5 days. Treatment was omitted for the next 3 days, and a subsequent treatment of atebrin alone for 3 days given, the dose being 0.1 gramme, t.d.s. The blood is examined daily during this course. Blood is examined on completion of the second short treatment. The patient is then put on quinine gr. x daily at night for 10 days. At the end of the period, the blood is re-examined and, if negative, atebrin alone, 0.1 g., t.d.s., is given for 3 days. This completes the treatment. So far none of the cases so treated has relapsed. The treatment is designed to anticipate the possibility of relapse about the beginning of the third week after the initial attack.

Atebrin musonate

Only 5 cases were treated in this series with a relapse rate of 20 per cent. Two injections only were used on consecutive days. Some modification of this treatment would seem to be essential and more extensive trial is necessary before any conclusions can be drawn.

Summary

Atebrin-plasmochin in combined tablet and in dragées and atebrin musonate in the various doses were tried in a series of 106 cases. The relapse rate was 11.32 per cent. Excluding the atebrin musonate series in which one out of five cases relapsed and the atebrin only series in which the relapse rate was 15.38 per cent, the relapse rate with atebrin-plasmochin combinations was 9.33 per cent.

The small difference in the dose of plasmochin in the combined tablets or dragées had no appreciable influence on the results.

Toxic symptoms in this series were limited to cases which showed excess or deficiency of gastric hydrochloric acid or pathological changes in the gall-bladder. No toxic symptoms were noted in normally healthy patients. The percentage of cases showing toxic symptoms was 4.7. Atebrin-plasmochin in dragées form was successfully exhibited where the ordinary tablets caused epigastric distress. This bears out the relation of the gastric pH to the production of toxic symptoms.

A scheme for the treatment of relapse is outlined.

Conclusions

Atebrin 0.1 gramme with plasmochin 0.0033 or 0.005 gramme given in dragées is the best treatment for malaria at present available, with the lowest relapse rate.

Atebrin musonate requires further trial before a definite conclusion can be arrived at. The dosage is probably insufficient.

Atebrin-plasmochin dragées are least likely to cause symptoms of intolerance, even in the presence of gastric or biliary disease. No relapses occurred in the series, in which dragées were used.

(Continued at foot of next column)

MASS TREATMENT WITH INJECTABLE ATEBRIN

By A. T. W. SIMEONS, M.D. (Heidelberg)
Bombay

IN the course of experiments conducted at the Colombo General Hospital during the malaria epidemic in Ceylon with atebrin-dimethylsulphonate (musonate) a method was elaborated by which it became possible to effectively treat severe cases of malaria with two injections given at an interval of 24 hours without any other additional treatment (Blaze and Simeons, 1935).

The results obtained in these experiments showed that it is possible to exercise a very rapid and lasting effect on a malaria infection by this particularly simple method. Although it is usually possible to cure a case of malaria with oral atebrin only, it is obviously a great advantage to have a simple, effective and quick treatment in certain cases. Apart from those very severe cases where quick results are urgently required this method would seem to have particular and hitherto unrealized advantages for conducting a 'blanket treatment'. It was therefore desirable to continue my experiments on a larger scale under well-controlled conditions permitting exact observation.

'Blanket treatment' of hospital staff

For this purpose the staff of the Kurunegalle Hospital was selected. Kurunegalle is a provincial town in Ceylon situated in one of the worst epidemic centres. The hospital staff consists of 65 persons, practically all of whom had had malaria within the last two months. Thirty-eight were actually suffering from clinical symptoms at the time and on an average there was a daily absence of about 20 per cent, in spite of the fact that nearly all were taking quinine or quinoplasmochin in varying doses. Twenty-eight persons had enlarged spleens and 36 blood slides were found to contain parasites

(Continued from previous column)

