F.A.U. teams but was unfortunately never available.

Other drugs worthy of mention include Distibinyl, which Sun (38) says is as good as other antimony compounds with the additional supreme advantage of being cheaper than comparable pentavalents. Chung and Chow (219) claim for a sodium salt of mannitol-antimonic acid that experimentally they found a rate of cure higher than had been obtained with any antimony compound previously, but their work does not appear to have been followed up.

(e) Neostam.

Turning now to a drug which was used in this campaign, viz. Neostam (B.W.& Co.) it should be said that although there was no choice, initially, since the F.A.U. was supplied only with this particular compound, there is no reason to regret the
circumstance and, although a variety of agents would have facilitated the appropriate treatments of the variety of cases, yet it can be said that Neostam proved very satisfactory as a main line of attack.

Previous reports on its use include that of Napier (220) in a small series when he gave doses varying from 0.05g. to 0.3g., on alternate days, with cure in 9 of 10 cases and death in one moribund patient. In another series the same author's (221) patients were given a course, lasting on the average 25.75 days, of approximately 11 injections from 0.1 g.-0.3g. and while vomiting occurred in about 50% of cases it was present after practically every injection in only a few instances. There were two deaths (4%) and at least 9 relapses out of 57 patients, but he now (59) states that its effect is satisfactory and suggests that it should be used in the same way as Neostibosan.

In an early series, Struthers (222) recommends a maximum dose of 0.2g. for an adult up to a total of 2-3g., given on alternate days, while Yates (195) a little later reported that it produced a mortality of 10%. Neostam was the main drug used by Clow (15) in Shensi, with a mortality of 14%, and a recurrence rate of 2%; he avers that it occupies a position between Urea-stibamine (which appeared more curative but more toxic) and Neostibosan.
(which was less potent but produced fewer reactions). He advocates a total dose of 3g. per 100 lb. of bodyweight but has given up to 8g. without ill-effect. Debono's (60) results, using the drug in 200 cases, were 1.5% deaths and 3.5% relapses. Scovel (1) while admitting that "many who used it (Neostam) reported that reactions were unusual" states that he did not find its use feasible because of severe vomiting and at times diarrhoea. Using the compound in Persia in the treatment of cutaneous leishmaniasis, Ball and Ryan (223) used a maximum dose of 0.2g. and found toxic reactions appearing in 45-90 min., viz. from mild nausea to severe projectile vomiting and diarrhoea, with collapse in 3 cases: they claim over 44% of cures.

From his experience in hospital practice in Honan, Early (202) states "I have gained the impression that this drug (Neostam) produces a more rapid and certain action than Urea-stibamine and is free from the occasional side-effects (he quotes 2 fatal reactions) of the other". He suggests that where a first course of Urea-stibamine has not been effective, a second course of Neostam should be given.

Generous supplies of Neostam were made available to the F.A.U. teams via American Red Cross and C.N.R.R.A., at first packed in 0.1 g. and
0.2 g. ampoules which is unnecessarily small where mass treatment is given, involving up to 150 serial injections and is also an expensive packing, producing a high incidence of breakage in transit. Fortunately, later supplies have been lg. amounts in toughened glass bottles which resist shock satisfactorily and take up less space.

Intravenous injections were made up in 5% solution with distilled water produced in copper stills, and solutions were not used more than one hour after preparation, having been made up with a minimum of aeration since this increases toxicity. Owing to the patients being mostly children, and some very young children, arm veins were not infrequently too small for use and it was necessary to inject via the external jugular vein in the neck.

To obviate this type of injection (which was very frightening to children) an attempt was made to give it intramuscularly in 25% solution as advised by the makers but, as will be mentioned later, this was a failure and was soon stopped.

Although setting up different standards on which to base dosage-calculations, there seemed to be fairly close agreement by the recognised authorities (vide supra) and by the manufacturers that the maximum total dose should be 3g. for an adult, given in 10-12 daily doses, so this rule was
adopted along with a close approximation to Napier's (59) method of calculating individual dosage. The following is the detailed schedule used throughout the campaign for Neostam therapy:—

1. Weigh the patient in kilograms: the total dose for the course is 0.1g. per kg. of bodyweight and the maximum single dose is one-tenth of this total.

2. To preclude untoward reactions in specially sensitive cases, the first and second doses were approximately one-third and two-thirds the maximum single dose.

3. As mentioned above, the maximum total was 3g. so patients weighing more than 30 kg. received no more than this dose.

Thus an adult weighing 60 kg. would have 0.1g. on the first day, 0.2g. on the second and 0.3g. on the third to the eleventh days, while a child of 15 kg. would receive 0.05g., 0.1g. and 0.15g. in the same way.

The total amount of Neostam used in the campaign was 6,016 g. which in 2,865 patients who completed treatment meant an average dose of 2.03 g., while 319 defaulters received an average dose of 0.66 g. The dose was calculated irrespective of age, sex or degree of illness and was not varied to any extent unless for a few patients experiencing reactions, or in the rare case who, having advanced disease, could be persuaded to go to hospital when there was need for a smaller dose given over a longer period preferably by injection on alternate days.
Treatment was started in all cases immediately the diagnosis was made, generally on the day of the first visit to the clinic, which was eminently satisfactory to the patients who like immediate action, and was in keeping with the advice of Lowe (2), who says that recent results of treatment in very early cases have been excellent and he is very doubtful regarding the soundness of the view that delay in treatment gives better results or fewer relapses; it certainly subjects the patient to additional weeks or months of debilitating fever. Napier (59) claims that the best results follow treatment undertaken when the disease has been present for 4-5 months and the patient's natural resistance has had time to develop, and suggests (263) that reinfection may thereby be avoided, but admits that, in practice, treatment should be instituted as soon as a definite diagnosis is made.

C. EVALUATION and COMPARISON of THERAPEUTIC METHODS.

This plan worked well and enabled the unqualified team members to calculate dosage exactly and easily, but a weakness (fully realised before embarking on the campaign) is that it does not permit much individualised treatment, for example in the advanced case, possibly with ascites or cancrum
oris. Nevertheless it cannot be overemphasised,

1. that the vast majority of the patients treated had had not the slightest hope of treatment and were therefore inevitably doomed to die otherwise,

2. that if an attempt at specific personal attention had been made it would not only have involved the use of many more medically qualified workers but also seriously slowed the entire programme, thus reducing the number of lives saved,

3. that the scheme was envisaged essentially as one of prophylaxis to save the lives of future inhabitants of the region,

4. that, as was hoped, even with this deficiency the results will stand comparison with any others.

The writer disagrees with Ho (39) in his calculation of dosage based on the number of Leishman-Donovan bodies present in bone-marrow before treatment, for the following reasons:

a. There is no evidence that the number of Leishman-Donovan bodies in any marrow smear is necessarily representative of the general concentration of parasites in the bone-marrow or any other organ.

b. If such a number was representative, there is no evidence that the curative amount of antimony is dependent quantitatively on the Leishman-Donovan bodies - it could well be a qualitative dependence, varying from strain to strain.

c. This system requires considerable painful investigation by trained staff, extends the period of treatment 3-5 times that of the usual course, and there seems no doubt that for a given number of workers the number of patients treated is substantially less over a given time, since in the writer's experience it is physically impossible, under present conditions of communications in China, to visit each week 7 centres sufficiently distant one from another to provide enough patients for a day's work. Obviously this means that travelling rather than treatment will occupy most of the teams' time.
d. Ho's defaulter rate is no less than that of the F.A.U. teams (10%) even though it would appear that one of the principles of the system is that patients are treated in the main still nearer their own homes than with the F.A.U. procedure, and it should be kept in mind that there was no military activity in Kan-su during his work which might encourage default, as in Honan.

e. The ultimate test is the cure-rate, and the Ho system seems to produce slightly poorer results than most others (including those of the F.A.U.). So far as can be extracted from his figures, total failures were at least 9.7% patients (including 2.1% resistant or relapsed, and 7.6% immediate or delayed deaths): it should be remembered that this series had all the advantages of hospital treatment—field work would give worse results.

f. There is no evidence that examination of a single marrow film which failed to show parasites means their total elimination from the body (vide infra "Criteria of cure") and there is an unreality in the suggestion that patients can be followed-up 3 months, 6 months and 1 year after treatment: this is, of course, scientifically immaculate, but anyone who has worked in China knows that not many patients will come any distance for a medical check, and the labour of searching for them is so great as to put it out of the realm of possibility. Admittedly, a surprising number of Ho's patients returned for short-term supervision (it would be interesting to know how far they had to travel) but so few came for the essential late observation that a special visit had to be paid to round them up, which was not possible in all cases. Early (20) mentions that his attempt to re-examine 179 patients after treatment was met with attendance by 21 patients only.

These points are laboured because this appears to have been adopted as the official treatment scheme for the control of kala-azar in China, despite the weight of past experience. It would seem to the present writer that the therapeutic approach
should rather be essentially that used in the case of early syphilis, where age, sex, size of lesions, blood reagin level, number of spirochaetes isolated from chancre, etc. play no part in the determination of the dose of penicillin, arsenic or bismuth to be given, this being calculated solely on the size of the patient and the experience of years in the treatment of this disease. It is not disputed that there may be a more exact indicator of the intensity of dosage needed for cure: what is equally undisputed is that such an indicator is quite unknown, and that until the universal ignorance on this point is dispelled it will be necessary to use a schedule which will be sufficiently generous just to surpass, in the large majority of patients, that amount of treatment which will eradicate the disease, even though in some cases (which are indistinguishable from the others) this means giving an excess of the drugs concerned. Such a system, hammered out through the years by bodies such as the Clinical Co-operative Group of America, represents the collective opinion of the world's authorities, in the absence of controlling tests like those operating, for example, in conditions like pernicious anaemia and diabetes mellitus, and it would seem reasonable to proceed along similar lines in kala-azar.
The decisive criterion in the treatment of both syphilis and kala-azar is the real percentage of permanent cures, and by that is meant the number cured in proportion to the number for whom treatment is made reasonably possible. This point is not often dealt with in reports of the efficacy of a certain drug but is clearly of an importance equal to that of the mere destructive power on the parasites or lack of toxicity of a therapeutic agent, both of which may be eminently satisfactory but unless put into operation cannot produce any success. The percentage of cures reported from the use of any particular drug usually either fails to record or is ignorant of,

1. the number of cases of the disease in the area concerned.
2. the number of those who might reasonably be expected to attend the clinics, taking into account such mundane things as knowledge that there is a clinic, ability to travel to it, ability to attend for the necessary length of time, the number of painful investigations to be undergone, the extent and unpleasantness of the therapy, the reactions to it and last, but certainly not least, the ability to pay for treatment.
3. the number of those defaulting with or without a reasonable amount of therapy.

Frequently it is difficult to assess the results of full courses of a preparation even on those who do complete treatment, since they will not report for follow-up, and very often figures are given which leave the fate of a substantial number of untraced patients to be guessed and which must
perforce rely on the state of those who could be traced, an unscientific proceeding which the writer is inclined to feel tends to paint a rather too optimistic picture, in China at least, where it has been observed that the relapses, failures and complications are sometimes hidden by the patients' simply retiring to their (distant) homes and thereby being lost to sight or record. Clow (14) mentions that his efforts to follow the results of treatment in 196 patients produced in all 70 visits by 34 of them, although all were asked to report at fortnightly intervals.

It is not being suggested that there is anything false about results of therapy given by the various authorities or that the well-known drugs have not got extraordinary potency, but rather that attention should be concentrated on the proper evaluation of these results with a view to the elaboration of a method of attack on the problem as a whole. In any series, therefore, the number of cures must be regarded in the light of all those who actually attended the clinic (i.e. including defaulters) and there should be constant vigilance that the conditions prevailing are of maximum attraction. Clinics should be held where patients may travel easily from their homes for treatment and be able to return in daylight; spleen and sternal punctures are painful
(especially the latter) and should be done only where necessary, the number of injections should be the minimum commensurate with adequacy, given as quickly and painlessly as possible and the drugs used must produce the least possible reactions, local and general.

Despite earnest endeavours along those lines in the F.A.U. clinics it cannot be said that at any time was there attained that peak described by McFadyen (30) when he states that "after the first few needles (the children) are a happy, hopeful lot". F.A.U. clinic children may well have been hopeful but especially just prior to injections their happiness was markedly concealed.

In another sphere, but with equal relevance, have appeared (224) figures illustrating this point most vividly. In a district of California, as late as 1940 only 26.6% of patients completed treatment for syphilis given on the old, prolonged, inconvenient and sometimes upsetting lines using arsenic and bismuth, whereas in 1946-7 using the new, rapid, convenient and non-reactive penicillin-in-oil-and-beeswax therapy, those completing treatment reached the astonishing figure of 96.6%.

The question of cost is the most important of all, and wherever this can be reduced it
All these factors have the greatest influence on the number of defaulters, and it would be most instructive to know the rates for clinics in China and in other countries. In the present series, 10% of Neostam patients and 11.3% of Pentamidine subjects left before completing treatment, but the Neostam figures varied from as low as 3.2%, in some areas, to 26%. This latter figure was due to sporadic Communist-Kuo-min-tang fighting in the hsien and was the largest single cause of default in this and other areas: other causes were difficulty of travel (e.g. snow in winter, heat in summer and mud in the rainy season), parents unable to stop work for as long as 10 days to bring child for the full course, and possibly the effect of reactions, e.g. an occasional extravavenous injection or painful hip following an intramuscular injection.

