The Influence of Acquired Resistance in the Epidemiology of Bilharziasis*

BY

V. DE V. CLARKE

Research Laboratory, Salisbury, Rhodesia.

INTRODUCTION

Bilharziasis ranks with tuberculosis and malaria as the three most important endemic diseases of man in Rhodesia. The prominence given to bilharziasis in the endemic diseases pattern arises from its high prevalence, particularly in the African population.

It is probable that bilharziasis was endemic in the country even prior to the arrival in the country of the European settlers in 1890, but it was not until Orpen (1915) described the results of a small survey that local infections were proven. He reported 182 (31 per cent.) urinary infections in 592 African prisoners examined in the Salisbury gaol. In the ensuing 15 years there was only scanty evidence of the prevalence of the disease. However, in the decade 1931 to 1940 the Annual Public Health Reports of Southern Rhodesia indicated increasing prevalence, and this stimulated interest in the problem and led to the establishment in 1939 of a specialised laboratory to study the parasites causing the disease. The unpublished records of the laboratory indicate that in more recent years the disease has increased not only in prevalence, but also in its intensity in infected individuals. Surveys show that the urinary form of the disease is more widespread than the intestinal form. Both forms are becoming more prevalent, but the rapid increase of the latter, considered by most authorities to be the more severe, indicates that a greater importance must be accorded to it in the future. The increasing gravity of the situation has accentuated the need for continued research in all aspects of the parasites and their host relationships.

The reason for the increase in prevalence and intensity can be found in the extensive agricultural development which has taken place in the last two decades. In the course of this development the programme of water conservation has resulted not only in the construction of large numbers of stable artificial reservoirs, but also in more permanent watercourses. The more numerous waterbodies, particularly the large numbers of stable and permanent waterbodies, have led to greatly increased snail populations, with a consequent increase in the incidence of the infections.

Prior to this programme of intense agricultural development, records show that transmission was at a low level in most areas of the country. This is probably because the natural ecological situations of Rhodesia do not in themselves provide the conditions shown by Shiff (1964a, 1964b) to be necessary for the establishment of dense snail populations. Shiff demonstrated that of the three species of snails concerned with the transmission of bilharziasis in Rhodesia, only *Bulinus (Physopsis) globosus* (Morelet) and *Bulinus (Physopsis) africanus* (Krauss) have the ability to maintain their species in the small temporary waterbodies. He showed that the third species, *Biomphalaria pfeifferi* (Krauss) is not adapted to survive seasonal desiccation since it has not the ability to reproduce rapidly enough, during short periods of suitable conditions, to re-establish populations decimated by desiccation. Previously this species was probably found only in the few permanent rivers. The numerous permanent waterbodies constructed in the course of the recent water conservation programme have provided conditions well suited to all three species, and the populations are now dense. The records of field surveys by the Bilharziasis Research Laboratory show that there has been a concurrent increase in the prevalence of both forms of the disease.

The extension of this agricultural development programme to the hot low-lying areas in the south and north of the country, and particularly the development in these areas of irrigation farming with its dense human settlement, can be shown to lead to intense perennial transmission of the infections (McMullen: Restricted Report, 1961). The economic development of Rhodesia demands the establishment of extensive irrigation systems in these areas. When these systems are fully expanded it is estimated that the production of sugar alone will support nearly one million people who will be concentrated in a small area. If no preventive measures are taken, the disease in these areas must be expected to reach the level of prevalence and intensity hitherto reported only from Egypt.

There are several possible methods of interrupting the transmission of the parasite. Clarke *et al.* (1961) and Clarke (1963) have shown that it is possible to reduce the transmission by the control of the snail populations with chemical molluscicides. It has also been shown that snail

---

* Portion of dissertation in part fulfilment of the requirements for degree of Doctor of Philosophy, Rhodes University.

populations can be reduced by environmental control (Pesigan *et al.*, 1958). However, at present complete eradication of the snails cannot be contemplated, and control measures must be directed to give maximum benefits in the form of prevention of illness and disability. Control measures in the past have been aimed too often solely at reducing the snail populations. Insufficient consideration has been given to reducing the infections in man or reducing the morbidity resulting from these infections. To obtain maximum control of the infections and the morbidity, the existing methods of control must be so employed as to take advantage of any natural processes, for example, in the host-parasite relationship, which in themselves help to limit these infections. One such natural process which requires investigation is the possible development of acquired resistance or immunity to infection. The term resistance is used here to describe the ability of a host to resist or withstand an infection by a parasite. Resistance may be innate, or it may be acquired as a result of an infection with the parasite. It may be temporary or permanent, partial or absolute. Resistance is used to describe any ability, whatever its nature, to withstand infection, and it includes immunity. This is a host response to a parasite which may protect the host against further infection, or prevent the development of an infection, or it may inactivate or even cause the death of the parasites of an existing infection. This then is the purpose of the present investigation; to study the effects of acquired resistance or immunity to *Schistosoma* spp. in man. Little is known of the mechanisms of resistance or immunity in helminthic infections and they may not be the same as those of bacterial or virus infections, which are well understood. However, the purpose of this study is to investigate the results and effects of resistance on the course of initial or subsequent infections, and no detailed consideration is given to the mechanisms of resistance, the way in which it acts, or the processes by which it is developed.

Bilharziasis has been repeatedly described as essentially a disease of children (Manson-Bahr, 1958; Honey and Gelfand, 1960) and it has been stated that this is because, by the time they have reached adulthood, the people have developed a resistance or an immunity to the infections (Dixon, 1934; Gerber, 1952). It has also been stated that it is a disease of non-indigenous people because such people have had no exposure during childhood by which to develop resistance (Newsome, 1956, quoting Fujinami, 1916).

For the hyperendemic irrigation areas of the hot, low-lying southern areas of Rhodesia, labour is being recruited largely from the western parts of the country where urinary infections are uncommon and intestinal infections are rare. Many of these people show no indications of previous exposure to infection. It is necessary to study the effects of exposing such people to intense transmission of both forms of the disease. The economically productive adults may well be severely affected by intense infections, with a consequent interference with the economic efficiency of these vital irrigation programmes.

One of the important effects of control programmes, or of the movement of people from non-endemic or hypoendemic areas to hyperendemic areas, would be the development, under certain circumstances, or the destruction under others, of acquired resistance or immunity.

The present investigation involves the study of the influence of resistance on the host parasite relationship in bilharziasis under different conditions of incidence and transmission of the two species of the genus *Schistosoma* Weinland, which commonly infect man in Rhodesia. These two species are *S. mansoni* Sambon and *S. haematobium* (Bilharz). The techniques which have been used are described in Appendix I.

Studies of the development of acquired resistance in laboratory animals by following an initial immunising infection with exposure to subsequent "challenge" infections have given direct evidence of resistance in animals. However, in man it is seldom possible to obtain such direct evidence and the few human experiments (Fisher, 1934; Clarke 1965 in Press) must be supported by indirect evidence derived from epidemiological studies. As stated by Vogel (1958), the experimental reinfection of human volunteers is the only completely reliable method of demonstrating the presence or degree of acquired resistance. Until such proof is available, conclusions must be based on epidemiological evidence supporting analogies between the courses of infections in man and in experimental animals.

Newsome (1956) asserts that clinical observation alone confirms the existence of some mechanism which increases tolerance of the worms or actively restrains the disease in older people. He discusses the work of Fujinami, who, in 1916, "remarked, what many have since described, that uninfected persons entering an endemic japonicum area become very ill, while the local inhabitants, at any rate the older ones, were less ill." Gelfand (personal communication) states that in Rhodesia, urinary bilharziasis, as a clinically manifested disease, is essentially a disease of children who appear to overcome the infection as they grow older. Honey and Gelfand (1960) reported that although it is a childhood disease, late sequelae, resulting from the tissue responses to earlier infections, appear in the second or third decades. They reported that 70 per cent. of the cases of demonstrated gross calcification of the bladder occurred before the age of 30.

Many reports refer to decreased passage of *S. haematobium* eggs in older people and some relate this decrease to the development of resistance. Gerber (1952) studied the prevalence of the disease in different age groups of people in several villages in the Boadjibu District of Sierra Leone. The people of the different villages were subjected in nature to different conditions of exposure to infection, and Gerber concluded that an immunological protection was evidenced. He stated that maximum protection was developed in people with a moderate initial exposure followed later by regular re-exposure to infection such as may be incurred by occasional exposure during one transmission season and followed by an exposure-free interval lasting to the next season. Pesigan *et al.* (1958) state that one factor in respect of the prevalence of *S. japonicum* in the Philippines, namely the downward trend with advancing age after the peak of prevalence is reached, could be explained as being partly due to host reaction, with an immunity mechanism. Several other workers, including Dixon (1934), Bassenes and Pantoja (1947), Cowper (1953), and Maclean *et al.* (1958), report on the downward trend of prevalence after the age of peak prevalence, and most of these authors suggest a possible relationship with resistance. Morley-Smith and Gelfand (1960) examined over 1,000 people from an African farming district of Rhodesia, and they found a steady fall in prevalence from the peak which occurred in the first decade of life. After the age of 40 there was no further decline and the proportion of people infected remained steady thereafter at approximately 15 per cent. They conclude that their studies support the existence of resistance acquired by the human body when the infection has been contracted some years previously.

The majority of these authors failed to consider that the decreased egg passage might have been due to decreased contact with infected water by the older people. However, under conditions existing in rural areas of Rhodesia, and particularly in the area in which Morley-Smith and Gelfand worked, it may be assumed that all people are regularly exposed to infection, since the only available water is invariably from a river or stream.

Manson-Bahr (1958) suggested that the development of resistance was dependent on the degree of transmission. He suggested that the decrease in the numbers of infections with advancing age, commonly occurring in east and southern Africa, was the result of the development of immunity which increased with age. He also suggested that in areas of very intense transmission, such as occur in Egypt, the repeated heavy infections of very young children may so weaken the children that the development of immunity is hindered. This, he states, alters the clinical picture of the disease in such areas.