Acknowledgments

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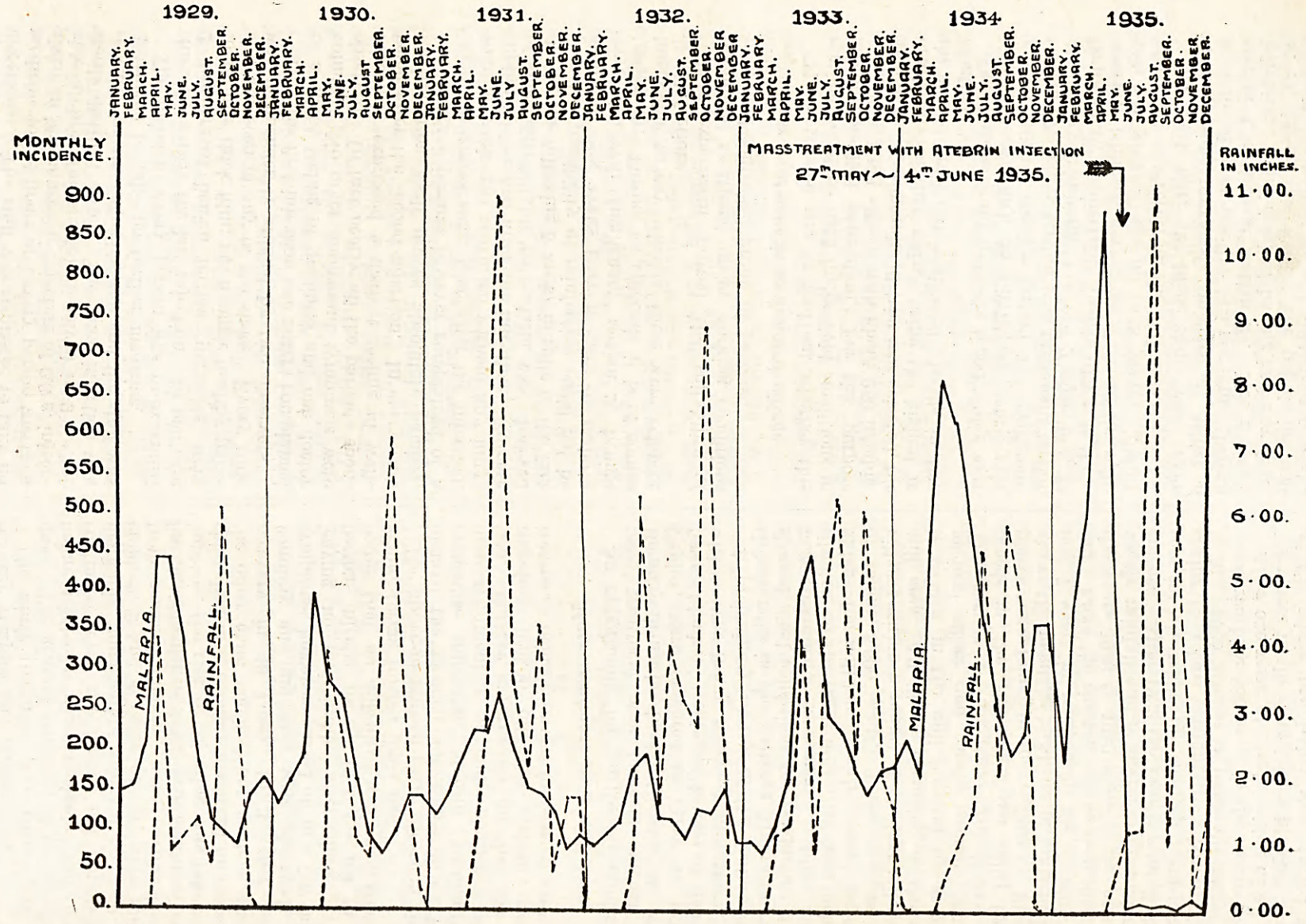

MALARIA & RAINFALL IN GOKAK MILL AREA 1929 ~ 1935.

(22 malignant tertian, 11 benign tertian and 3 malignant tertian *plus* benign tertian mixed infections). The staff was requested to take no medicine for 24 hours and every person was then given an intramuscular injection of 0.3 g. injectable atebrin (musonate) dissolved in 9 c.c. of sterile distilled water. The same injection was repeated on the following day and the staff was instructed to take no further medicine.

The blood of every person was re-examined three days after the last injection. In one case 2 degenerated benign tertian parasites were found in a thick film; not a single healthy parasite was seen in any of the slides. Every slide was independently studied by two observers.