As might be expected, the average age of defaulters was less than the general average, 9.2 years as opposed to 11.4 years, while the sex ratio was identical, 64:36, and the duration of illness much the same as the average, i.e. 10.8 months instead of 11.2 months. Thus the only remarkable feature of this class of patient is that he is younger than naturally should be.
his fellows, which conforms with the Chinese habit of mistakenly trying to shield the younger children from any unpleasantness, even ultimately at the cost of their lives. There seemed no evidence that general reactions such as vomiting or diarrhoea had a specially deterrent effect on attendance but it was suspected that default was commoner among those patients who did not show immediate improvement after a few injections, for the average peasant does not comprehend the idea of treatment-courses and has a tendency, noted above, not to persevere with therapy in the more serious cases. From the humane aspect this is unfortunate, but prophylactically speaking it is less regrettable, since many of these patients are too far advanced to respond to any treatment; some could be saved only by the unattainable hospital treatment and the remainder are simply sacrificed on the altar of ignorance, but all are more or less speedily removed from circulation as reservoirs of infection, which, from the purely scientific point of view, is as good as being cured.

By no means all those failing to complete their courses would relapse or be unaffected by treatment, since they had had on the average 38% of the amount of Neostam required and 45% of the Pentamidine prescribed: some had had only one or two injections
so, on the other hand, a substantial number may have had sufficient drug for a permanent cure. This average dose would indeed be rather more than Ho (39) would recommend for his patients as a routine. Nevertheless it is preferable to regard these patients as inadequately treated and to advise all workers that they should keep defaulter rate clearly in mind as one of the most important indices of the efficiency of their clinic's working.

In the present series the precautions against an unnecessarily high rate integrate to some extent with those to take care of 2. (page 17) i.e. to make it possible for the clinic to serve a certain area, and by that is meant that every case in the area may reasonably be expected to attend. Apart from the problem of expense, whose solution involves other than medical factors, a difficulty of present practice is the establishment of clinics in large centres which may be, as in Honan, 60-100 miles apart and thus not only out of reach but out of knowledge of the vast majority of cases in the area. Publicity is eminently possible via the remarkable Government network of magisterial authority which reaches to all corners of the kala-azar areas, but admittedly requires the constant stimulation of local and central authorities especially just before a drive in any particular area.
As to the best method of bringing treatment sufficiently close, geographically speaking, to the patient, little has been written of a detailed practical nature beyond the schemes of McClure (8) and Ho (13). Although in all probability involving a lowering of medical standards (e.g. by using the services of scantily trained local practitioners) which may condemn it to some, McClure's plan has the great advantage of being possible of application in any area where there is a central clinic, since it comprehends all the medical problems, covers its stipulated district thoroughly, and even, *mirabile dictu*, offers some chance for the solution of the financial problem. It can properly claim to try to wipe out the disease in a region, but that region will be small and always limited by the necessity of working strictly from the central clinic, but it may be that in time this difficulty could be overcome.

Ho's scheme requires a much higher standard of medical work over an impossibly large area and makes no valid proposition about the costs: to infer that the Chinese Government, which cannot provide military hospitals that its soldiers will willingly enter, or civilian clinics with even a skeleton supply of drugs for cheap therapy (as for malaria or relapsing fever) is to defray all expenses, is, to the present writer's mind, to be out of touch with reality.
His training scheme is excellent and to make use of the current civilian clinics would considerably raise their standards and enthusiasm, while ensuring that the work was under central control and over a wide area, but is necessary only to see how widely scattered were the clinics and what a comparatively small number of patients were actually treated during the time this method has been used in the Lan-chow region, to realise that it has no hope of success in the sense of clearing the disease completely from an area. To quote (13) "As a practical measure mass treatment of kala-azar patients has been found to be easy of execution and successful in results. For this a Central Field Station should be established in important centres at,

1. Lan-chow, to survey and treat patients in Kan-su, Shen-si, Ho-nan, Shan-si, Szé-chuan, Si-kong and Sin-kiang.
3. Tsing-kiang-pu for Kiang-su, S-Shan-tung, An-hwei and Hu-pei".

A glance at the map will show how much control there could be over such vast areas, and how much chance an impoverished nation has of putting such an ambitious plan into effective operation.

Both the above plans suffer from one drawback which is not always appreciated until it has been encountered in actual working, the fact that
even in the worst endemic area the number of cases in each village is small, and the difficulty of communication so great that unless with a flock of trucks, ambulances or jeeps using a fantastic amount of fuel, and thereby rocketing costs, it would be impossible to treat more than a handful of patients in a day if one had to visit them in their homes, allowing for the usual delays of Chinese practice and the fatigue of packing and unpacking apparatus. The writer has reason to know how really few patients can be even examined in a day by this village-to-village process, since this was the method adopted in his follow-up of treated cases.

The F.A.U. method would therefore be commended as a practical possibility which involves a minimum of travelling for the teams, who spend all their time on the diagnosis and treatment of as many cases as the working day permits and by combing an area thoroughly from centre to centre bring the therapy sufficiently near the patient to enable him to attend, and yet maintain an adequate medical standard with the employment of very few medical personnel.

No attempt has been made to guess how many cases remain to be treated in the area covered, or conversely what percentage of the total number suffering from kala-azar have been dealt with,
because, in common with workers elsewhere, it was not possible to make an accurate survey in any area, but the following points are perhaps worthy of note,

a. There is considerable variation in incidence within the Honan area, and in an intensive follow-up tour it was not uncommon to visit villages less than a mile apart, one of which would have quite a few cases and the other of which would be free of the disease.

b. Due to the comparatively scanty numbers in some hsien it may be that in the future teams will be working at less than full pressure when they come to pay further visits to these areas, and find insufficient cases even over a wide field to make up the numbers usually handled.

c. The effect of treatment in reducing the disease is well borne out by experience in a second visit to Yang-wu, the hsien which produced in the first visit much the largest number of cases, 658. In a diagnostic survey undertaken pari passu with a follow-up survey and covering not only a larger area but covering it more minutely, only 120 new cases were discovered, although this search was made after an interval of 8 months which had included a complete sand-fly season. Such gratifying evidence of success brings with it its own problems of how to re-organise the teams to deal most efficiently with a smaller number of cases scattered more thinly over the area than before.

D. USE of PENTAMIDINE.

1. Review of Diamidine Therapy.

While proceeding with Neostam treatment, a shipment of Pentamidine (May and Baker) and Stilbamidine (May and Baker) was received for clinical trial, and it was possible to make some comparison of value with the antimony drug.

In 1939, Adler and Tchernomoretz (225) gave an account of the action of Stilbamidine on experimental leishmaniasis in the Syrian hamster,
claiming this as the first instance of a drug not containing antimony having a marked therapeutic effect on an infection with Leishmania, the action being indisputable since it saved hamsters in whom leishmaniasis never regresses spontaneously. Later, Adler et al. (226) comment that Propamidine and Pentamidine are the most active of the diamidines in vitro, strikingly more active than Stilbamidine, but this is not entirely confirmed by Collier and Lourie (227) who state that at 34°C, the leishmanicidal titre of Stilbamidine is 1:2,000,000, equal to that of Propamidine but only half that of Pentamidine. They point out that in vitro activity in no way runs parallel with that in vivo, so that both tartar emetic and Neostam show an extremely low degree of activity in vitro.

Adler and Rachmilewitz (228) used Stilbamidine successfully in an infant which had relapsed after antimony treatment, injecting it intravenously every two days in a dosage of 1.7 mg. per kg. with no ill-effects of any kind, while Adams and Yorke (229) in the same year (1939) report success in one Indian case where the spleen became almost impalpable in 17 days, smears, cultures and animal inoculation from sternal marrow were negative and the patient seemed very well. Next year, the same authors (230) report another
successful case cured by Stilbamidine, and later Adams (231) treated another Indian case with Propamidine, the only reaction being an immediate transient fever: 2–3 weeks after cessation of injections the spleen was impalpable. Despite its apparently bland nature this particular compound has not been taken into general use. The same author describes yet another case (232) treated with intravenous Pentamidine (2mg. per kg.) over 8 days who left hospital apparently well on the way to recovery.

In the Sudan, Kirk and Sati (4) describe 2 deaths and 6 apparent recoveries (observed for 4 months) treated with doses of Stilbamidine varying from 1–2.6 mg. per kg., toxic reactions being negligible with the exception of an exacerbation of fever, transient epigastric discomfort with breathlessness and dizziness, all at the start of the course. Using Pentamidine they report (140) on 13 cases, 3 of whom died, one whose recovery was doubtful and 8 who were cured. From their description it seems fairly clear that these patients were not only of the advanced type but suffering from complications like cancrum oris, pneumonia and otitis media. At first they used short courses of 8–10 daily injections, but later a more intensive form giving 15 daily injections was adopted and total
dosage varied from 111 mg. per kg. to 19 mg. per kg. In another Stilbamidine series of 28 cases the immediate-recovery rate was 86%, and 2½ years later (233) the death-rate had risen to only 18% which is low for Sudan kala-azar, a deadly disease. They conclude that, in doses which are therapeutically effective, the toxicity of these compounds is low even with prolonged courses of treatment.

In India, Napier and Sen (234) state that a cure can be effected with an average total dose of 0.795g. Stilbamidine per 100 lb. bodyweight and had 7 successes in a series of 8 cases. Later Napier et al (235) report on a series of 101 cases treated with Stilbamidine up to a maximum of 1 mg. per lb. of bodyweight in 10-12 injections as the usual course, and this produced 2 relapses out of 35 cases whose fate was known. Nearly half of their patients were over 21 years of age and the mean duration of the disease was 8 months: the authors' conclusions are that in this type of case the results with Stilbamidine compare very favourably with those using Neostibosan, hitherto the best drug, while the outcome in antimony-resistant cases is almost as good as in the ordinary case. (In the Sudan, also, Kirk (236) sees hope at last for his antimony-resistant cases).

In another article Napier and Sen Gupta (237) relate their experience with Pentamididine used
in a maximum dose of 1 mg. per lb., starting with a small initial amount, working up to this level and giving a normal course of 10 injections, with 15 injections for resistant cases. Usually the size of the spleen was unaffected till about one week after the completion of the injection course, but then was reduced rapidly. As with the antimonials the authors consider that relapses all occur within 6 months, and following a course of the above dosage Sen Gupta reports (238) 2 complete failures and 12 relapses out of 32 cases, despite the immediate good clinical results. Later, Sen Gupta, in a further communication (239) suggests that Phenamidine, too, is inferior to the best antimonials and Stilbamidine (1 death and 3 resistant cases out of 30). Elsewhere, (21) he concludes that none of the diamidines tested has been found as effective as Stilbamidine.

Giraud and Revol (240) comment on the use of Pentamidine intramuscularly in infantile kala-azar in the south of France, the dosage being 1.5-2 mg. per kg. of bodyweight, with 3 injections weekly to a total of 12-15. Fever disappeared quickly and the splenomegaly slowly, but only 4 out of 11 patients were cured, and they conclude that it is useful chiefly in very young children or those
advanced cases in a delicate condition. Surprisingly, in view of these results, they compare it with the antimonials other than Urea-stibamine (which, in their opinion, holds first place).

Clow (15) refers to Stilbamidine as giving a more rapid response than Neostam, Neostibosan or Urea-stibamine. Using Pentamidine intravenously in doses up to 4 mg. per kg. in 2 oro-pharyngeal cases, Humphreys (241) found marked improvement in both, although one died later, cause unknown.

Three points remain to be discussed with regard to the diamidines, viz. cost, dosage and reactions.

a. As to the first, these compounds have a decided advantage in the treatment of a disease occurring in the poorest of the poor, being cheaper than any of the pentavalent antimonials, although the exact cost depends on a multitude of conditions prevailing all along the supply route (but would probably be about half). In the case of Pentamidine this may be partly due to the simpler packing in 100 ml. bottles rather than the ampoules of other drugs.

b. It should be noted that in the above series cases were usually treated with a daily dose of 1-2 mg. per kg. of any of the drugs, and this may well account for the poor results in some quarters.
as opposed to those gained by the F.A.U. teams using a higher dosage.

c. Thirdly, reactions to the drugs deserve to be considered together in the light of their peculiar nature. Some have already been mentioned, but perhaps the best descriptions have been given by Indian writers who have had an extensive experience in the matter. Sen Gupta (242) divides immediate reactions to intravenous Stilbamidine into three:

1. mild shock with generalised burning sensation, flushing and slight giddiness. Napier and Sen (234) agree, and add slight dyspnoea to the list, while these three authors (235) stress that all patients are likely to suffer from them to a greater or less extent.

2. moderate reactions, including the previous type plus vomiting, epigastric distress, more severe dyspnoea, feeble pulse and sweating. This is presumably due to a further fall of blood-pressure caused by the depressing action of Stilbamidine on the circulatory system to which Wien (243) has called attention, stating that low concentrations stimulated and high concentrations depressed the heart, but that the effect was small and transitory.

3. severe reactions, e.g. symptoms of collapse, to which Clow (15) refers as "not uncommon" and the more serious delayed manifestations of Kirk (244) ushered in by vomiting, passing into coma and death in 1-4 days, which he attributes to a toxic product occurring in irradiated solutions.

Most of the reactions can be mimicked by those following the injection of the antimonials drugs, but one seems peculiar to Stilbamidine, namely the post-diamidine neuropathy which Sen
Gupta (242) found appearing $2\frac{1}{2}-5$ months after the conclusion of treatment in 17 out of 104 cases, consisting of paraesthesia and/or dissociated anaesthesia of areas supplied by the sensory branches of the trigeminal nerve, such features as itching, formication or numbness being common complaints. It is said not to be dangerous to life or progressive, having a tendency to slow recovery. Napier and Sen Gupta (245) suggest that the lesion may be in the pons and of a toxic degenerative nature, and repeat that it did not seem to be progressive, some of the patients feeling that the area was decreasing as time went by. Later, however, Napier (246) reports that the condition had been found in more than half of the patients though symptoms were slight in the majority of cases: he recommends that this drug be reserved for antimony-resistant cases and quotes the forbidding results of Collard and Hargreaves (203) who found (in presumably more intelligent and more sensitive patients) that similar symptoms followed treatment in 22 out of 24 patients.