Surveys in Rhodesia

Results obtained from extensive surveys to assess the prevalence of both *S. haematobium* and *S. mansoni* in African communities in Rhodesia have revealed further and more detailed evidence of the development of resistance, and of the conditions of exposure and infection which give rise to increased protection. These surveys have been conducted in communities in different areas of the country, and these areas were chosen to give a range of climatic, topographical and other conditions which in turn influence the level of infection to which the community is exposed. In most cases an attempt was made to investigate stable and concentrated communities, which had similiar standards of nutrition, housing and hygiene, and which differed from one another as little as possible, excepting for the climatic conditions, and the extent and nature of exposure to bilharziasis. In all the communities investigated, with the exception of the combined community of the Chikwanda and Zimutu, and of the Serima tribal trust areas, adequate and balanced food rations are provided to all people by their employers.

Since these rations are all based on a recommended scale, the nutritional status of these communities is as uniform as is possible under African conditions.

The following communities, the situations of which are shown on the map of Rhodesia (Fig. 1) were investigated.

1. *The Chikwanda, Zimutu and Serima* tribal trust areas, covering 40,000 hectares, lie in the catchment area of Lake Kyle, which supplies water to the Triangle and Hippo Valley sugar estates. For the purposes of this study, these

three very similar areas are considered as having one large community. They are well watered areas, but because the soil is not fertile they are not heavily populated. These were the only areas examined where the people do not receive the balanced diet mentioned above.

The people are entirely dependent on natural surface water for all their needs, and latrines are absent, even from the schools; the standards of living and hygiene are therefore very low. Snails were common in all the waterways, but the populations were not dense.

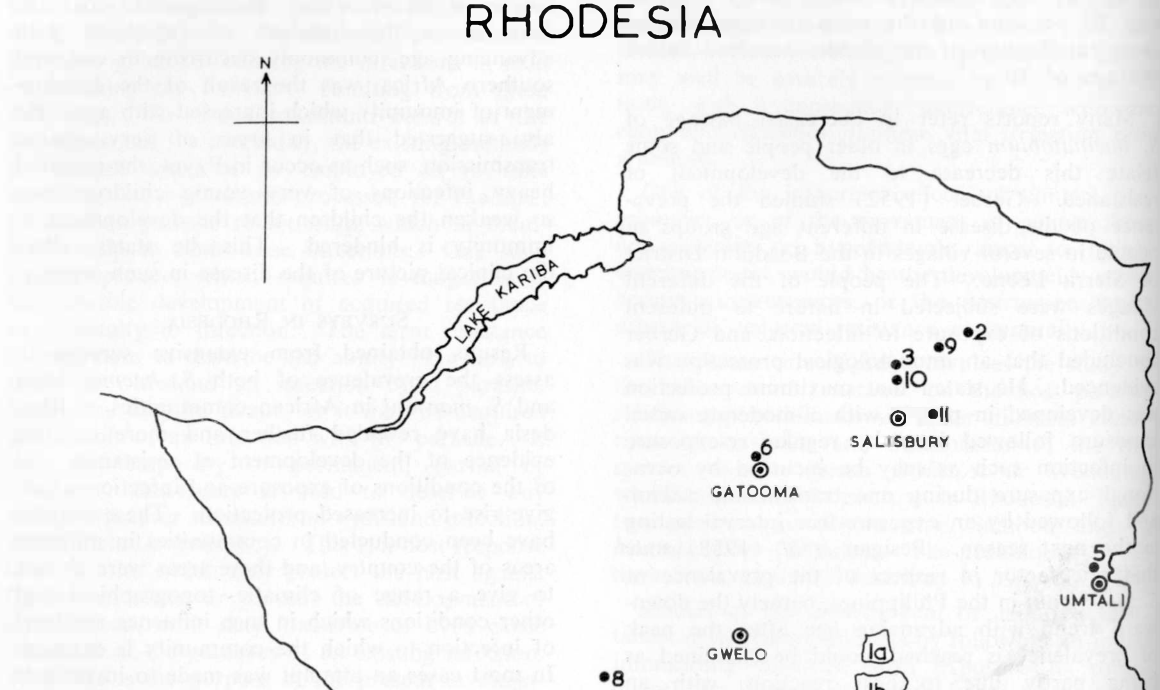

Fig. 1—Map of Rhodesia showing main towns and situations of communities examined.

Transmission of bilharziasis was believed to be essentially seasonal and it probably occurred only in two short periods of the year, from October to December (Shiff, 1964). Snail control measures were instituted late in 1959. These measures were based on the application of chemical molluscicides to all the surface water in the area. The snail populations were drastically reduced after two such applications, and thereafter the populations were kept to a very low level by the system of snail surveillance (Clarke *et al.*, 1961). These control measures have been maintained up to the present time. They have proved most successful, snails only rarely having been found after April, 1960.

Surveys to assess the prevalence of *S. haematobium* infections in children were undertaken in 1960 and 1962, being conducted on both occasions in the months of February and March. Single urine specimens were examined from each child, and, although no attempt was made to examine specimens from the same children over successive years, the same villages were visited on each survey.

2. *The Chipoli Irrigation Estate:* This privately owned, mixed farming estate, established early in this century, is situated approximately 112 km. north-east of Salisbury. The canal systems draw water from the Mazoe River. Most of the canals and all the furrows are unlined, and they support plant growth, particularly of *Nitella* spp. and *Potamogeton* spp.; they are normally cleared of this vegetation once a year, during the rains. The canals flow through two large dams, each impounding more than 50,000 cubic metres of water, and there are a further six dams on the estate impounding between 5,000 and 20,000 cubic metres each. All waters, including reservoirs, canals and furrows are heavily infected with snails, including *Biomphalaria pfeifferi* and *Bulinus* (*Physopsis*) *globosus.*

There is a labour force of 250, and the total African population is approximately 800. All domestic water is obtained from the canals, and the reservoirs and canals are also extensively used for swimming and fishing. Although latrines are supplied they are seldom used, the people preferring to use the citrus groves or the surrounding uncultivated lands for defaecation: urination occurs almost anywhere; the people, particularly the males, showing little desire for privacy. Contamination of the water with urine and faeces is therefore frequent.

Chipoli lies in the hot lower Mazoe Valley and, with the climatic conditions, the abundance of surface water, the extensive snail colonies, and the continuous and intimate contact the people have with the water, it would be expected that the level of transmission would remain high throughout the year.

A stool and urine specimen examination survey to assess the prevalence of bilharziasis was undertaken in February, 1964.

3. *The Mazoe Citrus Estates* extend in a narrow strip for a distance of 20 km. along the banks of the Mazoe River. These very large estates draw their water from the Mazoe Dam which impounds 35 million cubic metres of water. Considerably more than 1,000 people live on the estates.

Snails of the species *B. pfeifferi* and *B.* (*P.*) *globosus* are therefore plentiful throughout the canal systems. No attempt has yet been made to control the snail populations in this irrigation system. Transmission of both forms of the disease was expected to be high and perennial.

A survey to assess the prevalence of bilharziasis was undertaken in June, 1963. This survey included stool and urine examinations, fluorescent antibody tests, intradermal tests, and the plasma card flocculation tests.

4. *The Triangle and Hippo Valley* sugar estates are two contiguous irrigation estates situated in the very hot, low-lying arid and flat southern part of Rhodesia. The estates at present have 20,000 hectares under irrigation, which is partly of the flood type, and partly under overhead spray. It is planned to extend the irrigation in this part of Rhodesia to 50,000 hectares by the end of 1965, and to 300,000 hectares within the following seven years. At present the water for irrigation is brought from the large Kyle lake, near Fort Victoria, and from the Bangala dam on the Mtilikwe River.

The total population is at present over 11,000 people, but newcomers are swelling this figure by over 2,000 each month; it has been estimated that, within ten years, the production of sugar alone will support over one million people in the area.

The extensive canal systems, with large numbers of small night storage reservoirs, the unprotected drains leading away the regenerated water, the lack of sanitation or safe water supplies, the high temperatures throughout the year and the concentration of people make it certain that, unless some form of prevention is initiated, transmission of both forms of bilharziasis will be maintained at a very high level throughout the year. At present, the prevalence is not exceptionally high because the large majority of the people tested are new to the area.

A stool and urine examination survey was conducted during February, 1964.

5. *The Premier Citrus Estate,* 30 km. north-west of Umtali near the eastern border of Rhodesia, was brought under flood irrigation in 1898. Approximately 600 people reside on the estate. The water for the irrigation is brought from the Odzani River by means of an unlined canal which runs through three earthen night storage reservoirs. The houses for the labourers and their families are sited near the reservoirs and canals, which form the sole source of domestic water. Latrines are provided, but they are not always used. Although snails of both important species were found, they were not as plentiful as expected; no reason could be found to explain this fact. It was expected that incidence would be moderately high, and that transmission would be seasonal.

6. *The Golden Valley Mine* (gold) lies 20 km. north-west of Gatooma in the central part of Rhodesia. It is in a flat, dry, hot area and there is little surface water in the neighbourhood. Over 700 people live on the mine, and they are provided with piped domestic water from underground supplies. There is a temporary stream 3 km. from the mine, but since this stream is dry for several months each year, it is not considered to be an important source of infection.

It was expected that the incidence of bilharziasis would be low, and that transmission would be seasonal. A survey for bilharziasis was undertaken in December, 1963, and it included stool and urine examinations, intradermal tests and fluorescent antibody tests.

7. *The Bikita Minerals Mine* (lithium) lies 75 km. east of Fort Victoria, in an area watered by a large number of rivers and small streams. Over 200 pepole are employed on the mine and, with their families, there is a total population of over 600 people. The houses are provided with piped water from underground sources. It was expected that transmission would be seasonal, and even then at only a moderately high level. A stool and urine examination survey for bilharziasis was undertaken during March, 1964.