After the first injection two sisters complained of a slight feeling of giddiness and one doctor vomited. No other unpleasant symptoms were observed. In fact nearly all the patients spontaneously expressed a distinct feeling of well-being after the second injection. In every case the injection itself proved absolutely painless, two or three persons however complained of a slight tenderness some time after the injection. Routine work was continued without any interruption before and after the injection. No case of fever attributable to malaria was observed during the following 5 weeks in spite of the fact that the possibility of reinfection could not be excluded. Six weeks later 6 cases of malaria were observed: (malignant tertian 2, benign tertian 4). During an epidemic it is of course impossible to say whether these were relapses or reinfections.

This experiment proved the suitability of parenteral treatment under working conditions in a well-controlled group of persons.

Mass treatment in an isolated village

The next step was to find out whether this method could be used under field conditions in an uncontrolled population. For this purpose a small isolated village with about 250 inhabitants in the Kurunegalle district was selected, the death rate in that village being the highest in the whole area (60 registered deaths in two months).

One hundred and forty-six blood slides were examined of which 58 (39.72 per cent) were found positive (benign tertian 17, malignant tertian 37, benign tertian *plus* malignant tertian 4). Every inhabitant received 2 injections, 24 hours apart, of injectable atebrin (0.3 g. in 9 c.c. water). Children were given 1 c.c. of the solution per year of age up to 8 years; children above 8 years receiving the full dose.

One week later 124 blood slides were taken from persons previously injected of which 6 were found to be positive (4.5 per cent) (benign tertian 4, malignant tertian 2). Not a single inhabitant complained of having had any fever at all during this week. The population was carefully controlled over a period of 6 weeks during which time 7.6 per cent of the treated persons complained of having had fever. Here again it was obviously impossible to distinguish between relapses and reinfections.

The whole treatment was carried out in 3 days. The general condition of the inhabitants before treatment was extremely bad through continued fever and famine but improved remarkably immediately afterwards. Two small children, 2 and 4 years of age, were suffering from cerebral malaria, were unconscious and having convulsions. As their condition seemed hopeless, the risk of injecting was taken. One child died in a collapse about 20 minutes later, the other child vomited but made a complete recovery in 48 hours. In 3 other children vomiting and giddiness were observed; these symptoms, however, passed off in a few minutes leaving no undesirable after-effects. Those persons injected on the first day felt so much better that no difficulty was encountered in administering further injections.

The above-mentioned toxic effects in children induced the medical authorities of Ceylon to pronounce injectable atebrin unsuitable for mass treatment in an under-nourished population. Further experiments on this line were therefore broken off, the atebrin musonate treatment being reserved for special cases only.

Mass treatment in a mill area

An opportunity for further experiments in mass treatment was however offered by a Bombay firm who, having heard of the work in Ceylon, were prepared to carry all expenses for a 'blanket' treatment in one of their mills with a very heavy incidence of malaria.

A preliminary survey of the malaria at the Gokak mills in the Southern Mahratta country showed ideal conditions for conducting a carefully-controlled experiment. The mill is situated on the bank of a river and includes a village for mill-hands with a total population of about 5,600 souls. There are no other villages within a radius of about 3 miles of the mill area. All illness occurring in the village is treated in the mill hospital by a resident medical officer and careful records are kept. The carrier is *Anopheles culicifacies* which breeds in the river bed (no other breeding places were found in the vicinity). The chart shows the monthly incidence of malaria for the last 7 years in relation to the monthly rainfall. From the chart it can be seen that during the years 1926 to 1932 there is an increase in yearly rainfall and a decrease in malaria incidence. After 1932 the yearly rainfall drops or sets in late while the malaria incidence rises. Owing to a long drought from November 1934 to May 1935 there is an unusually high malaria peak, reaching 880 cases in the month of April.

After one week of careful oiling of all breeding places in the river bed, a blanket treatment of the whole population was started on the 27th of May 1935. Five thousand six hundred

and fifty people were treated (11,300 injections). This work was completed within 9 days with the help of two assistants. As it was intended to show that this method can be carried out in a minimum of time with negligible overhead expenses neither parasite rate nor spleen index were recorded. Every person in the mill area was treated including infants, pregnant women and persons suffering from other diseases.