This is much in excess of both the Calcutta figures and those of Snapper (247) using it in multiple myeloma, where 4 of 20 patients were afflicted with trigeminal anaesthesia of the dissociated type.
Used intramuscularly, Thompson (248) in N. Honan found it caused a great deal of pain and induration which make it useless for outpatient work, and was of opinion that the recommended dose of 1.5 mg. per lb. was too small. To overcome the pain of intramuscular injection, Snapper (247) dissolved the drug in 2½ procaine.

Reactions after intravenous Pentamidine are similar to the mild type following Stilbamidine but even more transitory, and Napier and Sen Gupta (237) did not find dyspnoea, palpitations or collapse, as occur subsequent to injections of the latter, although there is a slight fall of blood-pressure: nothing resembling post-stilbamidine neuropathy has been encountered, and even in the larger doses of Humphreys (241) there were no reactions. Kirk and Henry (249) in the Sudan, have had experience of neurological disturbance such as peripheral neuritis of the legs, while in a few cases they have known mental changes simulating epilepsy or even mania to occur and recur. Using it intramuscularly, Giraud and Revol (240) found the drug well-tolerated although the injections might be painful.

From the reports on the use of Stilbamidine intravenously, it did not appear to be a drug
suitable for use in field work, for the following reasons -

a. to use a shock-producing drug on outpatients is courting, if not disaster, at least a disruption of the usual clinic procedure since it would be necessary to provide facilities for patients lying down until the chance of this reaction had passed: such a scheme would require additional staff and accommodation, neither of which was available if large numbers were to be dealt with, and the measure, being unintelligible to them, would not be popular with patients.

b. it appeared that the general reactions following its use were not likely to be less common or less unpleasant than those subsequent to the use of the antimonials.

c. the risk of a substantial number of patients developing the facial neuropathy already described was too great, since it might well prejudice the decision of future patients to come forward readily for treatment.

Reports on the use of the compound intramuscularly were such that apparently the pain and induration resulting would discourage many patients from attending, nor did the results of this therapy seem outstanding, so Stilbamidine was not used in F.A.U. field work at all.

2. F.A.U. Schedule.

A report on intravenous Pentamidine by Napier and Sen Gupta (237) described much less alarming reactions than with Stilbamidine, and dyspnoea, palpitations, profuse sweating and collapse did not occur nor was there any evidence of "post-diamidino-stilbene neuropathy". In spite of
this encouraging report it was not thought appropriate to use the drug in this way, since there already was a potent intravenous drug in Neostam: thus it was felt that the former should be tried intramuscularly in an attempt to find an agent which could be used effectively on the small children with poor veins who slowed up the clinics' work, and in whom the risk of serious extravavenous injection was always a possibility. It was therefore decided to use the intramuscular Pentamidine in certain areas on all cases under the age of 12 years and give the usual intravenous Neostam to those above that age, comparing the results. Technically the only difficulty encountered was the tendency of the drug to crystallise out of the 10% solution (in which it is prepared) at the low temperatures prevailing in some injection rooms in winter, but this was countered by the simple, if unorthodox procedure of keeping the 100 ml. bottle in the trousers' pocket between injections.

At the time this work was done it had been realised that the previous dosage of 1-2 mg. per kg. of bodyweight was too small, and that amounts like Humphreys' (241) 4 mg. per kg. (previously characterised as colossal) were in fact rather on the low side: the manufacturers were by then advising 5-6 mg. per kg. The standard dosage adopted was
5 mg. per kg. of bodyweight for the individual dose which should be repeated daily for 10-12 days. In terms of a 20 kg. child this meant an initial dose of 0.5 ml. of the 10% solution followed by 10 daily doses of 1 ml., using the thighs in preference to the buttocks, alternately. For the reasons advanced in the case of Neostam no heed was or could be taken of age, sex or the stage of the disease and there seemed no reason to depart from this principal, or the above dosage, at any time.

E. SUPPORTIVE TREATMENT.

This would be strict rest in bed in hospital, ample high protein diet, especially eggs and liver (Sun (38)) supplemented by vitamins and iron therapy, and satisfactory adjuvant therapy for complications or coincidental disease. Practically none of these is possible but attempts were made to the limit in all directions, as has been or will be indicated.

F. TREATMENT OF COMPLICATIONS.

1. General sepsis.

Sepsis was encountered in various forms. The impetiginous skin lesions in the most severe cases were treated with Merthiolate (Lilly) so long as the supply lasted, and then with the 60-70% alcohol (which is the common social beverage in the
area) plus much advice with regard to general hygiene which was seldom, if ever, followed. Stocks of dressings, bandages, etc. were low, so that in reality not very much was done for this kind of lesion. Anything more extensive in the nature of skin ulceration, excluding cancrum oris, was sent to hospital if possible, with a view to skin grafting. Occasional boils and abscesses were incised and drained, and a few quite unsuccessful attempts were made to deal with otitis media.

2. Cancrum oris.

The septic condition carrying the greatest danger to life is, of course, cancrum oris and it is to be regretted that it was not possible to have agents at hand for its adequate treatment, since it seems clear that the use of penicillin will save many patients hitherto doomed.

Earlier lines of specific treatment included the antiseptic-intravenous arsenic regime of Fan and Scott (34) and Woods and Bell (32) and still apparently recommended by Wang Sung and Sung (143) in 1947, along with general dental hygiene. In a case of noma complicating small-pox, Chen (250) used antiseptics combined with local and general sulphanilamide with a favourable result. There seems little doubt, however, that all such regimes
will fall into disuse wherever penicillin is available: Vaizey (251) quotes cure in all of 3 cases in Ethiopia with intramuscular penicillin, as opposed to 80% mortality previously. The excellent results in non-tropical countries where it has been used on the less severe spirochaetal mouth infection, Vincent's angina, are typified by the work of Sweeney et al. (252) who report on the rapid cure of 43 patients following intramuscular penicillin q.3h. to an average total dose of 721,000 units, and attention to dental caries.

Sen Gupta and Chakravarty (146) describe the older forms of treatment, dividing them into,

a. that specifically designed to attack the Leishman-Donovan bodies

b. general treatment designed -

1. to increase resistance, e.g. nourishing diet, extra vitamins and, if necessary, blood-transfusions.
2. to combat infection (sulphonamides and intravenous arsenic).
3. to raise the leukocyte count, viz. pentnucleotide and liver injections.

c. local treatment with sulphonamides or antiseptics.

They treated 6 patients with a regime including -

1. penicillin 10,000-20,000 units q.3h. for a week intramuscularly, and either sprayed in solution or used as lozenges.
2. specific kala-azar drugs.
3. general supportive measures.

Results were uniformly good by this method,
and all patients recovered, temperature coming down after 24 hours, the foul smell lessening in 48 hours, and sloughs separating in 72 hours, while the end-results were considered fairly satisfactory.

Struthers (209) and Yates (37) pronounce on the efficacy of Solustibosan, especially in small repeated doses, in the specific treatment of kala-azar, emphasising that too vigorous attack with powerful drugs may light up a subacute noma possibly due to the sudden death of a large number of organisms, similar to the condition underlying the Herxheimer reaction, and the patient may die of too concentrated therapy. On the other hand, Lee and Chu (36) Fan and Scott (34) and Scovel (1) continued the usual routine treatment and found that the patient responded well, with an early limitation of the necrotic process. In the Sudan, Stephenson, (174) recommends Urea-stibamine as more effective than Neostibosan when treating cancrum oris.

Having no preconceived ideas about the management of this lesion, various local anti-septics were tried out including 70% spirit Merthiolate, picric acid, pure carbolic acid and nea-arsphenamine, combined with the removal of sloughs where possible, and general cleanliness, but this had no very beneficial effect so it was
decided to try oral sulphonamides in full doses (as recommended by Sati (144)) with bland dressings and removal of only loose sloughs. It has been argued that this type of drug, which may per se produce agranulocytosis as a toxic manifestation, should not be used in a disease characterised by leukopenia but this was not found to be a real danger and, since penicillin was not available, sulphadiazine became the standard anti-noma treatment.

General treatment was restricted by the materials at hand but an attempt was made to induce parents to feed their children with the maximum of protein foods such as meat, eggs and soya-bean curd, rather than the usual cheap carbohydrate dish of wheat paste, as a means of replacing some of the protein which was frequently lost in the urine, and thus to increase resistance. Multivite pills were given to a few of the worst cases only, since supplies were so short but, given over the comparatively restricted time the patient was under treatment, it is doubtful whether they represented more than a gesture.

Specific treatment was rarely capable of modification owing to lack of time, but sometimes it was possible to give longer courses of smaller doses of Neostam which was felt might obviate severe
reactions and give greater hope of cure. Cases which had to be treated in the clinics were so taken care of and formed a collection of all stages of severity, but 7 of the most severe cases were strongly urged to go to hospital and disappeared from sight, so that this series is not a complete representation of the disease as it actually occurs in the district. No case was considered too advanced for treatment with sulphonamides and in no case was treatment with Neostam delayed by the use of the former, but the two courses were given concurrently.

3. Anaemia.

As has been said, there were probably few patients who were not anaemic and therefore not in need of iron replacement, but supplies were small and were not increased to any large extent during the campaign. Blaud's pill was the only form in which it was available. Napier and Sharma (114) make the point that no attempt to repair the deficiency by supplying iron alone will produce any improvement, which must wait until the specific anti-kala-azar drugs have paralysed the newly-formed reticulo-endothelial cells and so stopped the excessive phagocytosis of red cells. Aversa and Crosca (253) declare that the improvement in the blood
picture with combined iron and antimony therapy is neither more rapid nor more accentuated than that observed in children treated only with antimony. Thus, probably each patient should be given a large amount of iron compound to take home with him only at the conclusion of specific treatment, so that he may start to replace his destroyed red cells and carry the process on far into his convalescence: the ordinary Chinese worker's diet is poor in iron (among other things) so that recovery is likely to be delayed unless the iron supply can be supplemented. Having regard to the small amount available it was decided to give it to the most grossly anaemic patients, where occasionally it might make the difference between succumbing to exhaustion, and recovery. Whether this did in fact happen is impossible to say.

4. Respiratory disease.

Respiratory complaints were graded roughly into three -

1. pulmonary tuberculosis
2. frank lobar pneumonia
3. bronchitis, bronchiectasis and a few cases of what seemed low-grade broncho-pneumonia.

On the subject of the first, Napier (254) has in the past written gloomily of its association with kala-azar as "a fatal combination" due to the
fact that antimony seemed to have little effect on
the protozoal disease but caused the tuberculosis
to undergo rapid extension in the lungs. More
recently, however, Sen Gupta (255) has stated that
probably in Stilbamidine we have a highly specific
anti-kala-azar drug which will not cause an
exacerbation of pulmonary tuberculosis. The few
cases where it was strongly suspected clinically
that the patients were actively phthisical (with
no facilities for laboratory confirmation of the
diagnosis) were treated with Neostam and did not
appear upset generally or focally by it, but
unfortunately disappeared from observation imme-
diately so that the end-results were unknown.
There was no opportunity to use either Stilbamidine
or Pentamidine on these cases.

The four cases of lobar pneumonia
recovered satisfactorily on sulphonamide and
their treatment was then completed successfully
with Neostam. Cases of bronchitis, mild and
severe were (especially in winter) many, but did
not seem to find this a handicap to recovery nor
was there any evidence that the bronchitis was
increased in severity by the use of antimonials.

5. Oedema.

Oedema could be graded roughly into
types (renal, cardiac, etc.) but with the exception
of those few due to mechanical factors like the pressure of a large collection of ascitic fluid or the presence of old rheumatic endocarditis all types were indirectly due to the leishmanial infection, although probably all emphasised by the prevailing malnutrition. So oedema was dissipated satisfactorily by the specific antikala-azar treatment and constant urging of the patients to adopt the high protein diets already described. 5 cases of generalised oedema were referred to hospital as their only hope of recovery. In other types of oedema the few measures possible were taken, but the patients were generally unwilling or financially unable to take advice to rest in bed. Those who have lain for any length of time on a Chinese bed will not be unduly surprised at this reluctance.

6. Ascites.

Patients with gross ascites due to kala-azar were generally moribund and removal of fluid made no difference to them, and so was abandoned after a time. One case was referred to hospital. In those with lesser collections of fluid the pressure did not seem detrimental and so was not relieved: in some cases the fluid increased with treatment but these patients usually died before the amount became embarrassing. Thus
it may be said that in the survivors the fluid cleared up as part of the general improvement, helped no doubt by the high-protein diet which was also advised in these cases. Scovel (1) states that he gave the drug (antimonial) in the presence of ascites without any untoward reactions.

7. Jaundice.

Jaundice was seen once or twice but followed the course of epidemic hepatitis and required no special treatment, although no antimony was given until the jaundice had disappeared.

8. Malaria.

Malaria was encountered on only one or two occasions in association with kala-azar and was treated concurrently with the antimonial injections. The results were satisfactory.
G. CONTRA-INDICATIONS TO TREATMENT.

Following the advice of Napier (59) no contra-indication to treatment was recognised except temporarily in the cases of pneumonia and epidemic hepatitis, and this system seemed justified. Scovel (1) says "antimony is definitely contra-indicated in the presence of jaundice, hepatitis (sic) nephritis or pneumonia". Ideally, there would be several contra-indications to the intensive schedule used, mainly in the advanced cases, but for reasons already given it was not practicable to heed these without sacrificing other more importance features of the work. Infrequently dosage was temporarily reduced because of general reactions like diarrhoea and vomiting, and rarely because of severe albuminuria. In the light of experience albuminuria was considered to be an expression of toxaemia due to the disease which would benefit from specific treatment, so no attention was paid to the example of Chakravarty (256) who suspends drug treatment when albuminuria appears in the course of therapy, but rather to the procedure of Struthers (207) who continued antimony injections successfully in spite of albumen and red cells in the urine.