8. *The Turk Mine* (gold) is in the western region of the country, 60 km. north-east of Bulawayo. The district is very dry, and there is no permanent surface water in the vicinity of the mine except for a large dam, impounding over 50,000 cubic metres of water, 6 km. distant. There is a piped water supply and the people have no need to visit the natural water for either washing, fishing or recreation, and therefore contact with infected water is limited. A stool and urine survey for bilharziasis was conducted in April, 1964.

9. *The R.A.N. Gold Mine* lies approximately 55 km. north-east of Salisbury. Over 120 men are employed on the mine and the total population is over 500 people. The houses of the labourers are provided with piped water supplies from underground sources. There is a permanent water reservoir within two kilometres of the mine, and it is used by the people for washing and swimming. There is also one seasonal stream which crosses one of the most used roads to the mine. There are snails in both the stream and the reservoir. The mine lies in the central part of the hot Mazoe Valley, and it was expected that transmission would be perennial, with intense transmission occurring during the summer. However, the people of the mine have limited contact with natural water, except for recreational purposes, and the incidence of infection was expected to be high without being exceptional. A survey which included stool and urine examinations, and intradermal and fluorescent antibody tests was conducted during May, 1964.

10. *The Iron Duke Mine* (iron pyrites) is situated 50 km. north of Salisbury in the southern part of the Mazoe Valley. It lies adjacent to the perennially flowing Yellow Jacket River, a short distance from the point where this river flows through the Mazoe irrigated citrus estates. The housing for the mine, which has 600 resident Africans, is provided with piped water for all domestic requirements, but the proximity of the river and of the canals of the irrigation estates made it appear likely that the incidence of both *S. mansoni* and *S. haematobium* would be high. Because of the permanency of the waters and the relatively high temperatures throughout the year, it was expected that transmission would be maintained throughout the year, with peak transmission occurring during the summer. The Yellow Jacket River was found to support very heavy populations of *B. (P.) globusus* and the canals of the irrigation estates were known to be infested with *B. pfeifferi* and *B. (P.) globosus*.

11. *The Arcturus Gold Mine,* 25 km. east of Salisbury, has a resident population of 800. The houses are all provided with piped water from an underground source, but the nearby streams and dams provide the people, and particularly the older children, with the opportunities for swimming, washing and fishing. It was expected

therefore that the incidence of both *S. mansoni* and *S. haematobium* would be high, but that the transmission would be seasonal. Stool and urine surveys for bilharziasis were undertaken in July, 1964.

The results of these surveys have been analysed in respect of the ages of the people tested, and the results are presented in Tables I and II. Where people of all ages were examined, they have been separated into eight age groups, selected to demonstrate the patterns of changes in prevalence and of egg production with increasing age. These groups were also selected because it was normally possible to obtain population samples of sufficient size for each group, and because estimation of age between such groupings was simplified. In some of the communities examined, it proved difficult to persuade people between the ages of 13 and 20 to volunteer for

Table I

S. haematobium INFECTIONS:

Results of Stool and Urine Examination Surveys in Seven Communities in Rhodesia.

	Age Groups Examined								
	Under 4	4-6	7-9	10-12	13-15	16-20	21-40	Over 40	Totals
A. CHIPOLI ESTATE:									
Number examined, males and females	9	76	55	25	13	21	101	35	335
Number passing eggs	8	73	54	24	12	19	73	20	283
Per cent. passing eggs	89	96	98	96	92	90	72	57	84
B. TRIANGLE AND HIPPO VALLEY SUGAR ESTATES:									
Number examined, males and females	30	87	66	38	42	106	237	116	722
Number passing eggs	9	26	39	28	28	58	79	8	275
Per cent. passing eggs	30	30	59	74	67	55	33	7	38
C. PREMIER CITRUS ESTATES:									
Number examined, males and females	25	37	77	54	19	28	148	70	458
Number passing eggs	0	10	37	32	9	10	23	10	131
Per cent. passing eggs	0	27	48	59	47	36	16	14	29
D. BIKITA MINERALS MINE:									
Number examined, males and females	18	40	66	106	77	78	22	20	427
Number passing eggs	1	8	22	60	41	34	4	2	172
Per cent passing eggs	6	20	33	57	53	44	18	10	40
E. TURK MINE:									
Number examined, males and females	18	25	100	76	13	15	114	102	463
Number passing eggs	0	3	13	10	5	4	15	1	51
Per cent. passing eggs	0	12	13	13	39	27	13	1	11
F. IRON DUKE MINE:									
Number examined, males and females	25	49	58	46	26	15	68	41	328
Number passing eggs	4	30	45	37	23	12	16	2	169
Per cent. passing eggs	16	61	78	80	88	80	24	5	52
G. ARCTURUS MINE:									
Number examined, males and females	32	62	74	54	52	33	105	52	464
Number passing eggs	1	10	25	34	36	17	30	4	157
Per cent. passing eggs	3	16	34	63	69	52	29	8	34

testing. It appeared that people of these ages were either too embarrassed to submit specimens, or they considered it lacking in dignity to do so. This was unfortunate since this was one of the most interesting age groups. The older people were more tolerant and they readily volunteered for testing, especially if they knew that they would be informed of the results, and infected persons could obtain treatment.

The Age-Prevalence Relationship and the Intensity of Infections

The relationship of prevalence of bilharziasis to age of infected persons, where the prevalence is assessed by stool and urine specimen examinations, has been investigated in these surveys and the results add evidence of the development of resistance to *S. haematobium* infections in all the communities, and to *S. mansoni* infections in the

Table II

S. mansoni Infections:

Results of Stool and Urine Examination Surveys in Seven Communities in Rhodesia.

	Age Groups Examined								
	Under 4	4-6	7-9	10-12	13-15	16-20	21-40	Over 40	Totals
A. CHIPOLI ESTATE:									
Number examined, males and females	8	70	51	23	15	24	95	32	318
Number passing eggs	4	58	47	20	10	12	56	16	223
Per cent. passing eggs	50	83	92	87	67	50	59	50	70
B. TRIANGLE AND HIPPO VALLEY SUGAR ESTATES:									
Number examined, males and females	30	87	66	38	42	106	237	116	722
Number passing eggs	4	10	11	19	10	17	24	8	103
Per cent. passing eggs	13	11	17	50	24	16	10	7	14
C. PREMIER CITRUS ESTATES:									
Number examined, males and females	21	36	73	56	15	28	148	68	445
Number passing eggs	1	6	9	19	3	2	32	8	80
Per cent. passing eggs	5	17	12	34	20	7	22	12	18
D. BIKITA MINERALS MINE:									
Number examined, males and females	20	37	60	84	67	59	21	20	368
Number passing eggs	1	1	3	5	2	7	3	1	23
Per cent. passing eggs	5	3	5	6	3	12	14	5	6
E. TURK MINE:									
Number examined, males and females	14	26	100	75	14	9	95	95	428
Number passing eggs	0	0	5	2	0	0	6	6	19
Per cent. passing eggs	0	0	5	3	0	0	6	6	4
F. IRON DUKE MINE:									
Number examined, males and females	6	27	45	50	24	7	29	11	199
Number passing eggs	2	11	35	29	14	7	11	2	111
Per cent. passing eggs	—	41	78	58	58	—	38	18	56
G. ARCTURUS MINE:									
Number examined, males and females	33	61	73	53	52	33	106	51	462
Number passing eggs	1	4	7	23	23	6	16	10	90
Per cent. passing eggs	3	7	10	43	44	18	15	20	19

communities of the Chipoli Estate, the Triangle and Hippo Valley sugar estates, and the Iron Duke and Arcturus mines (Tables I and II and Figs. 2 and 3).

In these communities there is a consistent pattern in the age-prevalence relationship. Even below the age of four, some of the children in most communities show infection. In older age groups the numbers of children showing active infections increase to higher and higher proportions with increasing age, until a peak is reached, normally between the ages of 7 and 15. After the age of peak prevalence, the proportion of people passing eggs decreases with age until, in the older adults, the proportion of people showing active infections is usually very low. For example, in the males of the community of the Iron Duke mine, the peak of prevalence of *S. haematobium* infections is 94 per cent., and this occurs in the age group 13 to 15 years. Subsequently the prevalence decreases with age until only 5 per cent. of the males over 40 years old are still passing eggs. Similarly, on the Triangle and Hippo Valley sugar estates, the peak of prevalence of *S. mansoni* infection is 50 per cent. and this occurs in the age group 10 to 12 years; thereafter, the prevalence decreases with age to 24 per cent. in the age group 13 to 15, to 16 per cent. in the age group 16 to 20, to 10 per cent. in the age group 21 to 40, and finally to as low as 7 per cent. in the older adults over 40 years old.

These results confirm a picture of the prevalence rising with age until a peak is reached, and thereafter decreasing, sometimes dramatically with advancing age, until in older adults a relatively low level of detectable infection is reached, after which no further decrease takes place.

The age at which peak prevalence is reached varies considerably and, generally, it appears to occur earlier in life in areas of high incidence, and later in life in areas of low incidence. In some areas, where the level of transmission is very high, the peak is reached in the first decade of life. An example of this is the prevalence of *S. haematobium* infections on the Chipoli Estate where 97 per cent. of the boys aged 7 to 9 years showed infections. All of the 49 girls between the ages of 7 and 12 were passing eggs. Where the level of transmission is low, the peak of prevalence is reached later in life. This is seen in the community of the Turk Mine where the age groups 13 to 15 years and 16 to 20 years showed the highest prevalence of *S. haemotobium*. The prevalence even in these two age groups was low when compared with that of the Chipoli Estate. Similar differences can be seen in the prevalence of *S. mansoni* infestations in the communities of the Iron Duke and Bikita Mines. At the Iron Duke mine where the prevalence is high, the peak of prevalence of 78 per cent. is reached in the age group 7 to 9 years, but in the Bikita mine community the peak of infection of 12 to 14 per cent. is reached in the age group 16 to 20 years and the young adults of 21 to 40 years.