The dosage of each injection (24 hours apart) was as follows :—

Strong and healthy adult males 9 c.c. (0.3 g. atebrin).

Strong and healthy adult females 8 c.c.

Weak or unhealthy adult males 8 c.c.

" " " " females 7 c.c.

In the case of children dosage was not given according to stated age but rather according to general appearance approximately as follows—

Infants appearing to be below 6 months ½ c.c.

Above 6 months and up to 2 years 1 c.c.

2	to	4	"	2 c.c.
4	"	6	"	3 c.c.
6	"	10	"	4 c.c.
10	"	12	"	5 c.c.
12	"	15	"	6 c.c.
15	"	18	"	7 c.c.

A small dose of magnesium sulphate was given to every person before the first injection.

After the second injection every patient was given 3 tablets of 0.02 g. plasmochin simplex (children correspondingly less) and instructed to take one tablet on three consecutive days beginning on the day after the second injection.

The only toxic symptoms observed after the injection of atebrin were a slight giddiness in about 1 per cent of the cases and three cases of fainting, none of which were serious. No mental derangement of any kind was observed.

The percentage of persons complaining of giddiness after the injection was slightly higher in those injected in the afternoon than in those that received their injection early in the morning. This seemed to suggest that the injected solution which was prepared in large quantities in the morning gradually deteriorated during the day. In order to get some more definite information on this point 500 doses were prepared one evening, kept overnight and injected the following morning. Out of this batch about 50 to 60 persons complained of giddiness within the next 5 or 6 hours. It was therefore decided to prepare smaller quantities of solution at a time and to discard any solution that could not be used at once. From then on out of about 3,500 injections only one case of giddiness was observed.

Since these observations Hecht has informed me that he has carried out pharmacological experiments which definitely show that no toxic substances are formed when atebrin-dimethylsulphonate solution is submitted to severe stability tests; it deteriorates only very gradually under normal conditions. Whatever the explanation of my observation may be the fact that the manufacturers put up the preparation in dry ampoules seems to emphasize the importance of using only freshly prepared solutions.

During the first half of the treatment the refilling of the syringe was done by means of a rubber tube from a bottle containing the solution attached to an adaptor with a three-way cock fitted to the syringe. In this way it was possible to refill the syringe rapidly under perfectly aseptic conditions. About half-way through the work, however, these adaptors began to leak and it became necessary to immerse the syringe into the solution for refilling, not a strictly aseptic procedure. The result was that whereas among patients injected with the adaptor no abscesses occurred, 49 cases of abscesses, mostly in young children and old and feeble adults, were observed among those injected during the latter part of the treatment. As it is known (Hicks, 1935) that the injection does not give rise to necrosis, I am inclined to believe that these abscesses were due to an unsatisfactory asepsis rather than to the injection itself.

The only serious incident was hæmoglobinuria occurring on the day after the last tablet of plasmochin (4 days after the second injection). In all, 4 cases were observed, 2 severe cases ending fatally and 2 mild cases. All 4 patients were Mohammedans, 3 belonging to the same household and all four natives of the same village situated a few miles further up the river, but all at the time residing in the mill area. All were taking treatment from a local physician for syphilis.

The two fatal cases were known to have been suffering from syphilis. The two mild cases, young brothers, believed that they were suffering from 'venereal disease', but had no specific history. All had previously suffered from malaria but were quite free of clinical symptoms at the time of treatment. The cases resembled in every respect those observed and described by Amy (1934) in the North-West Frontier Province of India. It is most unfortunate that laboratory facilities were not available for a detailed study of my cases. Of the two fatal cases one, a young man, died in 48 hours, the other made an apparently complete recovery but left hospital against orders and died 2 days later in his house of heart failure, an occurrence not uncommon in true blackwater fever.

There is nothing to suggest that these cases had anything to do with the atebrin (Chopra, Sen and Bhattacharya, 1935). They appear to be in some way connected with plasmochin. Perhaps the fact that all four were taking medicine (mercury ?) may help to throw some light on this perplexing problem, although I

have received a private communication from Col. Amy that there was not even a suspicion of syphilis in any of his cases.