H. PREVIOUS TREATMENT.

Unfortunately, no accurate record was kept
of patients who came for examination and were found to have had a satisfactory course of anti-kala-azar treatment at one of the trustworthy clinics, but the number certainly did not exceed ten during the whole period. Note was however taken of the treatment previously undergone by all patients before attending F.A.U. clinics for further therapy and the amounts, (which were discounted completely in assessing patients' current needs) are illustrative of the ineffectiveness of the established centres to deal with more than a small fraction of the infected population, and the futility of the great majority of "injections" given supposedly for their specific leishmanicidal action by the Government hospitals and the local private practitioners. It should be noted, however, that while there were only a handful of cases seen who had been treated in the permanent Mission clinics yet all of these were successfully cured, a tribute to the efficiency of the individual treatment practiced in these centres.

Most patients had at one time or another had some form of traditional Chinese treatment, ranging from the drastic "hot" or "cold" needles through the skin over the enlarged spleen to the innocuous skin-plasters or the mystical oral preparations reminiscent of the opening scenes of
"Macbeth". Naturally, one is unable to deny these any value since obviously only the failures would desire to come for further attention, but no case was heard of where "indigenous" medicine had had a success comparable to that in Napier's (59) case.

Out of 3,184 patients only 60 (1.9%) had had some type of intramuscular or intravenous injections the extent of the course being from 1 to 50 injections and the average number 6.7 per patient. 17 (28%) of these patients showed some improvement but none could have been regarded as even a tentative cure: there are three reasons for this:

1. use of weak antimonials like Antimosan.
2. insufficient number of injections or inadequate dosage of potent arsenicals.
3. simple fraud, using solutions of calcium gluconate, potassium iodide or other bland preparations.

Thus it is again evident that only the fringe of the infected population is being satisfactorily treated in the Mission hospitals, and beyond that, for one reason or another, there is no treatment worthy of the name.
REATIONS.

1. NEOSTAM.
   a. Local reactions.

   Especially at the beginning of the work, when the intravenous technique of some team-members was not yet perfected, it was thought desirable to use Neostam intramuscularly in those cases where, owing to the age of the patient or for other reasons, it was difficult to give injections into veins: this might occur towards the end of a course where perhaps the one available vein became thrombosed.

   The scheme followed was that of the manufacturers, using a 25% solution which meant that the volume of the dose was usually in the region of 0.1-0.4 ml, given into alternate buttocks daily, and it was soon found that practically every dose caused subsequent pain, tenderness, swelling and induration, while many of them resulted in abscess formation: greater dilution of the powder and/or prolonged massage of the site following injection and using the lateral aspect of the thigh instead of the buttock seemed to make no difference to their occurrence. Since a number of abscesses would arise in defaulters, of whose fate there is no accurate record, it is not possible to give a precise figure for its
incidence but it is thought that it would be not far short of 25%. No bacteriological investigation of these abscesses could be undertaken except by the crude method of making films from the pus, but from the negative results obtained and the clinical appearance of the abscess it was concluded that they were all due purely to chemical reaction, and in no case to sepsis.

After incision, removal of slough (which was frequently extensive) and drainage, all healed satisfactorily and no case was known to die of this reaction, but the suffering caused by even the non-fluctuating type was considerable, while those which required incision carried with them the dangers of general anaesthesia and of superadded infection in patients who were in no state to withstand any unnecessary burdens without consequent decrease in their chances of recovery. For these reasons this method of administration was soon given up, unless very occasionally where an injection even into a neck vein might not seem immediately practicable.

The incidence of accidental extravenuous injections became steadily less and less as technique improved and was at no time high, although subject to a slight seasonal increase in winter when veins were contracted by cold and fingertip sensitivity was reduced. Even a small
amount put outside a vein will cause induration and pain, while the majority went on to abscess formation and required to be incised. In the arm there was sometimes swelling extending from the palm to the shoulder, while in the neck there was usually considerable oedema extending down over the chest.

Without any hospital facilities the cure of these patients was difficult, and there was an insufficient supply of opiates to relieve their pain, while the necrotic process was advancing to the stage of ripeness, with the consequent tendency to open them at the earliest possible moment, sometimes, unfortunately, before the appropriate time. Two young children died due to extravasous injections in the neck, and one adolescent in an advanced stage of kala-azar died following a misplaced injection in the arm. All other cases healed satisfactorily with no contractures.

b. General reactions.

When dealing with outpatients it is necessary to depend entirely on their history for the incidence of general reactions, unless the latter are immediate since the cases are almost never under observation for any length of time. This may give a reasonably accurate indication of the frequency of phenomena like diarrhoea and vomiting but gives no real picture of their intensity, and it was found very difficult to get
GENERAL REACTIONS TO NEOSTAM

| Cases with diarrhoea twice daily | 12.7% |
| " " " thrice " | 6.3% |
| " " " vomiting twice " | 4.2% |
| " " " thrice " | 6.3% |

Introduction to the drug and its effectiveness in various conditions.
much impression of subjective reactions in patients who are unaccustomed to describing sensations precisely.

Probably the drug does cause nausea, slight giddiness and a feeling of apprehension in the majority of cases, but these were not of great moment. Assessment of the diarrhoea figures is considerably complicated by the widespread amoebic and bacillary dysentery which were likely to be more prominent in these cases, lacking in resistance as they were, so the figures are certainly indicative of a reaction rate greater than should be ascribed to the antimony. Details of alimentary disturbance were not recorded for all patients, since no steps were taken against minor degrees but only when it was judged that the reaction was imperilling either the patient's chance of ultimate benefit or his likelihood of continuing attendance. Thus there were no figures for the entire series but only from a random sample of 89 patients in one district which is believed to be representative, and is as shown. In only one or two of these did the reactions occur on more than one day and in no case was the severity sufficient to warrant interference with the frequency of the injections or the total dosage.

Over the whole series of 3,184 patients only 44 (1.5%) required some such modification,
which consisted in slight reduction of the individual dose, (with consequent prolongation of the course) increase in the dilution of the drug (ordinarily 5%) and increase in the time taken to complete the injection (normally 20-30 secs.). Patients were advised not to have a meal for some hours prior to the injections but this was a vain hope where injections were given over a whole day, necessitating a considerable wait on the part of some patients, who in any case did not understand the reason for this prohibition. In all cases, changes were satisfactory so that no one required to have even temporary cessation of treatment: equally, so far as is known, no case derived any permanent disability from these toxic manifestations.

Two other kinds of general response to treatment were experienced, namely abdominal pain and cough. The former was not common, but when it did occur was generally experienced towards the end of a course of treatment and usually over the enlarged spleen: for these reasons it was thought to be probably due to spleen shrinkage causing stretching of adhesions as a manifestation of the general resolution of the perisplenitis which is part of the disease. This may have some relationship to the post-injection discomfort experienced
by the patients of Chopra and das Gupta (257), although their complaint of distension was not found in F.A.U. patients and the authors ascribe the sensations to enlargement rather than contraction of liver and spleen.

Patients suffering from cough frequently had an exacerbation of this soon after injections but never to such an extent that it was necessary to alter the mode of therapy, nor did there seem to be any ultimate ill effects.

Consideration of these various aspects of antimonial therapy does not lend much support to the statements of Woods and Bell (32) that "the large doses------given in India and elsewhere cannot be tolerated by the Chinese", especially as they were speaking of Neostibosan, which is generally recognised to be one of the least disturbing of the antimony derivatives. Like most other patients the Chinese will complain of discomfort and inconvenience in the hope of securing an easier cure, but in the present series no evidence was forthcoming that, unless in the very advanced cases, even a moderately toxic drug like Neostam caused any real lowering of vitality or that the patients were sufficiently upset by reactions to be in danger of defaulting from treatment.
2. PENTAMIDINE.
   a. Local reactions.

   All injections were at first given into the buttocks, but later the lateral aspect of the thighs was utilised and it is felt that there would have been fewer serious reactions had this latter site been used throughout, presumably owing to the decreased chance of local necrosis which occurs in the fat of the buttock where it is subjected to fairly constant pressure in both children and adults and where the dispersing effect of muscle motion is not present to the same extent as in the thigh.

   Most patients who were of an age and disposition to give a rational answer stated that on any one day the site of the previous day's injection was fairly tender, and the site of the injection of two days past could still be located by slight residual tenderness, but neither this nor associated pain from the current injection was at all incapacitating: it was instructive to see children who had just averred the most excruciating agony at the site of their last injection (in the hope of avoiding another) walk sedately out of the clinic without the suggestion of a limp. That was, as it were, the baseline of local reaction: in addition to this, a number, which varied from 1-5%, developed a hot, red, tender
indurated area at the site of one or more injections but in each case this cleared up in a few days and beyond making walking rather painful had no ill-effects.

In a series of 80 unselected cases examined one month after the completion of treatment it was found that five (6.25%) had developed abscesses at the site of an injection, 3 in the buttock and 2 in the thighs, one of the latter having died. The nature of the abscess in this case was unknown, but all the others exhibited the same type of well circumscribed fluctuating slightly tender abscess, the size averaging 5 x 4 cm., which responded well to incision and drainage. None of the patients was febrile when examined but their general condition was poor, and they had either failed to gain weight or were starting to lose what they had gained since the end of the injections. On the other hand, all their spleens were decreasing at the rate to have been expected had there been no abscess present, and there seemed every reason to suppose that they would be as completely cured as the other survivors.

One peculiarity of these 5 lesions was that they developed, respectively,

1. immediately after the last injection of the course
2. a few days after this point
GENERAL REACTIONS TO PENTAMIDINE.

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<th>Cases with diarrhoea twice on 1 day</th>
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<td>3 days</td>
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<th>Cases with vomiting twice on 1 day</th>
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3. one week afterwards
4. 2½ weeks afterwards
5. 3 weeks afterwards

unlike the post-Neostam abscesses which invariably develop after 2-3 days. In this small series of post-Pentamidine abscesses the few seen were in no case so serious as those following Neostam, being much more circumscribed and indolent, and although there was one death it should be remembered that none of these patients had any treatment or even advice as to treatment owing to the long period before development, so that it is impossible to predict what the outcome would be if patients with such sequelae could be induced to report to hospital. Ghosal and Sinha's (258) cases who were all treated in hospital commonly developed brawny reactions, but every one responded to the usual care and hot fomentations and did not suppurate.

b. General reactions.

No case showed any signs of shock or collapse or any of the neuropathies associated with the intravenous injection of Stilbamidine, and general reactions (elicited by close questioning only) were confined to diarrhoea and vomiting, one or other of which affected 22 (27.5%) of 80 patients, as shown.

As with the diarrhoea following the injection of Neostam there was no indication of the nature of the condition, which in some cases may well have been due to dysentery (amoebic or bacillary) but
did not appear to cause the patients any deterioration in resistance, and it will be noticed to be very similar in amount to that encountered after intravenous Neostam, which might be an indication that much of it is of a non-specific nature. Vomiting was seen to take place very soon after intramuscular injection, by which it could scarcely have been caused, and this gave rise to the suspicion that much of it might be due to the apprehension and disturbance which was associated with any type of injection given to Chinese children. Again, the amount of it was not significantly different from that encountered with Neostam and certainly did not appear to affect the patients adversely.

No alteration was made in dosage on account of any of these reactions and so courses were maintained at their usual length.

In a series of 134 patients, the defaulter rate was 11.3% as against a rate of 6.5% in patients treated with intravenous Neostam in the same clinic, but it has to be remembered that the Pentamidine cases were all under 12 years of age and 64% of the total (for the whole campaign) Neostam defaulters were under 12 years, so that, taking into consideration that defection was twice as common in this age group, it would seem that the effect of the two
drugs on the defaulter rate is about equal. Also, in only two of the patients had there been any general reaction worthy of the name before defaulting, viz. one had vomited twice on one day only and one had diarrhoea twice on one day only, while none of them had had any particular local reaction. This to some extent served to confirm the feeling that defaulting is not dependent on the incidence of reactions, but rather on other factors like age, severity of the condition, speed of benefit from treatment and domestic conditions of patient or parent. Woods and Bell (32) mention most of these as reasons for their defaulters, who appear to have numbered 5.3%.

Summing up the reactions due to the two drugs, one would say that there is nothing to choose between their general reactions, while with Pentamidine a small number will inevitably develop abscesses which in the main will respond well to treatment, although the indications are, judging from a limited experience, that the isolated case may succumb if not seen and treated without delay. Except for errors of technique there are no local reactions with intravenous Neostam.
CRITERIA of CURE.

One of the drawbacks to the assessment of the results of any specific drug used against kala-azar is the fact that the effects are not easily estimated till some time after the conclusion of the injections. Using Neostibosan, Napier and Mullick (206) for instance, say that in half of their cases there was no clinical improvement till after the course was completed: Adams (231) found that, following injections of Propamidine, the spleen did not start to shrink for 4-5 days, while Adams and York (229) in a Stilbamidine case report that there was no improvement for 10 days after the last injection but by the 17th day after treatment the size of the spleen had so decreased that the organ was just palpable below the costal margin. Kirk (244) in the Sudan, dealing with perhaps the most intractable type of kala-azar, says that in long-standing cases the spleen may not disappear completely, due to fibrosis, while in other cases a splenic tumour which has been considerably reduced immediately after treatment may continue to shrink very slowly and disappear finally as long as 3-6 months later. He points out too, that complete disappearance of the splenomegaly is no guarantee of cure, nor is a negative sternal, gland or spleen puncture, and in this he is supported by Shortt (162) who emphasises
that the parasites may be missed in the very small amount of material examined, since if present they would be expected to be in small numbers at this stage. It is then pertinent to recall Napier et al. (235) "it was found that parasitological evidence is no more reliable than clinical. In a large proportion of the cases reported (35) a sternal puncture was done before discharge: in every case a negative result was obtained, though in two cases a relapse occurred later".