At present there exists no satisfactory method for assessing the numbers of worms living or active in an individual, nor for assessing the average worm burden in a community or a section of a community. However, the numbers of *S. haematobium* eggs passed in the urine of an individual can be accepted as an indication of the activity or intensity of the infection. In urine examination surveys for *S. haematobium* infections in the communities of the Chipoli and Premier Estates and of the Bikita, Turk, Iron Duke and Arcturus mines, the eggs present in the

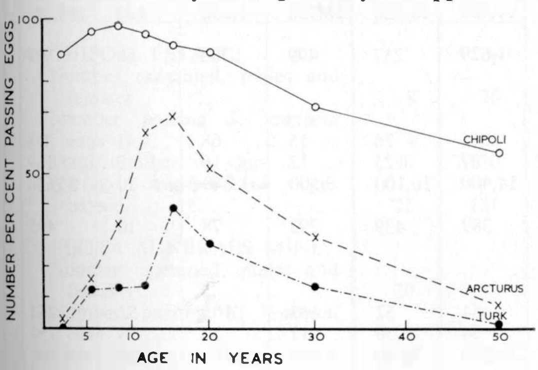

Fig. 2—Prevalence of *S. haematobium* infections in relation to age in three communities of Rhodesia.

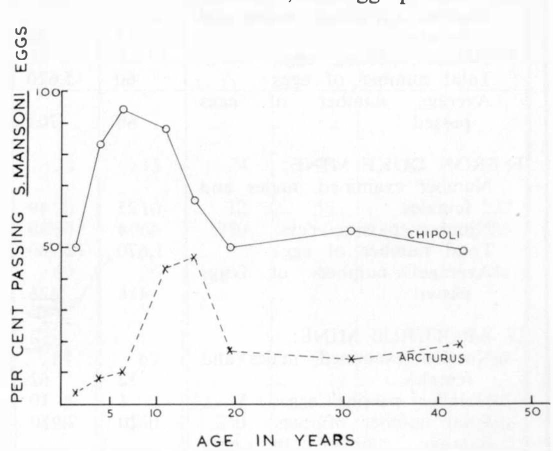

Fig. 3—Prevalence of *S. mansoni* infections in relation to age in two communities of Rhodesia.

urine samples were counted and the results for the different age groups were examined in terms of the average egg output in the infected members of the community. The results are presented in Table III and Fig. 4. The numbers of *S. mansoni* eggs in stool specimens at Chipoli Estate and the Bikita mine were also counted. The results are presented in Table IV. Counts of *S. mansoni* eggs in stool specimens were only made at Chipoli and Bikita. Egg counting in stool specimens is unsatisfactory since it is at present impossible to obtain reproducible results. The results in these two areas are only included because they indicate a tendency for decrease in numbers of eggs passed in older age groups.

The significance of the differences in the average numbers of eggs passed was established by the Kruskal-Wallis one way analysis of variance method (Seigal, 1956).

It can be seen from the tables and figures that, with the exception of the *S. mansoni* egg counts for the Bikita mine community and *S. haematobium* at the Turk mine, there is a consistent pattern of egg production in all the areas examined. In the other areas, the average egg count for the people passing eggs increased

Table III

S. haematobium INFECTIONS:

Results of Stool and Urine Examination Surveys in Five Communities in Rhodesia.

	Age Groups Examined								
	Under 4	4-6	7-9	10-12	13-15	16-20	21-40	Over 40	Totals
A. CHIPOLI ESTATE:									
Number examined, males and females	9	76	55	25	13	21	101	35	335
Number passing eggs	8	73	54	24	12	19	73	20	283
Total number of eggs	12,240	187,650	173,460	85,140	4,670	12,040	43,230	3,420	521,850
Average number of eggs passed	1,530	2,571	3,212	3,548	389	634	592	171	1,844
C. PREMIER CITRUS ESTATES:									
Number examined, males and females	25	37	77	54	19	28	148	70	458
Number passing eggs	0	10	37	32	9	10	23	10	131
Total number of eggs	0	5,950	65,710	28,670	2,860	940	3,070	880	108,080
Average number of eggs passed	0	595	1,776	896	318	94	133	88	825
D. BIKITA MINERALS MINE:									
Number examined, males and females	18	40	66	106	77	78	22	20	427
Number passing eggs	1	8	22	60	41	34	4	2	172
Total number of eggs	60	5,620	35,780	97,760	10,520	16,950	1,230	120	168,040
Average number of eggs passed	60	703	1,626	1,629	257	499	308	60	977
F. IRON DUKE MINE:									
Number examined, males and females	25	49	58	46	26	15	68	41	328
Number passing eggs	4	30	45	37	23	12	16	2	169
Total number of eggs	1,670	12,780	39,920	14,400	10,100	3,500	1,240	20	83,630
Average number of eggs passed	418	426	887	389	439	292	78	10	495
G. ARCTURUS MINE:									
Number examined, males and females	32	62	74	54	52	33	105	52	464
Number passing eggs	1	10	25	34	36	17	30	4	157
Total number of eggs	20	2,950	12,650	20,180	8,230	9,480	4,520	230	58,260
Average number of eggs passed	20	295	506	594	229	558	151	58	371

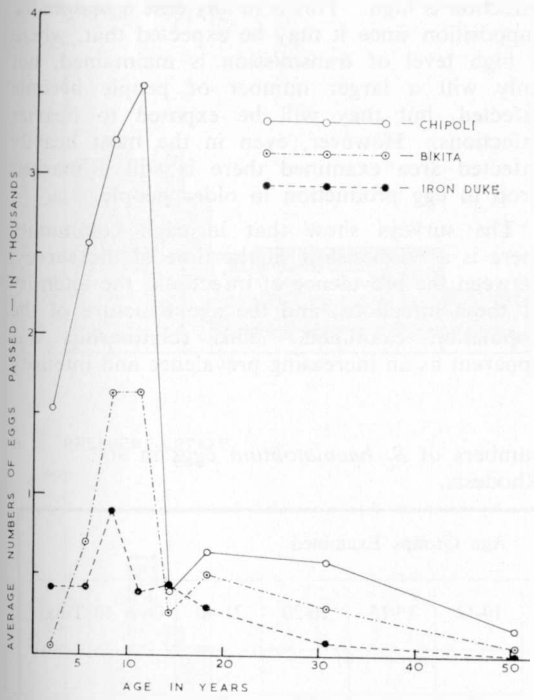

Fig. 4—Average numbers of *S. haematobium* eggs passed by different age groups in three communities of Rhodesia.

rapidly to a peak, usually occurring between the ages of seven and 12. Thereafter, the decrease in average egg production was dramatic within the two age groups succeeding the peak. There was often a second minor peak occurring between the ages 13 to 20 years, after which there was a further decrease in egg production with advancing age. This decrease in later life was slow but steady, without the dramatic decrease such as occurs immediately after the peak of egg production. No adequate explanation of this second minor peak can be given, but it is believed that it represents the more frequent contact with water by the young adults, particularly the young women, who, because of domestic duties, are so often compelled to have daily contact with surface water.

An examination of the proportions of infected people, in the different age groups, who pass large numbers of eggs, reveals a similar pattern of younger people passing more eggs than the older people. Examples of this are given in Table V and Fig. 5 for *S. haematobium* infections. It can be seen that the proportion of children passing more than 200 eggs of *S. haematobium* in a one-hour specimen rises in early childhood and reaches a maximum for the community usually in those people between the ages of five and 10 years. There is a subsequent

Table IV

S. mansoni INFECTIONS:

Results of Stool and Urine Examination Surveys in Two Communities in Rhodesia.

Number of eggs passed.

	Age Groups Examined								
	Under 4	4-6	7-9	10-12	13-15	16-20	21-40	Over 40	Totals
A. CHIPOLI ESTATE:									
Number examined, males and females	8	70	51	23	15	24	95	32	318
Number passing *S. mansoni* eggs	4	58	47	20	10	12	56	16	223
Total number of eggs	90	7,620	3,550	1.380	266	750	2,280	650	16,586
Average number of eggs passed	23	131	76	69	26	63	41	41	74
D. BIKITA MINERALS MINE:									
Number examined, males and females	20	37	60	84	67	59	21	20	368
Number passing *S. mansoni* eggs	1	1	3	5	2	7	3	1	23
Total number of eggs	120	80	110	120	160	230	50	190	1,060
Average number of eggs passed	120	80	37	24	80	35	17	190	46

decline in this proportion and very few adults are found to be passing eggs in large numbers. The general trend of average egg production follows the same pattern as prevalence with advancing age; both prevalence and egg production rise to a peak in early life, and then decrease progressively with age. The age of peak prevalence usually occurs at approximately the same age as the peak of average egg production, or before it.

By comparing the proportion of heavily infected people in different areas, it can be seen that the severity of infection, as judged by the egg production, is greatest where the prevalence of infection is high. This is in any case a reasonable supposition since it may be expected that, where a high level of transmission is maintained, not only will a larger number of people become infected, but they will be exposed to heavier infections. However, even in the most heavily infected area examined there is still a marked drop in egg production in older people.

The surveys show that in each community there is a relationship, at the time of the survey, between the prevalence of infections, the intensity of these infections, and the age structure of the population examined. This relationship was apparent as an increasing prevalence and intensity

Table V

Proportion of infected persons passing large numbers of *S. haematobium* eggs in six communities in Rhodesia.