Except one not quite typical case described by Lindberg (1935) blackwater fever as such is unknown in the Gokak district.

Immediately after the mass treatment, not a single case of malaria was observed. Through the carefully conducted anti-larval campaign I tried to exclude as far as possible a reinfection after the mass treatment so that all cases of fever occurring after treatment could be registered as relapses.

In spite of the fact that an occasional reinfection may have been included among the registered relapses, the figures, as can be seen from the chart, are surprisingly low considering the fact that no quinine or other anti-malarial remedy has been dispensed during the 7 months of observation. The total numbers of malaria cases for each month after the blanket treatment are as follows :—

June	2
July	10
August	5
September	9
October	6
November	15
December	8

Every relapse has been immediately treated with 2 injections and the villagers (after extensive propaganda) seem to have realized the importance of bringing every fever case for treatment so as to prevent a further spread.

Discussion

The first experiment (Kurunegalle Hospital) shows that my method, *i.e.*, the treatment of a case of malaria with two injections of atebrin-dimethylsulphonate at an interval of 24 hours, is practicable without interference with the routine work of the treated person. The two field experiments, one in the Ceylon village and the other at Gokak, show that my method is particularly suitable for blanket treatment and it therefore appears to be a useful addition to our therapeutic armament.

The method was originally devised for the treatment of the actual acute malaria attack. In this respect I am inclined to consider the results satisfactory.

It is only from the Gokak experiment that we can gather some information regarding the relapse rate after this abbreviated treatment. Here too I am inclined to consider the results better than were to be expected considering the very small quantity of atebrin given. I am, however, not surprised by the fact that other authors have found a higher relapse rate after two injections of atebrin musonate, as it must be borne in mind that my experiments were all conducted in highly endemic areas during a particularly high incidence. We must presume that the population in these areas had already acquired a considerable degree of immunity and that therefore very small doses of atebrin were sufficient to produce good and lasting results. On the other hand when dealing with first infections it will probably be necessary to give a longer treatment in order to prevent relapses and achieve a permanent cure, be it by an oral after-treatment or further injections at longer intervals.

Summary

(1) A hospital staff of 65 persons received two injections of atebrin-dimethylsulphonate at an interval of 24 hours. Parasites and fever were completely controlled in 3 days. No further malaria fever was observed during the following 5 weeks. No serious toxic symptoms were observed.

(2) During a malaria epidemic in a village in Ceylon, all inhabitants including children (240 persons) were treated with two injections. Every person so treated was free from clinical symptoms of malaria during the following week. Before injection the parasite rate was 39.72 per cent; one week after injection the parasite rate was 4.5 per cent. During the next 6 weeks 7.6 per cent of the population complained of having had fever. The general condition of patients very considerably improved immediately after treatment.

(3) In a mill area blanket treatment of 5,650 persons with two injections was completed in 9 days. Solution more than a few hours old produced giddiness in a small percentage of persons and very occasionally fainting. The former symptom was only observed in one case with fresh solution. Forty-nine abscesses in small children and weak adults are ascribed to unsatisfactory asepsis and not to the injection as such. Four cases of hæmoglobinuria after plasmochin are observed in patients who are receiving anti-syphilitic treatment from a hakim. A possible connection between syphilis, mercury, plasmochin and hæmoglobinuria is suggested. During the 7 months a total of 55 relapses was observed, and treated with two injections as before.

Acknowledgments

My thanks are due to the medical authorities in Ceylon for permitting preliminary experiments and to Messrs. Forbes, Forbes, Campbell and Company, Bombay, for their support and help in carrying out the mass treatment at Gokak.

To Dr. Malshett, the resident medical officer at Gokak, and to my assistants Doctors Devasahayan and Swamidass for their enthusiastic co-operation.