It is felt that the opinion of such authorities must weigh heavily against the procedure of Ho et al. (163) who use sternal puncture not only as an indicator of the amount of treatment required but also as the criterion of cure in the individual patient.

As listed by Scott and Li (184) the signs of cure are cessation of fever, reduction in the size of spleen and liver, increase in red and white cell counts and haemoglobin, and physical appearance of well-being, but Kirk and Sam (140) rightly stress that from the size of the spleen and the weight of the patient at the time of discharge from treatment little or no information of any prognostic value can be obtained. Struthers (259) is definite that "the globulin-precipitation test and the aldehyde test cannot be relied on as indicative of cure". Most experienced workers seem
to base a strict evaluation of their results on the statements of Napier and Sen Gupta (237) that if a patient relapses he does so within 6 months after a course of treatment: thus an examination of all the patients in a particular series at or after this point will give a complete picture of the results due to the method employed. F.A.U. experience is at variance with Scovel's (1) statement that "it is probably safe to say that these patients who successfully completed treatment without any mishaps returned home to regain good health" since a few cases will be cited later who left the Honan clinics "without mishap" apparently benefited by the treatment for some months, but then showed clinical relapse with parasites in films from spleen puncture.

It would therefore seem wise to use Napier's dictum as the criterion of cure in any individual case, and it was with this in mind that in estimating the results of Neostam treatment the survey was made sufficiently long after treatment had been given that the average period elapsing was 8.6 months (range 6-10 months) and it was felt with some confidence that the results after such an interval were unlikely to alter. Due to the conditions prevailing in the area concerned it was found impossible to check Pentamidine results after
an average interval of more than 5 weeks, so that they cannot have the same weight or finality. In both cases the method of approach was the same, i.e. the appropriate district was revisited and a selected area, including large and small villages, was systematically combed so that all patients who had visited the clinics from these villages were traced, in addition to the small group who heard of the team's presence and came in from other villages or areas which were not actually visited. Fortunately only very few had moved their dwelling and a definite statement was obtained as to their condition of health from neighbours and friends: in each case a cure seemed to have resulted, so it was felt justifiable to include them in the series.

Deaths occurred in patients outwith observation so that no proper impression could be got of the cause of death and it was considered legitimate to take the pessimistic view that they were attributable to kala-azar, although intercurrent disease may have been wholly or partly responsible. A few defaulters were encountered, the majority seeming to have been cured, but it was thought unwise to include such a small number in the results since they might give a false impression of the amount of Neostam necessary for cure. All other patients found were questioned
personally or their parents interrogated on the question of fever, splenomegaly, bodyweight, complications (e.g. noma) and any point about their well-being which they might advance, after which each patient was given a general physical examination, with particular reference to the size of spleen and liver, state of nutrition and relief of complications. All these points were recorded, and where there seemed any doubt about the cure the subject was requested to have a spleen puncture performed. It was felt that this was essential before subjecting patients to a second course of treatment, and it is surprising that Scovel (1) seems to regard clinical signs alone as sufficient evidence of relapse to warrant the giving of more treatment. In the few cases which show such signs it should be possible to discover the parasites, if necessary by repeated puncture of the spleen, and thus exclude diseases like chronic malaria which may give a confusing clinical picture. Some patients, especially those with few symptoms, refused to co-operate but their number was not sufficiently large to upset the dependability of the results. Patients requiring further treatment were so instructed.

By thus tracking down the patients it seemed that the figures were very little weighted,
if at all, so that conclusions from them, with minor reservations, may be regarded as legitimate and well-founded.

<table>
<thead>
<tr>
<th>Patient Series</th>
<th>Total Number</th>
<th>Male</th>
<th>Female</th>
<th>Average Age</th>
<th>Case</th>
<th>Examinations</th>
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The above table shows the patient series, total number, male, female, average age, and number of examinations.
<table>
<thead>
<tr>
<th></th>
<th>Total district cases</th>
<th>Cases Re-examined</th>
<th>Entire Series</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average age</td>
<td>13.4 yr.</td>
<td>12.4 yr.</td>
<td>11.4 yr.</td>
</tr>
<tr>
<td>Average duration of illness</td>
<td>9.2 m.</td>
<td>9.7 m.</td>
<td>11.2 m.</td>
</tr>
<tr>
<td>Cancrum oris</td>
<td>4%</td>
<td>3.9%</td>
<td>4.2%</td>
</tr>
<tr>
<td>Generalised Oedema</td>
<td>0.9%</td>
<td>3.4%</td>
<td>3.9%</td>
</tr>
<tr>
<td>Ascites</td>
<td>0.45%</td>
<td>1.1%</td>
<td>0.72%</td>
</tr>
<tr>
<td>Average amount of Neostam given</td>
<td>2.14 gm.</td>
<td>2.16 gm.</td>
<td>2.03 gm.</td>
</tr>
</tbody>
</table>

PATIENTS in YANG-WU HSIEN
RESULTS.

Two surveys were made, one in an area where Neostam had been used exclusively, and one where both Neostam and Pentamidine were given, which latter afforded some degree of comparison between the two drugs.

USE OF NEOSTAM.

These patients were located at Yang-wu hsien which is quite heavily infected with kala-azar, and had produced a total of 658 cases fully-treated during the stay of the teams. The number of cases re-examined, having completed treatment, was 179 (27.2%) an adequate proportion on which to base conclusions as to the results of therapy in the absence of any undue element of selection: while this was largely obviated by the method of contacting the patients, the statistics confirm this by being fairly comparable in the hsien and total cases, as shown. It will be seen that though the patients are of the same average physical type in the two series there is a difference in the gravity of their disease, many more of the severe type being included in the rechecked series, which should tend to worsen the result, but this is to some extent balanced by the fact that in the original series one severe case of cancrum oris and two cases of generalised oedema were sent straight to hospital
and so do not appear on the records, although they should properly do so. The fate of none of these cases is known, but it is likely that some may have died and so it is thought that, taking these features into consideration, the results probably represent fairly closely the true picture of the situation.

1. **Previous treatment.**

This consisted of one patient's having had 9 intramuscular injections of an unspecified anti-kala-azar drug 3 months before starting Neostam treatment, but deriving no benefit. The usual number had been needled, incised and plastered according to tradition, without benefit.

2. **Specific treatment.**

This consisted exclusively of Neostam intravenously and intramuscularly in the usual dosage, starting with a reduced amount in case of idiosyncracy. Cancrum oris was treated with full doses of sulphonamides, vitamins and mouth washes, while iron was given to the most severe cases of anaemia.

3. **Reactions.**

Some diarrhoea and vomiting did occur but not to an extent sufficient to necessitate interruption of treatment or reduction of dosage and none of the patients seemed to have been seriously inconvenienced by it. Out of 8 patients given intramuscular
Neostam, one developed an abscess which remained sterile and was incised with the evacuation of pus and slough, the patient making an uninterrupted recovery. Another two patients developed painful indurated swellings at the site of injection which did not soften but gradually disappeared within two weeks.

   a. On cancrum oris.

The details of results here are not of great value since there seems little doubt that the treatment of choice is local and parenteral penicillin; nevertheless those treated did represent a varied selection and may offer some basis of comparison with other series. Among the re-examined cases, 6 out of 7 were completely healed, while one patient's cheek had healed but a residual sinus constantly drained saliva from his mouth to the exterior: a simple plastic operation would no doubt have served to complete the cure.

Over the whole series of 3,184 patients there were 101 cases of noma: 7 of the most severe type were advised to go to hospital and may have done so, but their fate is unknown, while of the remainder there were 9 known deaths. Thus, taking the most pessimistic view, the immediate mortality lies somewhere between 9% and 16%. Fan and Scott's (34) mortality was 15%, one of Struther's
(207) 5 cases died, while Clow's (14) mortality was 64%, and Stephenson's (174) similar, 67%, but since there are so many differing factors in each series it would be unwise to draw any conclusions. For example, probably F.A.U. cases were on the average less severe than in other series, since patients were pursued to their homes, and therefore the condition was found in all stages, the early ones being relatively easily dealt with, while other workers have had to treat patients attending of their own volition, in whom the condition would surely be advanced in the majority of cases.

There was a feeling that the cases improved more quickly when given oral sulphonamides in full doses as well as specific treatment, with no particular surgical interference beyond the removal of loose sloughs. This was confirmed by some of the mission doctors of the neighbourhood who had not used sulphonamides for this purpose previously but were favourably impressed by these results: it remains therefore the best alternative where penicillin is not available, but since the latter has such a powerful and yet non-toxic action on the spirochaetes every effort should be made to use it, especially on advanced cases.

b. On septic gums.

One case of the sixteen suffering from this condition still showed slight residual sepsis,
but the others had recovered, having had only potassium permanganate washes (of dubious value) as local treatment, the improvement being due to the heightening of resistance subsequent to the use of anti-kala-azar therapy.

c. **On anaemia.**

All cases of gross anaemia had been relieved on re-examination but a minor degree existed in the majority of adult cases. Iron therapy had been quite inadequate and the effect of specific treatment in this type of patient seems to be the removal of the erythrolytic effect of the parasites (or their toxins) when he reverts eventually to his normal state of nutritional anaemia. In the case of the smaller children, however, the foreign members of the teams were puzzled by their excellent general condition which made them conspicuously fat and almost ruddy, among the children clustered around on these village visits, who had not had kala-azar. It appeared on investigation that those suffering from kala-azar were given food of extra quality and quantity, probably at the expense of other members of the family, so that they developed a state of health superior to their comrades who had not been fortunate enough to contract the disease. Questioning about whether they had put on weight invariably raised a laugh among the crowd, so obvious was the answer
and so ridiculous the inquiry.

d. On oedema and ascites.

6 cases of generalised oedema had
cleared up completely and two patients had lost the
ascites which had been quite severe at the beginning
of treatment. In the complete series there was a
known death-rate of 33% in patients with ascites,
although this probably represents the results
which might be expected in the more severe type
since clinic examinations were sometimes too hasty
to detect the smaller amounts of abdominal fluid.

The ascitic patients fall into two
significant groups which are worthy of mention—

1. The number who survived treatment
had an average of 10 injections, i.e. they
were not adversely affected by the antimony
and, although it would be unwise to generalise
from the small number followed up, yet from
this and all the information gathered about
the fate of the other cases it would seem
that they did go on to complete cure. Their
average age was 14.4 years.

2. The number who are known to have
died had an average of 5.7 injections, i.e.
they all died before the end of their courses,
and it seems reasonable to infer that their
inevitable end was hastened by the potency
of the antimony dosage. The average age here
was 10.3 years.

These two groups would suggest that if
a patient with ascites survives the course of
injections, he has a good chance of recovery, and
that the more the shock of the course can be temp-
ered the more patients will survive to go on to cure.
ALBUMINURIA AT THE END OF TREATMENT.

<table>
<thead>
<tr>
<th>Albuminuria Grade</th>
<th>Percentage of Patients</th>
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<tbody>
<tr>
<td>+</td>
<td>0.4%</td>
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<tr>
<td>++</td>
<td>0.8%</td>
</tr>
<tr>
<td>+</td>
<td>0.9%</td>
</tr>
<tr>
<td>±</td>
<td>1.1%</td>
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</tbody>
</table>

0.4% of patients showed albuminuria ++
0.8% " " " " +
0.9% " " " " ±
1.1% " " " " ±
e. On albuminuria.

Only in the relapse cases or in those where it could be due to conditions other than kala-azar was albuminuria found on a second examination. Over all cases it was the usual experience that albuminuria cleared up partly or completely during the course of injections, without any specifically renal therapy like Chaudhuri's (213) strong alkaline diuretics, those shown being the only exceptions. 1.1% of patients showed some progression of the albuminuria during treatment, but this was entirely unrelated, so far as could be discovered, to any adverse sign elsewhere. Unfortunately, none of these could be followed up on the road to recovery, and it would appear that whatever may be the effect of alkalis or other drugs, the renal condition will gradually clear up under the influence of specific leishmanicidal drugs alone.

f. On fever.

1. 165 (92%) patients had had no fever since completing treatment.

2. 7 (4%) patients complained of having experienced fever since the termination of their course, but this could be associated with causes other than kala-azar. These patients were urged to have spleen puncture to confirm this by excluding
kala-azar relapse, but they did not all respond.

In each case the weight was increased and the spleen either not palpable or greatly reduced in size.

a. No. 119. fever associated with cough for 15 days: slight bronchitis at the time of examination. Did not come for spleen puncture.

b. No. 246 - fever associated with cough and ? haemoptysis one month before examination: has chronic bronchitis. Spleen puncture showed no Leishman-Donovan bodies.

c. No. 346 - fever associated with cough for 10 days: ? primary tuberculous focus in lungs. Would not come for spleen puncture.

d. No. 510 - fever associated with intermittent cough and sputum for 2 months. According to chest signs, probably pulmonary tuberculosis in left chest. Spleen puncture showed no Leishman-Donovan bodies.

e. No. 1,161 - fever associated with chest signs of marked chronic bronchitis. Did not attend for spleen puncture.

f. No. 1,211 - fever associated with intermittent dyspnoea, cough and purulent sputum. Spleen puncture showed no Leishman-Donovan bodies.

g. No. 1,374 - fever associated with "catching cold". Cancrum oris healed, no sepsis of gums now, weight up, spleen much reduced (8 cm.) and still shrinking, according to patient. Spleen puncture showed no Leishman-Donovan bodies.