	Age Groups Examined								
	Under 4	4-6	7-9	10-12	13-15	16-20	21-40	Over 40	Total
CHIPOLI ESTATE:									
Number of people passing eggs	8	73	54	24	12	19	73	20	283
Number passing over 2,001 eggs	3	24	18	9	0	1	5	0	60
Number per cent. passing over 2,001 eggs	37.5	33	33	38	0	5	7	0	21
Number passing over 201 eggs	5	51	34	16	6	6	25	4	147
Number per cent. passing over 201 eggs	63	70	63	67	50	32	34	20	52
PREMIER ESTATE:									
Number of people passing eggs	0	10	37	32	9	10	23	10	131
Number passing over 201 eggs	0	4	27	16	4	2	5	1	59
Number per cent. passing over 201 eggs	0	40	73	50	44	20	22	10	45
BIKITA MINE:									
Number of people passing eggs	1	8	22	60	41	34	4	2	172
Number passing over 201 eggs	0	5	16	42	11	16	2	0	92
Number per cent. passing over 201 eggs	0	63	73	70	27	47	50	0	53
TURK MINE:									
Number of people passing eggs	0	3	13	10	5	4	15	1	51
Number passing over 201 eggs	0	2	5	5	0	1	5	0	18
Number per cent. passing over 201 eggs	0	67	38	50	0	25	33	0	35
IRON DUKE MINE:									
Number of people passing eggs	4	30	45	37	23	12	16	2	169
Number passing over 201 eggs	2	12	26	11	10	5	1	0	67
Number per cent. passing over 201 eggs	50	40	58	30	43	42	6	0	40
ARCTURUS MINE:									
Number of people passing eggs	1	10	25	34	36	17	30	4	157
Number passing over 201 eggs	0	4	12	17	10	6	6	0	55
Number per cent. passing over 201 eggs	0	40	48	50	28	35	20	0	35

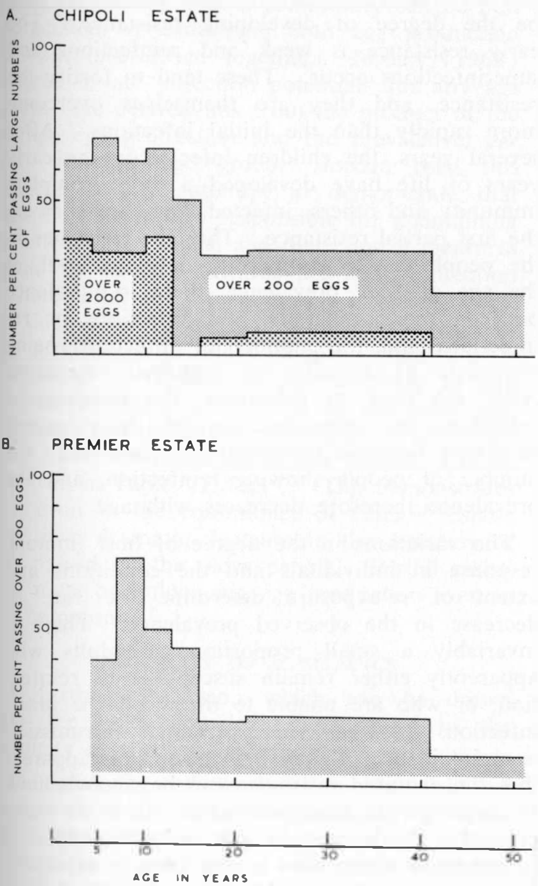

Fig. 5—Proportions of infected people passing over 200 or 2,000 *S. haematobium* eggs in one hour in two communities of Rhodesia.

with age until a peak was reached, usually between the ages of seven and 20 years. Thereafter, the prevalence and intensity of infections decreased with advancing age.

It is logical to assume that as the individuals pass from one age group to the next, the proportion of these individuals passing eggs and the numbers of eggs passed by the infected individuals will either increase or decrease in a similar manner. Although prevalence refers essentially to the number or proportion of people examined who are infected at the time of the survey, it can be assumed that the results reflect the changing pattern of prevalence and intensity in a group of indivduals as they pass from the youngest age group through to the oldest.

On this assumption it seems that there is a dynamic pattern of prevalence with age. Few if any infections are found in the youngest children examined, except in areas of intense transmission. As they progress through the age groups, more and more of them become infected until a peak of prevalence is reached. After this peak, people appear to lose the infections and the prevalence decreases. There is a corresponding decrease in the numbers of eggs passed by those individuals who remain infected.

It might be argued that the children between the ages of seven and 20 years are likely to have more contact with water than the older people, and that the differences in the extent of exposure to infection may account for the decrease in prevalence observed in older people. This argument, which is discussed later, cannot explain the striking decrease in prevalence and egg production which is seen in older people.

There are two possible explanations for the decrease in egg production with age. Firstly, that the deposition of fibrotic tissue resulting from the prolonged passage of eggs through the bladder or intestinal wall forms a mechanical barrier to further egg passage, or secondly, that the acquired resistance is developed by the host. In fact it is probable that both these factors influence the pattern of egg production in different age groups since it has been established that extensive fibrosis of the bladder wall can result from an infection, and it will limit or prevent egg passage. However, there are several reasons for rejecting the contention that fibrosis is the sole factor limiting the passage of eggs. These are:

(a) In the community of the Chipoli Estate where infections are at a very high level, and where it would be expected that fibrosis of the bladder wall would be severe, the egg production shows the least tendency to decrease of all the areas examined. This is entirely contrary to the expected if it is accepted that fibrosis alone limits egg passage.

(b) The decrease in egg passage in human cases is often accompanied by a relief in clinical symptoms. This would hardly be the case if, in fact, the activity of the worms was maintained and the eggs were trapped in the body. A much more pronounced pathogenesis would be expected to result if such was the case.

(c) In areas of high *S. mansoni* prevalence (Table II, Fig. 6) there is also diminished egg production in adults. This cannot be explained as resulting from fibrosis of the intestinal wall.

(d) In animal experiments, with *S. mansoni* or *S. japonicum* infection in monkeys, the fall

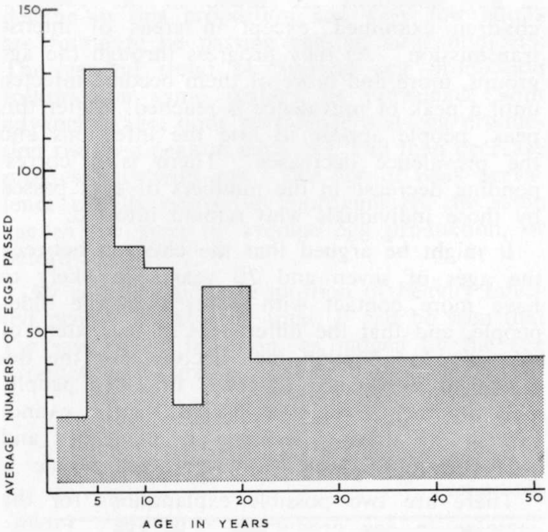

Fig. 6—Average numbers of *S. mansoni* eggs passed by infected people of different age groups of the Chipoli Estate.

in egg production in individual monkeys has been repeatedly observed (Vogel and Minning, 1953; Jachowski *et al.*, 1963) without any reported evidence of substantial fibrosis at autopsy. McMullen (personal communication) states that monkeys which have been exposed to very heavy infections of *S. mansoni* were examined after death. These monkeys had shown strong resistance to infection, yet no fibrosis could be found which could be attributed to the infection.

It must be concluded therefore that the older people have acquired a resistance to the infections and that this resistance influences the activity, and probably the life span, of the parasites, resulting in decrease in egg production in older people. This resistance is probably a host response, and it is therefore an immunological resistance.

It appears that there is a relationship between the development and the degree of resistance on the one hand and the degree, nature and duration of infection, re-infection and superinfection on the other.

A theoretical interpretation of this relationship can be suggested as follows:—

In the earliest years of exposure to infection the children are lacking in any resistance and infection takes place. Slightly older children are more frequently exposed to infection, and more of them become infected. At the same time, those that are infected develop partial resistance, and the longer they are infected the greater will be the degree of developing resistance. The early resistance is weak and reinfections and superinfections occur. These tend to fortify the resistance, and they are themselves overcome more rapidly than the initial infections. After several years, the children infected in the early years of life have developed a more complete immunity and others, infected later, are showing the first partial resistance. Thus the resistance in the people in the community develops until, at the age of peak prevalence, there is a balance between the number of new infections or re-infections and the number of infections being overcome as a result of acquired resistance. After the peak of infections, the numbers of infections overcome because of the acquired resistance becomes progressively greater than the number of people showing reinfection, and the prevalence therefore decreases with age.

The variations in the degree of host immune response in individuals and the conditions and extent of re-exposure determine the rate of decrease in the observed prevalence. There is invariably a small proportion of adults who apparently either remain susceptible to reinfection, or who are unable to throw off the initial infection. In areas where perennial transmission is maintained at a very high level, it is apparent that the acquired resistance can be overwhelmed by exposure to heavy infection; it is in these areas that the decrease in observed prevalence will be less pronounced than it is in areas of moderate transmission. A possible example of this is seen in the results for *S. haematobium* infections in the community of the Chipoli Estate.

Many authors have commented on observed differences in egg prevalence relationships in the two sexes. It appears from the present studies, however, that these differences are not the results of differences of immune responses in the sexes, but rather to the different exposure patterns related to occupations and sociological habits of the sexes. This is particularly striking at Chipoli where the prevalence in adult women was higher than it was in adult men. This is because the only sources of domestic water are the heavily infected canals and furrows. In the course of their domestic duties the women are compelled to have regular contact with the water of these canals, but the system of irrigation in practice on this estate does not require regular or prolonged contact with the water by the men.

The egg production patterns in relation to age, and the age-prevalence relationships have so far been considered separately. However, the full effects of resistance in a community can be best appreciated by examining both egg production and age prevalence together. Jordan (1963) referred to an "infection potential" for any age group. He derived this from the product of the average egg production and the prevalence, *per cent.*, in that age group. Jordan used this measure only to attempt to demonstrate that children were largely responsible for maintaining the infection of snails, and that control measures should be directed towards preventing infection in these children. However, this infection potential does demonstrate that dramatic decrease in egg production in older people, when this is considered in relation to the decrease in age prevalence which is observed in the same age groups. The infection potentials of the age groups examined at Chipoli and Premier Estates are given in Table VI, Fig. 7. This demonstrates that, even in the community of Chipoli Estate, there is a dramatic decrease in the numbers of eggs passed by the older people. Partial resistance must be influencing egg production even in this community.