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RHEUMATIC HEART DISEASE IN THE BOMBAY DECCAN

By L. B. CARRUTHERS, B.A., M.D., C.M.
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THE conception that rheumatic fever and its concomitants are rare or entirely unknown within the true tropics has long been in favour. Seemingly it received strong confirmation when Clarke (1930) published his notable paper on the geographical distribution of rheumatic fever. Rogers and Megaw (1930) in India and Swift (1931) and Longcope (1931) in America have supported this view. However, in the same year that Clarke published his paper, Hughes and Yusuf (1930) reported 25 cases of heart disease of rheumatic origin from Lahore, while Stott (1930) at Lucknow reported 20 cases of mitral stenosis. Two years later, Hodge (1932) reported six cases of rheumatic disease from Jalpaiguri, Bengal. Nevertheless, in each of these cases the objection can be made that they were not from within the true tropics. More recently, Kutumbiah (1935) from Vizagapatam and Banerjea (1935) from Calcutta have published series of cases of rheumatic heart disease to which this objection cannot be taken. It is our purpose to help further to clarify this subject by reporting our experience at Miraj.

Miraj is situated in the Bombay Deccan, 160 miles south of Poona at an elevation of about 1,800 feet and well within the true tropics. The Presbyterian Mission Hospital is an institution of 270 beds caring for about 5,500 outpatients and approximately 3,200 inpatients yearly, the majority of the latter, namely 70 per cent, being surgical. In the period under discussion, from 1st November, 1933, until 1st November, 1935, there were 6,248 admissions to the hospital, 4,281 (68.52 per cent) being surgical and 1,967 (31.48 per cent) being medical. During this period of time there were 100 cases of cardiac disease admitted, distributed according to diagnosis as shown in table I. These formed 1.60 per cent of the total admissions and 5.08 per cent of the medical admissions. In this group there were 47 cases of rheumatic origin, forming 0.75 per cent of the total admissions and 2.44 per cent of the medical admissions. In reference to the temperate climates, Tice (1920) states that about 5 per cent of all patients met with in general practice have chronic valvular disease of the heart and Davis and Weiss (1931) have found that rheumatic heart disease made up 9.1 per cent of 5,215 autopsies performed in Boston. Although there seem to be no statistics for the incidence of rheumatic heart disease in hospital practice in the temperate zones that

TABLE I

(Terminology according to the *Standard Classified Nomenclature of Disease*, Amer. Med. Assoc., 1935)

Hypertensive heart disease	..	11 (11 per cent)
Unclassified	2	
Hypertension of the greater circulation	6	
Hypertension of the lesser circulation	0	
With emphysema	3	
Arteriosclerotic heart disease	..	28 (28 per cent)
Sclerosis of the coronary arteries	27	
Coronary thrombosis	1	
Syphilitic heart disease	..	10 (10 per cent)
Unclassified	1	
Aortic regurgitation	3	
Syphilitic aortitis	2	
Aneurysm of the aorta	4	
Subacute bacterial endocarditis	..	4 (4 per cent)
Rheumatic heart disease, inactive	..	25 (25 per cent)
Mitral regurgitation	4	
Mitral stenosis	4	
Mitral stenosis and mitral regurgitation	6	
Mitral stenosis and regurgitation with aortic regurgitation	1	
Mitral stenosis and regurgitation with aortic stenosis	1	
Mitral stenosis and regurgitation with tricuspid regurgitation	1	
Mitral stenosis with tricuspid regurgitation	1	
Mitral stenosis with aortic stenosis and tricuspid regurgitation	1	
Sclerosis of the mitral valve	2	
Sclerosis of the mitral, aortic and tricuspid valves	1	
Sclerosis of the mitral and tricuspid valves	1	
Sclerosis of the tricuspid valve	1	
Sclerosis of the mitral and aortic valves with adherent pericardium	1	
Rheumatic heart disease, active	..	22 (22 per cent)
Mitral regurgitation	4	
Mitral stenosis	9	
Mitral stenosis and regurgitation	2	
Mitral stenosis and regurgitation with aortic stenosis and regurgitation	1	
Mitral stenosis and regurgitation with tricuspid regurgitation	2	
Mitral stenosis and aortic regurgitation	1	
Mitral stenosis and regurgitation with aortic regurgitation	1	
Mitral stenosis and tricuspid regurgitation	1	
Sclerosis of the mitral, aortic and tricuspid valves with adherent pericardium	1	

Note.—Among the rheumatic hearts, paroxysmal auricular fibrillation and chronic auricular fibrillation were each seen twice.

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