Despite the absence of spleen puncture in 3 of the cases none of them was thought to be a likely relapse, and they are, therefore, included among the cures.
3. Two cases had exhibited fever of unknown origin.

a. No. 106 - aet. 5, with splenomegaly for 1 year, had no fever currently but said he had malaria two months previously which was not relieved by quinine (given in small doses probably). He had lost some weight recently and said that his spleen, which had not diminished after treatment, enlarged when he had fever. He failed to appear for spleen puncture and bloodfilms, but his globulin precipitation (water) test had been reduced from ++ to +.

b. No. 462 - aet. 9, with splenomegaly for 2 years, said to have had fever but no chills 2 months and also 10 days before re-examination. The spleen had increased slightly with fever but the reduction following treatment had been about 9 cm. His weight had remained up even during the periods of fever. He also did not attend for spleen puncture but a "water" test showed a reduction from ++ to negative.

Neither of these cases seemed likely to be recurrent kala-azar, principally on account of their good general condition and the negative serological reaction (which would both be unusual in a relapse) and the fact that such late relapses are almost unknown: nevertheless, in the absence of exact evidence as to the nature of their fever both must be regarded as in the "suspicious" category.

4. Two cases of proved kala-azar relapse currently exhibited fever,

a. No. 204 - male, aet 13, having had splenomegaly for 2 months before treatment. The latter had been completed without mishap and he lost his pyrexia, gained weight and his spleen became impalpable. Some months
later (no accurate estimate could be elicited) he again had pyrexia and began to lose weight, while his spleen gradually enlarged till it became even larger than before. Spleen puncture showed many Leishman-Donovan bodies.

b. No. 493 - male, age 43, with splenomegaly for 1 year before treatment, lost his fever after it and had some diminution of the size of his spleen, while his weight started to increase and did not decrease thereafter. Some months later his spleen increased to its pretreatment size and he developed intermittent fever. Spleen puncture showed many Leishman-Donovan bodies.

Both these cases were noted for retreatment with Pentamidine on the next visit of the teams to this area.

g. On weight.

1. 172 (96.7%) patients were found to have increased in weight subsequent to injections, due allowance being made for the natural growth of children.

2. 4 (2.3%) patients had either lost weight steadily since having injections or had started to gain and then lost it.

a. No. 106 (vide supra) a case of possible relapse.

b. No. 204 (""") a case of proved relapse.

c. No. 346 (""") probably a case of pulmonary tuberculosis.

d. No. 510 (""") probably a case of pulmonary tuberculosis.

h. On splenomegaly.

The following changes in the position of the lower edge of the spleen had occurred since the
completion of injections.
1. Shrinkage of 4 cm............4 patients (2.2%)
2. " 6 cm............7 " (3.9%)
3. " 8 cm............8 " (4.5%)
4. " 9 cm............9 " (5.0%)
5. " 11 cm............4 " (2.2%)
6. " 13 cm............6 " (3.4%)
7. " 14 cm............2 " (1.1%)
8. Spleen no longer palpable 132 " (73.7%)
9. Size of spleen was unchanged in 2 patients (1.1%)
   a. No. 106 - a possible kala-azar relapse.
   b. No. 493 - an actual kala-azar relapse.
10. Spleen showing ultimate increase in size
    2 patients (1.1%)
   a. No. 204 - a kala-azar relapse
   b. No. 1,459 - a kala-azar relapse. Male aet. 56, having had splenomegaly for 3 years, who said he was still free of fever and that his weight had gone up since the injections but that his spleen which had decreased in size slightly following injections had been once more increasing for 3 months.
Spleen puncture showed many Leishman-Donovan bodies.

In only 2 of the 40 spleens which had diminished but were still palpable had the shrinkage process stopped at the time of re-examination: the others, according to the patients (or parents) were still slowly diminishing, this prolonged period of resolution being in accord with the experimental work of Harrison and Fulton (261) in hamsters.
It will be seen from the fore-going that none of the signs and symptoms mentioned is alone an infallible guide to relapse but that the presence of any one of them occurring months after a course of treatment should warrant a full re-investigation.

5. Deaths.

1. Due to cause other than kala-azar.

No. 202: this patient was freed from fever and the spleen became steadily smaller after the Neostam course but death occurred 3 months after treatment, due to "dysentery" in the opinion of relatives. Though quite violent intestinal symptoms may commonly attend the terminal stages of kala-azar it is unlikely to have happened in this case in the prolonged absence of high fever and splenomegaly. It would seem legitimate, therefore, not to include this as a death due to kala-azar, since it seemed to be coincidental only.

2. Due directly to kala-azar.

a. No. 642: male, aet. 5, with splenomegaly for 5 months prior to treatment. Patient died shortly after completion of injections, but it was not possible to get any information about the manner of death since no relatives were available to describe it: in the opinion of neighbours he was not improved by the treatment, and so it is proper to consider this as a therapeutic failure.

b. No. 1,405: female, aet 1, with splenomegaly for 3 months before treatment. The child was much better after injections, according to her grandfather, having no fever and the spleen becoming smaller, but 4 days after the last injection she developed high fever and her death was accompanied by convulsions. On such information it was not possible to define the precise cause of death, but it must be considered as due to kala-azar.

These 2 cases give a rate of 1.1% for the
DEATHS

No. of Patients

Age in Years.
series of 179 cases which were traced, but to this should be added the deaths which were already known to have occurred in the hsien, mostly quite soon after the end of treatment. In fact none of these had been inpatients from the area of re-examination but it was decided to apply the immediate death-rate here as well, in order to get a clear picture of the minimum results that might be expected. The latter rate was 1.5%, so that the total known death rate is 2.6%.

The known death-rate for the entire campaign, (i.e. deaths actually reported to the teams) was also 1.5%, the average age of the patients being 8.4 years. This latter figure is not of any particular significance since the range was from 1-35 years, but reference to the diagram will show that, excluding 3 patients, the age group was 1-15 years and the average age 6.4 years, as opposed to an average for all cases of 11.4 years, thus showing that the young child should have special care if he is to survive. The sex ratio was of interest, being male: female = 52:48 which, considering the overall sex ratio of 66:34, indicates a greater susceptibility in females: this may well be due, at least in part, to the greater care and attention bestowed on Chinese males, resulting in the latter's
better nutrition — a phenomenon which was evident in and out of clinics. The average duration of illness, 1 year, was not significantly above the general average of 11.2 months, which seemed at first surprising, since the greatest mortality would have been expected in the most advanced cases, but consideration of the cause of these deaths shows that the presence of complications is even more dangerous than simple severity or mere chronicity of infection.

Thus the fatal cases for the series, so far as they were known, could be placed in the following broad categories:

1. due to associated "dysentery"...........7%

   The diagnosis here was made by relatives so that it is not capable of confirmation and may have been either bacillary dysentery or the terminal stages of kala-azar: even if the former, they might not have happened had the patients not been weakened by the kala-azar.

2. Due to necrosis following extravenuous injections........7%

3. Associated with ascites alone...........7%

4. Associated with generalised oedema, including ascites........19%

5. Complicated by cancrum oris.............21%

6. Considered to have died in the terminal stages of kala-azar........39%

   This last is a very unsatisfactory category, since most of the cases in it were described
in their final stages by relatives or friends and no other classification seemed to be appropriate, but had these cases been admitted to hospital, apart from probably saving some lives, the exact type of death could have been observed and this category reclassified into the pneumonias, dysenteries, renal failure, cardiac failure, etc., which would occur. Thus in Scovel's (1) series only 10% of his deaths were in uncomplicated cases but "practically all" his severely ill patients were admitted to hospital and therefore could be observed and sorted out as well as being given adequate treatment.

It will be seen from these results that a considerable reduction in the death rate would be possible, given certain circumstances. A small number of deaths due to extravenuous injection is probably inevitable when personnel changes fairly frequently, where intelligent help in holding small children steady (a major, if not always appreciated factor) is not available, and where in winter the temperatures in the clinics are so low that sensation in the fingers is minimal.

A vigorous investigation of all patients for bacillary dysentery could be carried out if sulphonamides for treatment were available, but since this was not so, stool examination was super-
fluorous, and undoubtedly some of the deaths occurred in patients where the exhausting effect of the dysenteric process was sufficient to turn the tide of the disease in the wrong direction. Given adequate supplies of drugs too, some investigation of the more serious cases of amoebic dysentery might have been made, in an effort to give these patients all the assistance at the critical time in their resistance, both to the disease and to the shock of treatment.

As previously mentioned, the whole outlook for cancrum oris would seem to have changed with the advent of penicillin, and future workers should expect a considerably diminished mortality in such cases following the use of appropriate quantities of a preparation so lethal to spirochaetes, even in the absence of hospital facilities, i.e. mobile clinics could dispense treatment of considerable value.

Nothing short of the ability to institute full hospital care is likely to affect greatly the results of treating cases showing ascites and generalised oedema, although a less intensive antimonial regime might save a few cases who react fatally to the usual dose of these drugs, but would slow down any campaign, with the loss of many lives in those thereby left untreated.
In the last category, those dying in the terminal stages of kala-azar, would undoubtedly be patients who properly should have been classified otherwise, and for whom something might have been done even in field clinics, but since many of these are patients who, for a multitude of reasons (fear, ignorance, parental selfishness, economic necessity, etc.) go off and die, pathetically, in an atmosphere of fatalism in their homes, no miracle of science will save them until they can be induced to regard, accept and use modern medicine to some extent as Western minds do.

Summing up the results of using Neostam in this manner, it is assumed that the patients in section F.2. above were febrile from causes other than kala-azar, that those in section F.3. may be potential relapses and that No. 202 was a non-kala-azar death, thus getting the following:

- **Number of patients cured**........172(94.6%)
- **Doubtful - possibility of relapse**..2(1.1%)
- **Proved relapse**.........................3(1.7%)
- **Deaths (actual and expected)**
  
  2 + expected 3

  (2.6%)
USE OF PENTAMIDINE.

This work was done in Chung-mou hsien, in the southern part where the soil is very sandy and the population is sparse but has a considerable kala-azar infection. Patients age 12 and under were treated with intra-muscular Pentamidine, while others were given intravenous Neostam. In all, 134 cases were injected with Pentamidine, but of these only 80 were followed up for re-examination. Cases were not selected from any clinical viewpoint but were those living in the villages accessible to the examining team: only those who were not at home when the visit was paid were omitted, the last being a slight departure from the practice when following up the previous Neostam series, where (in the few cases concerned) a firm statement by friends or relatives that a patient had no fever, spleen had decreased in size or vanished and weight had markedly increased after an average period of over 8 months, was felt to be evidence sufficient to stamp him as a cure. In this present series, however, the average period elapsing since completion of treatment was only 34 days, so that anything less than a careful personal examination could not be accepted.

The usual questions were asked and the usual special points were investigated by physical
## PATIENTS IN CHUNG-MOU HSIEN.

<table>
<thead>
<tr>
<th></th>
<th>Total District Cases</th>
<th>Cases Re-examined</th>
<th>Entire Series</th>
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<tbody>
<tr>
<td>Average age</td>
<td>9.5 yr.</td>
<td>6.5 yr.</td>
<td>11.4 yr.</td>
</tr>
<tr>
<td>Average duration of illness</td>
<td>1 yr. 2 m.</td>
<td>1 yr. 2 m.</td>
<td>11.2 m.</td>
</tr>
<tr>
<td>Cancrum Oris</td>
<td>3.8%</td>
<td>2.5%</td>
<td>4.2%</td>
</tr>
<tr>
<td>Generalised Oedema</td>
<td>4.4%</td>
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</tr>
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<td>Septic gums</td>
<td>9%</td>
<td>13.8%</td>
<td>6.7%</td>
</tr>
<tr>
<td>Anaemia</td>
<td>13.4%</td>
<td>18.8%</td>
<td>8.8%</td>
</tr>
</tbody>
</table>
examination. Certain features in this series are similar to the picture of the patients generally, and some are different, mainly due to the selected age group, since the conditions (geographic and economic) were not at variance with those in other areas, except for the combination of the very sandy nature of the country and the cold weather which prevailed during the treatment visit. The relevant figures are shown, demonstrating that, while the cases followed up were less affected by severe complications but had more than their share of the general complaints, there was no selection according to sex or chronicity of disease.

No patient was sent to hospital from this area, for the adequate reason that there was none nearer than 40 miles, a gruelling journey over sandhills. For the same reason no patient had had any previous treatment.

a. Specific treatment.

All injections were given intramuscularly, daily, in the buttocks or thighs alternately, starting with a small dose in case of idiosyncracy: further experience suggested that this was probably quite unnecessary.

Cancrum oris was treated with the usual sulphonamide regime, but anaemia was even less
adequately dealt with than in the Neostam series, since supplies of iron were running out and had not yet been replaced.

b. Reactions.

No case seemed to experience any immediate adverse effect from the injections, and none of the 27.5% of patients who had some degree of diarrhoea and vomiting was sufficiently upset to have the treatment amended or prolonged. The local reactions have already been quoted, and although having an unfortunate tendency to develop late, can probably be reduced in number by putting the drug into thighs only and concentrating on immediate massage.


1. On anaemia.

All cases of gross anaemia were markedly improved, although some patients had a minor degree still present: the improvement was certainly due to the Pentamidine rather than the meagre iron supply available. As in the Neostam cases, the average general nutrition had improved tremendously even in just over one month, the effect of the drug treatment being reinforced by the efforts on the part of parents to supply extra food to the sick member of the family, even after a cure had been definitely established. Some of the younger patients were scarcely recognisable despite the short interval since the conclusion of treatment.
2. On septic gums.

One case, originally with gingivitis, still had a single patch of sepsis on his gums but this was said to be improving. All the other cases had lost their oral sepsis as part of the general clinical improvement.