Specificity of Resistance

A further conclusion which can be drawn from the epidemiological data refers to the specificity of the acquired resistance.

The majority of workers in the field of immuno-diagnosis have demonstrated a cross antigenicity between the species of the genus *Schistosoma*, and other workers, including Anderson (1960) and Sadun (1963) have reported cross antigenicity between the genus *Schistosoma* and other genera including *Trichinella, Heterophyes* and *Fasciola*. However, Anderson *et al.* (1963) demonstrated genus specificity of certain fractions of antigen extracts where the crude extracts gave cross reactions between related genera. Despite the evidence that antigen extracts contain a multiplicity of antigenis fractions, the intergeneric and the intrageneric nature of the antigen-antibody reactions in immunodiagnosis has led to the belief that acquired resistance will follow a similar pattern of cross reaction between the species of *Schistosoma*, and that resistance acquired as a result of infection by one species will protect the host against infection by a second species.

No conclusive work has been reported on interspecies resistance in animal experiments, and, up

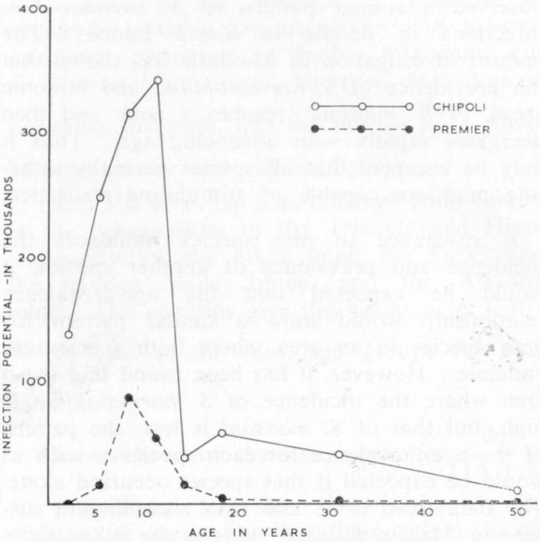

Fig. 7—*S. haematobium* infection potentials (Jordan, 1963) of different age groups in two communities of Rhodesia.

Table VI

S. haematobium: Infection Potentials in Age Groups at the Chipoli and Premier Estates.

	Under 4	4-6	7-9	10-12	13-15	16-20	21-40	Over 40	Total
	Age Groups Examined								
CHIPOLI:									
Mean egg production	1,530	2,571	3,212	3,548	389	634	592	171	1,844
Per cent. passing eggs	89	96	98	96	92	90	72	57	84
Infection potential	136,170	246,816	314,776	340.608	35,788	57,060	42,624	9,747	154,896
PREMIER:									
Mean egg production	0	595	1,776	896	318	94	133	88	825
Per cent. passing eggs	0	27	48	59	47	36	16	14	29
Infection potential	0	16,065	85,248	52,864	14,946	3,384	2,128	1,232	23,925

to the present, there has been no information on the specificity of resistance in man.

The pattern of prevalence increasing to a peak, usually in children or young adults, and then decreasing with advancing age, has been observed for all the species of *Schistosoma* normally infecting man. Pesigan *et al.* (1958) showed this pattern for *S. japonicum* infections in the Philippines, where the peak of prevalence occurred in young adults. Basseres and Pantoja (1947) found the peak of prevalence of *S. mansoni* infections in Minas Gerais, Brazil, in the 15 to 24 year group, and a reduced prevalence was observed in the older people. Gerber (1952) observed a similar pattern of *S. haematobium* infections in people in Sierra Leone. The present investigation in Rhodesia has shown that the prevalence of *S. haematobium*, and in some areas, of *S. mansoni*, reaches a peak and then decreases rapidly with advancing age. Thus it may be accepted that all species normally infecting man are capable of stimulating resistance.

If resistance to one species influences the incidence and prevalence of another species, it would be expected that the age-prevalence relationship would show a similar pattern for both species in an area where both species are endemic. However, it has been found that in an area where the incidence of *S. haematobium* is high, but that of *S. mansoni* is low, the pattern of the age-prevalence for each species is such as would be expected if that species occurred alone. The data from urine and stool examination surveys in African children living at the Bikita mine (Tables I and II) show that resistance to *S. haematobium* infections is acquired early in life, with a peak of prevalence occurring in the 10 to 12 year age group. However, in the same people there is neither evidence of resistance to the *S. mansoni* infections nor any evidence of the resistance to *S. haematobium* having any influence on incidence of *S. mansoni*.

It has already been shown that a low incidence of either species will delay or prevent the development of resistance, and in this community it is apparent that although the incidence of *S. haematobium* is sufficiently high to stimulate the development of resistance to that species, the incidence of *S. mansoni* would appear to be too low to do so. If however, the development of resistance to *S. haematobium* had conferred any protection against *S. mansoni* infection, it would be expected that the prevalence and incidence of *S. mansoni* would have decreased with that of *S. haematobium*.

The fact that the prevalence of *S. mansoni*, as detected by stool examination, did not decrease after the age of peak prevalence of *S. haematobium*, indicates a lack of protection to *S. mansoni* infections; there is a lack of cross resistance between the species from *S. haematobium* to *S. mansoni*. In the community of the Chipoli Estate, the incidence of both *S. mansoni* and *S. haematobium* is sufficiently high for both species to stimulate resistance independently. It is unfortunate that no area was found in Rhodesia where the incidence of *S. mansoni* was high enough for the development of resistance, but where incidence of *S. haematobium* was too low to do so. Therefore, it can only be hesitantly presumed that resistance to *S. mansoni* confers no protection against *S. haematobium* infections.

This indication of species specificity of resistance can be supported by the examination of *S. mansoni* infections in people showing resistance to *S. haematobium*. If resistance acquired as a result of infection by one species affords a protection against infection by a second species, it would be expected that the infections of the second species which do occur, would occur only in those people who had not yet developed resistance against the immunising species.

Fig. 8 presents, in the form of a histogram, the age prevalence relationship of *S. haematobium* infections in the communities of the Triangle and Hippo Valley Estates. It may be assumed that, without the influence of resistance, the prevalence would have increased with advancing age; at the very least, it would have remained, in older people, at the level reached at the age of peak prevalence, as represented by the line of expected prevalence E. The difference between the observed level of prevalence and

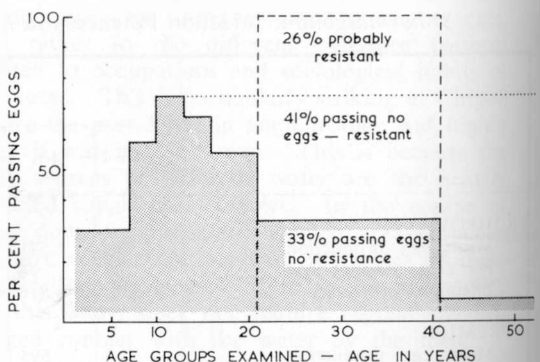

Fig. 8—Age prevalence relationship of *S. haematobium* infections in the community of the Triangle and Hippo Valley sugar estates.

the expected level E, represents the number of people who have developed sufficient resistance to overcome or inactivate the infections. The people still passing eggs must be those who have not developed sufficient resistance to overcome their infections. If resistance has an inter-species influence it would be expected that any infections of *S. mansoni* which occur would be in those people who are still showing active infections of *S. haematobium*. In the age group 21 to 40 years, the prevalence of *S. haematobium* infections is 33 per cent., and 41 per cent. have apparently developed sufficient resistance to have overcome their initial and any subsequent infections. This latter group of 41 per cent., being resistant to *S. haematobium* infections, would also be free, or virtually free, of *S. mansoni* infections if the resistance against *S. haematobium* also afforded protection against *S. mansoni*. In this age group, 24 people were found to be passing *S. mansoni* eggs, and if there is an inter-species protection, the majority of these people should have been in the 33 per cent. who had not developed resistance and who were still passing eggs, i.e. the majority of *S. mansoni* infections would have occurred as double infections with *S. haematobium*. In fact, only 11 of 24 *S. mansoni* infections in this group occurred as double infections. Conversely, if resistance is species specific and there is no inter-species influence, the *S. mansoni* infections should be randomly distributed through the population, without regard to the distribution of *S. haematobium* infections. However, as the proportion of *S. haematobium* infections increases, there would be more double infections distributed by chance. Therefore, in the same age group 33 per cent., or eight of the 24 *S. mansoni* infections, would be expected to occur as double infections with *S. haematobium*.

If resistance to *S. haematobium* conferred resistance to *S. mansoni* the proportion of *S. mansoni* infections occurring as double infections would increase beyond the proportion of the community showing *S. haematobium* infections. However, if resistance is species-specific, the probability of *S. mansoni* infection of an individual would be independent of whether or not that individual is infected with *S. haematobium*.

These concepts may be expressed in ratios as follows:—

If the resistance is species-specific the ratio of double infections (d) to single *S. mansoni* infections (s) would then be the same as the ratio of the number of people showing active *S. haematobium* infections (i) to the number of people free of *S. haematobium* infection (f).

Therefore $\dfrac{d}{s} = \dfrac{i}{f}$

or $\dfrac{d}{d + s} = \dfrac{i}{i + f}$

and $\dfrac{d\,(i + f)}{i\,(d + s)} = 1$

but i + f can be taken as the total number of people examined (e) and therefore

$$\frac{de}{i\,(d + s)} = 1 \text{ (unity)}$$

If there is an inter-species influence of acquired resistance, the proportion of *S. mansoni* infections occurring as double infections with *S. haematobium* would increase with age as resistance increases, and the ratio $\dfrac{de}{i\,(d + s)}$ would become greater with advancing age.

Table VII gives the data obtained from surveys in the communities of the Triangle and Hippo Valley Estates, the Bikita mine, the Turk mine, the Golden Valley mine, and the Arcturus mine. The columns give the values of e, i, d, s and $\dfrac{de}{i\,(d + s)}$ for four age groups for each community.

The results show that the values for $\dfrac{de}{i\,(d + s)}$ are significantly greater than unity in the majority of areas, but that these values do not increase with age. The fact that they do not increase with age supports the previous evidence that resistance in man acquired as a result of *S. haematobium* infections conveys little or no protection against subsequent exposure to *S. mansoni*. It also indicates that the decrease in prevalence of *S. haematobium* is not due to a lack of exposure in older age groups since, if this were so, both *S. mansoni* and *S. haematobium* would be found together in only those people who continued to have contact with water and exposure to infection. Since it is suggested that as they grow older, fewer and fewer people are exposed, it would be expected that the proportion of double infections would rise. It has been demonstrated that this does not happen.

The fact that these values of $\dfrac{de}{i\,(d + s)}$ are consistently greater than unity, although they do not increase with age, can be explained by any or all of the following reasons:

(a) The ratio ignores the number of people who fall above the line E (Fig. 8), including those who appear to be naturally resistant to all schistosome infections. These would weight the values to give a ratio above unity.

(b) There must surely be some individuals or groups of individuals who by inclination, habit or by nature of occupation have greater contact with infected water throughout their lives, e.g., in African people girls are given domestic duties,

Table VII

Distribution of *S. mansoni* infections in relation to *S. haematobium* infections in six communities in Rhodesia.

	No. examined e	No. passing *S. haematobium* eggs i	No. passing both *S. mansoni* and *S. haematobium* eggs d	No. passing *S. mansoni* eggs only s	$\frac{de}{i(d+s)}$
TRIANGLE & HIPPO VALLEY ESTATES:					
Up to 6 years old	117	35	8	6	1.91
7—12 years old	104	67	19	11	0.98
13—20 years old	148	86	17	10	1.08
Over 20	353	87	11	21	1.39
TOTAL:	722	275	55	48	1.40
BIKITA MINE:					
Up to 6 years old	58	9	0	2	0
7—12 years old	172	82	6	2	1.57
13—20 years old	155	75	2	8	0.41
Over 20	42	6	1	3	1.75
TOTAL:	427	172	9	15	0.93
TURK MINE:					
Up to 6 years old	42	4	0	0	0
7—12 years old	176	23	3	7	2.30
13—20 years old	26	8	0	0	0
Over 20	218	17	0	3	0
TOTAL:	462	52	3	10	2.05
GOLDEN VALLEY MINE:					
Up to 6 years old	141	8	0	10	0
7—12 years old	74	13	2	7	1.26
13—20 years old	12	3	2	0	4.00
Over 20	93	12	1	12	0.60
TOTAL:	320	36	5	29	1.31
ARCTURUS MINE:					
Up to 6 years old	94	11	1	4	1.71
7—12 years old	128	59	22	10	1.49
13—20 years old	85	53	21	8	1.16
Over 20	157	34	10	16	1.78
TOTAL:	464	157	54	38	1.73
Totals:					
Up to 6 years old	452	67	9	22	1.96
7—12 years old	654	244	52	37	1.57
13—20 years old	426	225	42	26	1.17
Over 20	863	156	23	55	1.63
TOTAL:	2,395	692	126	140	1.64

including fetching and carrying of water, washing of dishes and laundry, from a very early age. Throughout their lives they would continue to be exposed more than the boys and men who do not have exposure forced on them as a daily routine.

(c) It is possible that some people are generally more susceptible to infection or penetration by cercariae.

The presence in any age group of any community of a proportion of such people who, because of greater exposure or greater susceptibility, are more likely to become infected with either or both species of *Schistosoma* would result in the value for $\frac{de}{i\,(d + s)}$ being considerably greater than unity.

Comparison of Results of Specimen Examinations with Serological or Immunological Tests

Further evidence to support the existence and development of resistance in man can be derived from a comparison of the results of surveys undertaken by the examination of stool and urine specimens with the results of tests for detectable antibodies in the same people. Two such surveys have been conducted in the course of the present study; these were in the communities of the Golden Valley mine and the R.A.N. mine. A few people in each of the age groups were unable to produce urine or stool specimens. In very young children administration of skin tests proved difficult. There are, therefore, some discrepancies in the numbers examined or tested by the two methods. In the great majority of cases the same individuals were tested by both methods. The results are given in Tables VIII and IX and Figs. 9 and 10.

Table VIII and Fig. 9 show the results of specimen examination surveys and intradermal testing at the Golden Valley mine. This is an area of low prevalence, and the proportion of people passing eggs of either *S. haematobium* or *S. mansoni* reaches a peak of 44 per cent. in the age group 13 to 20 years. Forty-five people in this age group were examined, and 20 (44 per cent.) were found to be passing *S. haematobium* or *S. mansoni* eggs.

In the very young children, under four years old, the prevalence based on specimen testing was slightly higher than the prevalence by intradermal testing; this is to be expected, since it is known that the skin test lacks sensitivity in the very young (Sadun, personal communication). In the age group four to seven years the prevalence by skin testing is higher than that shown by specimen examinations, and thereafter there is a progressively greater difference between the two methods of testing as age increases. After the age of peak prevalence this difference is exaggerated as the number of people passing eggs drops. In the adults over the age of 40 years only 13 per cent. of the people tested were passing eggs, but 85 per cent. of these same people gave positive skin test reactions.

Table VIII

THE GOLDEN VALLEY MINE:

Comparison of intradermal tests with specimen examination surveys in determining the age-prevalence relationship for *Schistosoma* spp.

	Age Groups Examined						
	0-3	4-7	8-11	12-20	21-40	Over 40	Total
Stool and Urine Examinations:							
Number of people examined	97	113	91	45	113	75	534
Number of people passing either *S. haematobium* or *S. mansoni* eggs	10	18	27	20	33	10	118
Number per cent. passing eggs	10	16	30	44	29	13	22
Intradermal Tests:							
Number of people tested	95	116	96	49	140	106	602
Number showing positive reactions	9	43	58	38	121	90	359
Number per cent. showing positive reactions	9	37	60	78	86	85	60

Table IX and Fig. 10 show the results of specimen examination surveys and intradermal and fluorescent antibody testing in the same people. A similar pattern of prevalence was seen. The specimen examination surveys showed that a peak of 57 per cent. was reached in the age group 16 to 20 years, after which the expected falling off of the numbers of people passing eggs was apparent, until in the adults over 40 years old only 17 per cent. were still passing eggs of either *S. mansoni* or *S. haematobium*. The intradermal tests gave positive results in 95 per cent. of the people in the age group 16 to 20 years, and there was subsequently

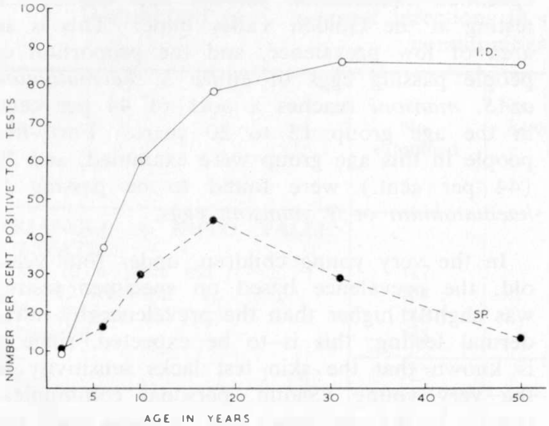

Fig. 9—Comparison of age-prevalence of *S. haematobium* and *S. mansoni* infections assessed by specimen examination (SP.) with results on intradermal tests (I.D.) in the community of the Golden Valley Mine.

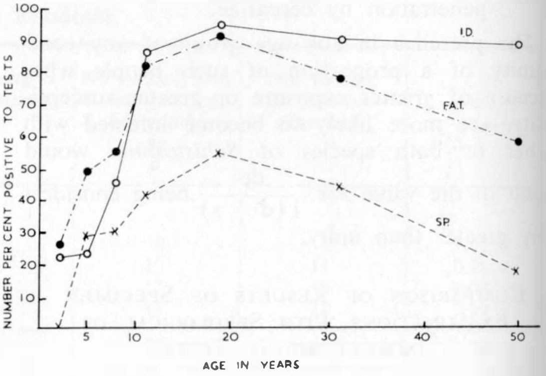

Fig. 10—Comparison of age-prevalence of *S. haematobium* and *S. mansoni* infections assessed by specimen examination (SP.) with results of intradermal tests (I.D.) and fluorescent antibody tests (F.A.T.) in the community of the R.A.N. Mine.

Table IX

THE R.A.N. MINE:

Comparison of fluorescent antibody tests, intradermal tests and specimen examination surveys in determining the age-prevalence relationship for infections of *Schistosoma* spp.

	Age Groups Examined								
	Under 4	4-6	7-9	10-12	13-15	16-20	21-40	Over 40	Total
Stool and Urine Examinations:									
Number of people examined	12	31	37	21	1	21	79	72	274
Number of people passing either *S. haematobium* or *S. mansoni* eggs	0	9	11	9	1	12	36	12	90
Number per cent. passing eggs	0	29	30	43	—	57	46	17	33
Fluorescent Antibody Tests:									
Number of people tested	15	42	46	23	2	22	83	75	308
Number showing positive reactions	4	21	26	19	2	20	65	44	201
Number per cent. showing positive reactions	27	50	57	83	—	91	78	59	65
Intradermal Tests:									
Number of people tested	13	29	38	21	1	20	79	73	274
Number showing positive reactions	3	7	18	18	1	19	72	65	203
Number per cent. showing positive reactions	23	24	47	86	—	95	91	89	74

only a very slight fall in prevalence to 89 per cent. in the adults over the age of 40. The results of the fluorescent antibody testing were similar to those of the intradermal tests up to the age group 16 to 20 years, at which age 91 per cent. were giving positive reactions. However, after this age there was a decrease in the proportion of people with positive fluorescent antibody reactions until, in the adults over 40 years old, only 59 per cent. showed positive.