3. On cancrum oris.

Two cases only were included in this series: the first had improved after the injections, sulphadiazine and local antisepsis and was healing satisfactorily, but his face was still tender. To complicate matters, and almost surely slowing down the process of resolution this patient had developed bilateral oedema since treatment, so that his general condition was poor although there was no suspicion that his kala-azar had not been cured. The other case had been completely relieved of his noma although his gums still showed some sepsis.

4. On generalised oedema.

This had disappeared from the two cases concerned. It should be remembered that in view of the comparatively short interval since the end of their courses and the fact that an intramuscular drug might be expected to have a slower action than one given intravenously, the above cases are not to be compared in this respect too closely with those treated with Neostam.
5. On fever.

a. 62 patients had had no fever since the conclusion of therapy.

b. 9 patients were reported to have had fever which could be ascribed to causes other than kala-azar, viz.

No. 11 - had had associated cough for 10 days, probably due to bronchitis.

No. 25 - had associated bilateral otorrhoea due to otitis media.

No. 77 - had fever associated with cervical adenitis, probably due to drainage from a septic mouth for 4 days.

No. 78 - had fever associated with a "cold" for 7 days.

No. 83 - had fever associated with a cough for the previous week.

No. 124 - had fever associated with cough for the previous week.

No. 151 - had fever associated with diarrhoea, probably due to bacillary dysentery, for 3 days.

No. 153 - had fever associated with cough for 6 days.

No. 210 - had fever associated with a "cold" for 3 days.

In all these cases it was felt that the associated condition had been sufficient to account for such fever as may have been present according to the patient's story. It seemed unlikely that any of it could have been due to a relapse of kala-azar, since in every case the spleen had decreased in size and the weight had increased, except in case No. 25 whose general condition was poor owing to his
otitis media, and No. 210 who had a post-injection abscess of his buttock. It should be emphasised that of these 9 patients only No. 25 actually had fever at the time of re-examination.

c. 2 patients were reported to have had fever for which no cause could be discovered.

No. 91 — was alleged to have had fever 27 days after the last injection, for no known reason. His spleen had decreased 6 cm. and was still diminishing, while his weight, which was said to be I.S.Q. seemed to have increased (there was no opportunity of reweighing him) and he certainly looked well-nourished. There was no fever at the time of examination.

No. 111 — was reported to have had 4 days fever 28 days after the last injection, with no apparent cause. The spleen had decreased 4 cm. and was still getting smaller, while the cancrum oris which had been present for 10 days before the beginning of injections had healed completely, although his gums still showed some sepsis. His weight, which was said by the parents to be I.S.Q. seemed in fact to have increased materially. There was no fever at the time of this examination.

Having regard to the inability of the average Chinese parent to give precise clinical information, principally due to his lack of understanding of the questions or their importance, observation of the above two patients did not lead to any feeling that they were in danger of relapse, or that the fever (if it had existed) was of significance.
6. On Weight.
   a. Weight much increased.............49(61.3%)
   b. Weight increased..................16(20%)
   c. Weight unchanged..................4 (5%)
   d. Weight decreased..................4 (5%)

   Of the 81.3% whose weight had increased there is little to say beyond that they were progressing normally in other respects. Of the 4 cases whose weight was said to be unchanged, 2 (nos. 91 and 111) have already been considered (vide supra) and 2 had had no fever after the course of injections, were said to have good appetites and appeared to be in good health, having spleens that had decreased 4 cm. and 6 cm. respectively. Of those whose weight was stated to have decreased, one was No. 25 with bilateral otitis media and cancrum oris, while the other three were cases with abscesses following the intramuscular injections, which were ripe for incision and drainage but had not yet had this carried out.

7. On Splenomegaly.
   a. Shrinkage of 2 cm..................13(16.3%)
   b. Shrinkage of 4 cm..................22(27.5%)
   c. Shrinkage of 6 cm..................17(21.3%)
   d. Shrinkage of 8 cm..................14(17.5%)
   e. Shrinkage of 9 cm..................3 (3.8%)
   f. Spleen no longer palpable.........4 (5%)
The few cases whose spleens were no longer palpable had had splenomegaly for 6 months, 7 months, 6 months and 3 years, respectively. The above figures, of course, give only a rough indication of the reduction in size of the spleen which shrinks in many unmeasurable directions. In this connection, Napier and Sen Gupta (237) describing their intravenous Pentamidine series, remark that after about a fortnight from the commencement of treatment a spleen, previously enlarged to 3"-4" below the costal margin, became quite replaceable under the ribs.

It will be seen from the foregoing description of the surviving patients that, while they had not all made uninterrupted progress, it was significant that all had experienced diminution in the size of the spleen, which alone makes it likely that so far there had been no relapse, and is supported by the fact that all the other unfavourable signs could be accounted for by extra-kala-azar factors.

d. Deaths.

1. Male, aet. 3, who died 2 days after the last injection, had had splenomegaly for 1 month before coming to the clinic. Fever
stopped after 2 injections and the spleen started to decrease in size, while his general health seemed to improve until 2 days before death when he refused to eat, did not sleep and died with convulsions. He did not seem to have any pain, cough, vomiting or diarrhoea, and no local reaction. His parent knew of no other disease he could have had.

2. Male, aet. 11, died 3 days after the last injection: he had had splenomegaly for more than 1 year. There was some fever accompanying his last two injections, but no more after that and he felt generally better, appetite improving, slight increase in weight, while the spleen was no longer palpable (i.e. parents could no longer feel it). Subsequent to injections both lower limbs were swollen and painful, but he could walk. He had no headache, vomiting, paralysis, dysuria or cough but black stools 2-3 times daily for 2 days before death. Parents thought he died of some disease other than kala-azar, but cannot describe the actual death.

3. Female, aet. 6, died 10 days after the last injection: she had had splenomegaly for 6 months and fever continued for 3 days after the end of the injections. The spleen did not decrease in size and her general condition seemed to deteriorate after the 5th injection, although she had no dysuria, vomiting, headache, or paralysis. Appetite failed then too, and she developed cough and black stools for the next 7 days. Death was accompanied by facial oedema and ? cyanosis of lips. L. thigh was slightly swollen.

4. Female, aet. 3, who died 18 days after the conclusion of injections: she had had splenomegaly for more than one year. Fever continued till death (although the spleen became much smaller) appetite did not return, and the weight remained I.S.Q. She had no vomiting, but some diarrhoea after the last injection, no dysuria or paralysis but general oedema for 4 days before death, which was accompanied by
convulsions. There was no local reaction and her parents knew of no other disease present, except a cough which she had had for one year.

5. Male, aet. 6, who died 18 days after the last injection, having had splenomegaly for over one year. He was generally improved after injections and played games in his usual fashion till the day before death. Spleen had decreased slightly, appetite was a little improved but he seemed still to be losing weight. There was no pain, vomiting, diarrhoea, headache, paralysis or cough, but he developed high fever on the day before death. His parents said he had no local reaction, and knew of the presence of no other disease which might be implicated.

6. Male, aet. 9, who died approximately 3 weeks after the cessation of injections, having had splenomegaly for 3 years. He had slight fever until death but the spleen had almost disappeared (i.e. in the parents' opinion). His appetite did not improve and weight remained I.S.C., but he had no headache, paralysis, vomiting, diarrhoea or cough. He did not pass much urine nor did he drink much, but developed facial oedema with epistaxis during the last 4 days of life. He had no local reaction and no concurrent disease, so far as his parents knew.

7. Male, aet. 4, who died 26 days subsequent to the end of injections' course, having had splenomegaly for one year. His fever disappeared after the injections, spleen became impalpable 6 days later, and child appeared better generally until 5 days after the injections when his left thigh began to swell, gradually getting worse and discharging pus before death. No headache, no vomiting, slight diarrhoea, no paralysis, poor appetite, wasting, no dysuria but facial oedema and ? cyanosis just prior to death.

Since an investigation is almost entirely dependent on these vague and possibly misleading
descriptions for assessment of the various causes of death, it would be unwise to attempt to draw any but the most general conclusions. Some of the cases were in quite good general health when treatment started, and all seemed to be improved at the end of the injection courses: it may be therefore that some died of intercurrent disease, but without proof that flare-up of the latter was not due to the patient's lowered resistance as a direct consequence of kala-azar or the temporary reaction to treatment, these deaths must be put down as having resulted directly or indirectly from kala-azar or its treatment with Pentamidine.

It is still, however, legitimate to review the possibilities with regard to future improvement in results: perhaps the only confident statement to be made is that No. 7 appears to have been directly due to the necrosis following an injection, and might have been saved with suitable surgical attention to the thigh. Of the others, one might hazard an opinion that No. 1 and No. 5 were due to the Herxheimer type of therapeutic paradox, where the sudden death of so many organisms is thought to result in the mass liberation of toxin and consequent serious reactions: No. 2 and No. 6 seem most likely to have been due to the direct toxicity of the drug, while Nos. 3 and 4 suggest
the type of death sometimes seen subsequent to the treatment of an advanced case with Neostam, although the end was delayed longer than it is wont to be with the latter drug. Could patients who have not immediately improved after Pentamidine therapy be observed with a view to the clear definition of their reactions, it would no doubt be possible to allocate them to precise categories, with equally precise attempts at relief, but this is not possible in field work of the present type.

Summing up the impressions gained of the use of the drug in this particular way, stress should be laid on its cheapness, ease of administration and transport, and even in this short observation it is clear that non-fatal reactions are not of a serious nature: the diarrhoea and vomiting may be discounted, while the abscesses are easily dealt with in comparison with those following extra-venous or intramuscular injections of Neostam, being well localised and therefore much less distressing to the patients. On the other hand the mortality of the present series is higher than with Neostam, and many more cases would require to be treated to confirm or disprove this as a constant feature of the compound before any deviation from the present dosage should be undertaken in order to reduce the
mortality, since such a measure might well reduce the cure-rate as well. In this connection, however, it is interesting to observe that in the case of five defaulters who had an average of 50% of required treatment, none complained of fever following injections, 2 had "weight much up", 2 "weight up" and one "weight I.S.Q.". In 4 cases the splenomegaly had been reduced and in one case was unchanged. In one case cancrum oris was improving, and the general condition of all of them had benefitted. It may therefore be that a slight decrease in the intensity of treatment is worthy of trial, while bearing in mind that the improved cure rate in the present series, even though subject to confirmation later, may legitimately be claimed as due to the individual dose being higher than in previous series of other workers.

It was not possible to perform spleen puncture on more than a few of the cases re-examined, but no examination revealed Leishman-Donovan bodies and clinical evidence, as detailed above, suggests that no patient had relapsed since treatment and that, apart from intercurrent infection which might delay matters, all the surviving patients were on the way to recovery. This would make the results of treatment, after 5 weeks, as follows;
Presumed free of infection........73 patients (91.3%)
Relapses.........................None
Deaths.............................7 patients (8.7%)

Before drawing conclusions from these figures as to the value of Pentamidine it would be necessary to examine the cases 6 months after treatment as a final check on relapses, although the progress of those described as "free from infection" had been so steady, and their state after 5 weeks so nearly that of the patients who could be pronounced "cured" 8 months after Neostam, that it is difficult to imagine that any substantial number would relapse.

A preliminary report on the condition of 20 patients at the conclusion of treatment with intramuscular Pentamidine is given by Ghosal and Sinha (258). The dosage, as in the F.A.U. series, was that now advised by the manufacturers, i.e., 4-5 mg. per kg. daily in 10 doses, and subsequently fever disappeared, splenomegaly receded, weight usually increased, and general well-being improved. No general reaction was experienced in any case but local reactions are described as "quite common". As with the F.A.U. series, time will be the best judge of the ultimate results of this method of treatment.

It is felt that these preliminary results are sufficiently encouraging to make this drug the rival of the antimonials in efficiency and practicability for this type of work, and possibly as experience with other dosage schemes grows, the drug of choice.
### PATIENTS IN CHUNG-MOU HSIEN.

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<tr>
<th></th>
<th>Total District Cases</th>
<th>Neostam Cases</th>
<th>Pentamidine Cases</th>
<th>Entire Series</th>
</tr>
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<td><strong>Male: Female</strong></td>
<td>68:32</td>
<td>75:25</td>
<td>69:31</td>
<td>66:34</td>
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<td>15 yr.</td>
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<td>11.4 yr.</td>
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<td><strong>Average duration of illness</strong></td>
<td>14 m.</td>
<td>18 m.</td>
<td>14 m.</td>
<td>11.2 m.</td>
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<td><strong>Cancrum Oros</strong></td>
<td>3.8%</td>
<td>6.3%</td>
<td>2.5%</td>
<td>4.2%</td>
</tr>
<tr>
<td><strong>Generalised Oedema</strong></td>
<td>3.9%</td>
<td>4.4%</td>
<td>6.3%</td>
<td>2.5%</td>
</tr>
<tr>
<td><strong>Septic gums</strong></td>
<td>6.7%</td>
<td>9%</td>
<td>15.6%</td>
<td>9%</td>
</tr>
<tr>
<td><strong>Anaemia</strong></td>
<td>8.8%</td>
<td>13.4%</td>
<td>9.4%</td>
<td>8.8%</td>
</tr>
</tbody>
</table>
SECOND NEOSTAM SERIES.

For comparison with the above Pentamidine results are the results of the re-investigations of 32 patients treated with Neostam at the same time, and re-examined along with the cases of the former series. The main difference is that the antimony series was confined to patients above 12 years of age, but was otherwise unselected either at the time of treatment or of re-examination. Other details were as shown.

From the table it will be seen that these Neostam cases are of a somewhat more severe type than the comparable Pentamidine series. None had had any previous treatment and they were all dealt with in the orthodox manner as previously described. There were no local reactions, all injections being given intravenously, and general reactions were moderate to slight.

A. SPECIFIC EFFECTS OF THERAPY.
   1. On Cancrum Oris.

   One case, where the lesion had been present for 15 days before treatment, had cleared up completely, while the other, present for one year, was healing, but still tender: otherwise both cases were well.

   2. On Septic Gums.

   Of the five cases, two had cleared up, two showed slight sepsis still, while one was
unchanged, this being a patient (No.135) with advanced pulmonary tuberculosis and extreme cachexia.


All three cases of gross anaemia were considerably improved.

4. On Oedema.

In the 2 cases of generalised oedema the condition was no longer evident on re-examination.

5. On Fever.

a. No fever since completing injections.......25 patients

b. Fever due to causes other than kala-azar..4 patients

1. No. 40 - had fever associated with mumps for the previous 4 days.

2. No. 45 - had fever associated with malaria for 8 days: cured by Chinese drugs.

3. No. 135 - had fever associated with advanced pulmonary tuberculosis, principally affecting his R. lung.

4. No. 186 - had fever associated with renal failure.

The first 2 cases showed no evidence of relapse, and the weight in both cases was up, while their splenomegaly was much reduced. No. 135 was seriously ill, while No. 186 was moribund and will be referred to later.

c. Fever of unknown origin.........................2 patients.

1. No. 33 was said to have had fever for 3 days, 2 weeks after the end of injections but was afebrile on re-examination,
weight, being much increased, spleen much reduced and still decreasing. Spleen puncture showed no Leishman-Donovan bodies.

2. No. 50 was said to have had fever for the 10 days preceding re-examination but was afebrile on investigation, and spleen puncture revealed no parasites. Weight was increased and splenomegaly much reduced.

None of the above cases suggested relapse since all their unfavourable signs or symptoms could either be explained on non-kala-azar lines or did not seem of much consequence.

6. On Weight.
   a. Patients showing much increase in weight...17(53.1%)
   b. Patients showing moderate increase in weight..12(37.5%)
   c. Patients whose weight had decreased..........2 (6.3%)

   The continued loss of weight is easily explained in the 2 patients concerned, who are the cases of pulmonary tuberculosis (No. 135) and probable renal failure (No. 186).

7. On Splenomegaly.
   a. No diminution since injection....................1(3.1%)
   b. Diminution of 2 cm. since completing injections..2(6.3%)
   c. "  4 cm. " " " 11(34.4%)
   d. "  6 cm. " " " 8(24.4%)
   e. "  8 cm. " " " 7(21.9%)
   f. Spleen no longer palpable.......................2(6.3%)

   The patient whose spleen showed no change was No. 135, the tuberculous case: those whose spleens were no longer palpable had suffered from kala-azar for 6 and 7 months respectively.
B. DEATHS.

1. No. 7 - Male, aet. 28, with splenomegaly for 2 years, was in very poor general condition when treatment was started. He had had irregular fever for 2 years with accompanying loss of weight, ulceration of one foot, back and chest, none of which sites showed any Leishman-Donovan bodies and may have been of syphilitic origin. He had no reaction to treatment except diarrhoea twice after the 8th injection, but his condition began to deteriorate from that time and he died 2 days later.

2. No. 186 - Female, aet. 17, with 3 years splenomegaly was almost comatose when examined again, with high fever, pulse 120 b.p.m. and bounding, B.P. increased, oedema of face and neck. She was said to have had generalised body pains, more especially in her eyes, a few days after the completion of injections and retired to bed where she developed gradually increasing headache, dyspnoea, loss of appetite but no vomiting or diarrhoea. Her face did not start to swell until 6 days before re-examination (24 days after last injection) and she had no dyspnoea or reduction in amount of urine passed. Albuminuria had been present throughout treatment in moderate amount. She refused to go to hospital (and indeed almost surely the journey would have been too much for her) so apart from general advice no relief could be given, and since she almost certainly died, her case has been included in this section.

Thus, since none of the patients gave any evidence of relapse, the results of this short series would be.

Patients presumed free of infection........30(93.7%)
Relapses.........................................................None
Deaths (de facto or impending).................2 (6.3%)

These results are not significantly different from those of the comparable Pentamidine series or from those accepted as final in the larger Neostam series.
REVIEW OF RESULTS.

Results of treatment with the various recognised anti-kala-azar drugs in the hands of numerous workers have already been quoted, and include cure-rates ranging from Clow's (15) probable 84% to Chung et al.'s (260) probable 95%, using modern antimonials in China: rates in India are comparable, while they are distinctly lower in the Sudan. Reports of the use of the newer diamidine compounds suffer from the disadvantage of an incompletely standardised dosage, and range from Sen Gupta's (238) 60% of cures with Pentamidine to the same author's (242) 98% of cures with Stilbamide, both series being in India. It is well to keep in mind when considering these results that they are frequently founded on rather unrepresentative samples of the population followed-up, and almost always refer to patients dealt with either as in-patients of hospitals or in clinics backed by hospital facilities to be used if necessary, while in most cases treatment would be given by a fully-trained staff.

Having regard to these points it is suggested that the present figures will stand comparison with any others, especially as they were produced in circumstances the reverse of those just
cited, and have the additional advantage of satisfactorily aiding solution of the problem to which they were directed, by representing the results of treatment of a high proportion of all kala-azar cases in the district: with a civil war going on all around, 10% of defaulters is to be considered an understandable number, and one which can be remedied on subsequent visits.

The results lend no support to statements like that of Struthers (207) that the Chinese patient does not tolerate optimum doses of the antimonials, or that of Kirk and Sati (4) (quoting Schmidt and Peters, who later seem to incline to the grouping of Chinese and Indian varieties) to the effect that Chinese patients seem particularly sensitive to antimony so that toxic reactions are common, the death rate is high and prolonged hospitalisation is necessary for cure.

Especially to be refuted is their opinion that "it has proved difficult to adopt a standard scheme of treatment as in India", for if this were true there would be no hope of ever getting rid of the disease, since therapy which requires a high degree of individualisation is unlikely to be practiced en masse in China, under any circumstances which can be foreseen. Fortunately too, in China (and certainly in Honan) there seems to be no
hint of the development by local strains of Leishmania of that antimony resistance to which Napier et al. (235) refer as causing a steady deterioration in results during recent years: even though this should occur it is now more than likely, as Lowe (201) says, that those few cases which do not respond to pentavalent antimony can be treated with one of the diamidines, which appear to be effective in the cases where antimony is not.
The only true sequelae encountered were the results of complications or misadventures, since the orthodoxly treated case is either cured, relapses or dies, there being in kala-azar no subacute or chronic state lasting longer than about three years, nothing comparable to the wide range of sequelae possible in diseases like tuberculosis or syphilis.

A small number of patients in the F.A.U. series will be able to exhibit scars at the elbow where Neostam went astray, a few scars will be seen in the neck to mark similar errors of technique, while not a few buttocks and thighs are reminders of the unsuitability of Neostam for intramuscular injection, and also of the fact that intramuscular Pentamidine is not an innocuous weapon.

Following treatment of cancrum oris, some patients died, most recovered and, of the latter followed-up, the majority healed without too much contraction of their scars, although not all of them had perfect cosmetic results. In only one was there a really unsatisfactory repair, where a noma had perforated before coming to the clinic with the loss of much buccal tissue, so that when healing occurred a sinus was left which drained saliva constantly. The patient, a cheerful little boy, was quite undisturbed by this, but to obviate the detriment
which he would experience as he grew older it was impressed on his parents that a simple plastic repair would do what was necessary.

Strictly speaking, in this series which included only two visits to any of the districts of the area, the problem of relapse was a sequela of the disease, but when the present phase of the campaign was ended this was represented by only the 3 cases in Yang-Wu hsien which, from the accounts given of their experience subsequent to treatment, are relapses and not cases of drug-resistance, and (although time will tell) no special difficulty is expected in their re-treatment since there is the choice of diamidine compounds should they prove at all unresponsive to more Neostam.

For the future also is an investigation into the age and sex of relapsing cases, in an endeavour to find out whether it is only coincidence that two of the present three cases were among the oldest patients dealt with.
CONCLUSIONS.

The stimulus for this work, medically speaking, arose from the fact that in this part of China nothing was being done which was calculated to reduce the ravages of kala-azar, although in numerous centres traditional treatment was being dispensed in a scientifically impeccable manner, and had been for 20 years past. It was thus an inescapable conclusion that the need for this region was a plan designed to deal with the facts of the situation and not with any preconceived notions which might be applicable to other circumstances. It is only too easy to fall into this error by imposing on a large, poor and ignorant Chinese community, orthodox and undiluted Western medicine which, not unnaturally, fails to have the effect desired.

This is not in any way meant to minimise the difficulties which will certainly beset the introduction of any organised medicine in such a backward community, but rather to emphasise that the overcoming of such difficulties is possible only to those who appreciate their existence, although even then not probable. To be faced squarely are these basic facts:-
1. All cases must be reached and treated, or the disease will continue to flourish.

2. Many patients cannot, or will not travel more than a very short distance to a clinic. To the Western mind it is almost incredible that Napier (3) can report from an area under his care that "though it was realised by the inhabitants that there was a considerable amount of this disease in the district the very large majority were not making an attempt to attend any of the Calcutta dispensaries, where suitable treatment was available". These people were suffering from a condition which has a mortality of around 90% and were only 5 miles from almost certain cure in Calcutta.

3. Most patients are unable to pay enough to cover even the bare cost of the drugs used.

4. Prophylactic work does not require many highly skilled workers, but requires them to be employed full-time and continuously.

Distinctly subordinate, though still important considerations are:

A. The fewer reactions produced by treatment the more popular it will be: similarly, short courses appeal to patients more than long ones.

B. The more effective the drugs used the greater will be their advertisement value, but even
so, patients are fundamentally reluctant to attend, and do not understand the principles of treatment so no method of persuasion should be neglected.

C. If it is accepted (as the present work attempts to show) that the results with modern drugs are little different in the well-equipped hospitals and in the more primitive field clinics, then science does not demand more than can be done in the latter, but it should be remembered that the slight difference represents life instead of death to a few complicated cases, greater comfort to some advanced cases, and permanent benefit to many from such measures as plastic surgery, treatment of co-incidental disease and generally a greater possibility of some individualised therapy.

D. Once a clear picture of the results has been obtained there is no need for any further follow-up of cases, while continuing to use the same drugs in the same area in the same way, since there is no reason to suppose that these figures would change materially.

It is submitted therefore, that although the F.A.U. plan is imperfect in many ways, it offers a rational scheme of attack designed to deal with the specific problem presented, by the adoption of all measures which, by the experience of others or
by personal experiment have been found especially suited to the circumstances of kala-azar in N. Honan.

To reiterate the main features:-

1. The use of fully qualified medical staff is minimal (in keeping with the difficulties of their recruitment) yet sufficient supervision is exercised to obviate any irremediable mistakes in diagnosis or treatment of the disease, its complications or the reactions arising therefrom.

2. Previously unskilled talent, of Chinese "middle-school" level (of which there is plenty) may quickly be trained in dogmatic, standardised procedures of diagnosis and treatment which (let it be again stressed) are quite adequate for the cure of that type of patient who forms the bulk of the work in any campaign.

3. When, and only when these masses have been dealt with, comes the period when diagnosis becomes less easy because patients are younger and in the earlier stages of the disease, or have been referred for diagnosis from former visits when no conclusion was reached. Treatment then offers greater opportunities for the skilled wielding of therapeutic weapons, since not only does the management of the smaller children present special problems but at this phase there will arise the necessity of dealing with a miscellany of patients, including relapses from previous visits, the sequelae
of complications such as ascites and the facial distortions of cancrum oris, the insufficiently treated defaulters from previous visits, and the possibility of giving second courses to any patients who might be considered worthy of them. Fortunately it is just at this time that the volume of the clinic's work will have slackened greatly, and there should be ample time and opportunity for a more exact and leisurely approach to this second stage of the campaign.

4. The running costs of such a project are not high in comparison with the results achieved. In a properly integrated scheme, salaries and transport (which need not be petrol-driven for long-term work) might be provided by the Chinese Government, the day-to-day cost of board and lodging by the local authorities (who gain "face" by this) while apparatus and drugs are the most easily obtained items in the programme, since F.A.U. experience has been that the large organisations, like the Red Cross of various countries, and smaller charitable groups all appreciate both the humanitarian appeal and medical efficiency of this solution to a problem which may thereby become non-recurring.

5. There is ample precedent for the success of such a scheme, although never carried to its
logical conclusion in a large area, especially
as there seems no reason to suppose that Chinese
cure-rates should be in any way inferior to those
obtained in India, now that it is no longer
necessary to rely solely on various antimony
compounds and that treatment of the grave cancrum
oris has been revolutionised by the discovery of
penicillin. If this can be accomplished in one
area there seems every reason to expect that it
can be repeated in other contiguous areas, to
form an ever-widening region where at least one
of the terrors of the East is absent.
SUMMARY.

1. A serious and mounting problem due to kala-azar exists in China, and is probably as active in N. Honan as in any other area.

2. In the face of traditional lines of therapy the disease continues to increase in amount and to spread geographically.

3. It is suggested that the only prophylactic approach with a hope of success is that designed to treat all cases of the condition, and destroy all infected dogs.

4. The *sine qua non* is that treatment is taken to the patient, and is given either free or at a very low, uncommercial rate.

5. The type of disease encountered in this region is not substantially different from the Indian variety, except for the welcome absence of post-treatment dermal leishmaniasis.

6. It is submitted that a simplified and standardised method of diagnosis and treatment, using a minimum of fully-trained staff, is eminently suited to the problem.

7. Statistics are advanced to show that, in terms of the entire infected population of the limited area, preliminary results obtained were comparable
with any others anywhere, and that the prospects for the completion of the work in future visits are encouraging.
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