Fig. 10 shows that there is again a progressively greater divergence between the results of specimen testing and serological testing. This divergence with increasing age is regular up to the age of peak prevalence, but after this age the rapid decrease in the numbers of people passing eggs exaggerates the divergence.

Since it is known that detectable antibodies can persist for a considerable, but not necessarily indefinite, period after cure, whether or not this cure is spontaneous or chemotherapeutic, it can be presumed that both the fluorescent antibody test and the intradermal test will detect not only active but also cured infections, or inactivated infections where no eggs are being passed. Repeated specimen testing aimed at the detection of both *S. haematobium* or *S. mansoni* eggs in the urine or stool will detect only the active infections. It can be presumed, therefore, that the differences in the prevalence, as determined by the fluorescent antibody test or the intradermal test, on the one hand, and by specimen examination on the other, represents the proportion of inactive or cured infections. In areas such as the two under discussion, where very few of the infections are cured by chemotherapy, the cause of these differences may be ascribed to spontaneous cure or inactivation of the worms.

The divergence between the results of the specimen testing and the immunological testing before the age of peak prevalence suggests that inactivation of the worms occurs very rapidly in some people, but that re-infection can take place. However, with advancing age more and more children are able to overcome an existing infection and resist subsequent exposure to re-infection. The longer a person has been infected or exposed to re-infection, the less re-infection will occur, until the age is reached where the numbers of people who overcome their infections equals and then exceed the number who are re-infected. From this age the prevalence, based on detection of eggs, will decrease with advancing age. However, as long as any antigen either from inactivated but still living worms, or from eggs deposited in the tissues, remains in the body, antibodies will be detectable. There is only a slight falling off of the proportions of people showing apparent infection by either of the immunological tests.

A further comment can be made on the age-prevalence of infections as assessed by immunological tests. In neither of the areas examined did the proportion of people positive to the immunological tests exceed 95 per cent. This has been confirmed by two other series in African communities (Clarke *et al.,* unpublished data). It appears, therefore, that up to 5 per cent. of the community never show detectable antibodies. The error in the negative results of the fluorescent antibody test has been shown to be low, and it is possible that a portion of this 5 per cent. of the people have never contracted the disease despite probable exposure. This small group might then possess a protection against infection which is not the result of previous infection. Such a protection could not be regarded as an actively acquired resistance and it would be natural (passive) resistance, according to Boyd's classification (Kagan, 1958). The results of the survey at the Chipoli Estates (Table I, Fig. 2) indicate that where the people are constantly exposed to massive infections, such natural (passive) resistance, and actively acquired resistance, may be partially overcome by the excessive exposure.

The Comparison of Prevalence of S. haemotobium Infections Before and After a Period during which Transmission has been Partially Prevented

Partial or total interruption of transmission of *Schistosoma* spp. can be effected by chemical control of snails, and the comparison of the prevalence of *S. haematobium* infections in the children before and after a period of control furnishes additional evidence of the influence of acquired resistance.

A satisfactory snail control programme was maintained in the Chikwanda and Zimutu and in the Serima areas of Rhodesia for a period which included the years 1960 to 1962. The control was based on the use of the chemical molluscicide "Bayer 73" (the ethanolamine salt of 5, 2'-dichloro-4'-nitro-salicylic-anilide) which was applied to all natural waters at a concentration of 0.5 parts per million if the water-bodies were found to be harbouring vector snails. All water was inspected at six-week intervals, and if any persisting foci of snails were found the chemical was applied immediately to eliminate those foci. No quantitative sampling of the snail populations was done, but manual searching for snails demonstrated that successful control of the snails had been achieved and very few snails could be found during the period under consideration. However, the results of urine examination surveys in the children undertaken in February and March of 1960 before control, and again in the same months of 1962 after two years of control, indicate that a low level of transmission was probably maintained, since some new infections were contracted during the period between the surveys.

The results of the surveys are presented in Tables X and XI and Figs. 11 and 12. In assessing these results no attention has been given to the migrations of people or families into or out of the control area, nor to the children who might have received chemotherapeutic treatment for the disease. It is believed, however, that the numbers concerned constituted only a very small and insignificant proportion of the total numbers examined.

It had been anticipated that the most marked effects of the snail control would be apparent in the younger age groups. It was found, in fact, that the decrease in prevalence believed to be the result of the control measures became progressively more marked with increasing age up to the age of highest prevalence in 1960. Similar patterns of prevalence following control measures were recorded by Berry (personal communication), working in Egypt.

Fig. 11 shows the observed age prevalence of *S. haematobium* infections for the Chikwanda and Zimutu areas for both 1960 and 1962. Also illustrated is the "expected" 1962 age prevalence curve which is based on the assumption that transmission had been totally interrupted during the two-year period and that no resistance, with its consequent inactivation of the infections, had developed. The "expected" 1962 prevalence for each age group under these conditions would then be the same as for that same group of children in the first survey when they were two years younger, i.e., 51 per cent. of the eight- to nine-year-old children showed *S. haematobium* infections in 1960; if no new infections occurred, and if none of the existing infections died out, there would still be 51 per cent. of the children, now aged 10 to 11 years, showing infection.

The decrease in infection was less than expected in the younger age groups and this is probably the result of incomplete control of transmission. The decrease in prevalence in the older children is progressively greater than expected, the difference being greatest at the age of peak prevalence in the first survey. The peak of prevalence in 1962 is in an older age group than in 1960.

The theoretical interpretation of the relationship between the prevalence of infections and the degree of developing resistance, discussed under the section dealing with the age-prevalence, can be extended to include the differences observed before and after control.

It would appear that where transmission is lowered by snail control the very young children, with little or no resistance, continue to become infected. The slightly older children develop resistance largely as a result of infections contracted before the control was initiated; this resistance partially protects them against the low level of exposure to re-infection and it overcomes some of the original infections. Still older children have developed stronger resistance, and even more of the original infections are overcome.

Under normal conditions of transmission the low degree of resistance in young children is overcome by the normal exposure to superinfection, but as the resistance develops in strength the extent of superinfection is lessened until a balance between acquired resistance and re-infection or superinfection is reached. Where the extent of exposure is decreased by the control measures, the developing resistance can overcome the existing infections or the subsequent mild re-infections earlier in life, with the result that the fall in prevalence is greater than expected in the older children.

The effects of the control measures will not only be reflected in the decreased prevalence of infections, but also in decrease in the intensity of the infections, because the individuals will be exposed to smaller numbers of cercariae. It must be expected, therefore, that with prolonged control, acquired resistance will take longer to develop.

Discussion

The two main objectives of this study have been to present evidence that resistance to infections of *Schistosoma* spp. is developed in man and to draw conclusions on the relationship between acquired resistance and the transmission of the parasites.

The reports of many authors have clearly demonstrated that animals develop a resistance to infections of *S. mansoni*, and some indications have been obtained on factors which influence

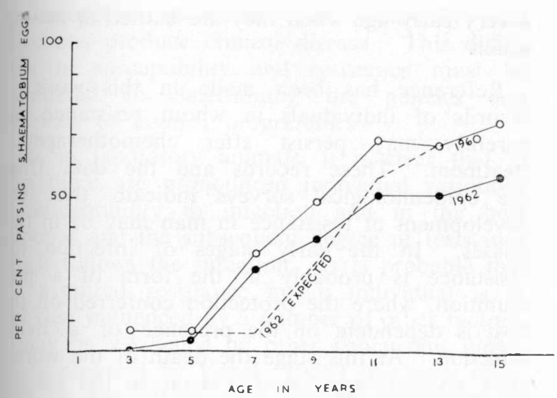

Fig. 11—Results of urine examination surveys for *S. haematobium* infections in African children in the Chikwanda and Zimutu areas in 1960 and 1962, before and after a period of effective snail control.

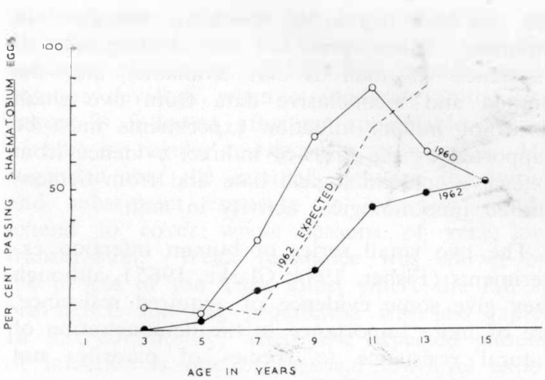

Fig. 12—Results of urine examination surveys for *S. haematobium* infections in African children in the Serima area in 1960 and 1962 before and after a period of effective snail control.

Table X

Results of Urine Surveys for *S. haematobium* infections in African children in the Chikwanda and Zimutu areas in 1960 and 1962.

	Age Groups Examined							
	Under 4	4-5	6-7	8-9	10-11	12-13	14-15	Total
1960 (BEFORE CONTROL)								
Number of children tested	272	412	407	392	145	97	62	1,787
Number passing eggs	11	20	127	201	94	62	44	559
Number per cent. passing eggs	4	5	31	51	65	64	71	31
1962 (AFTER CONTROL)								
Number of children tested	61	86	367	504	397	441	234	2,090
Number passing eggs	0	3	95	203	180	205	132	818
Number per cent. passing eggs	0	3	26	40	45	46	56	39

Table XI

Results of urine surveys for *S. haematobium* infections in African children in the Serima reserved area in 1960 and 1962.

	Age Groups Examined								
	Under 2	2-3	4-5	6-7	8-9	10-11	12-13	14-15	Total
1960 (BEFORE CONTROL)									
Number of children tested	—	131	178	204	186	64	47	44	854
Number passing eggs	—	9	9	72	120	54	30	25	319
Number per cent. passing eggs	—	7	5	35	65	84	64	57	37
1962 (AFTER CONTROL)									
Number of children tested	2	54	74	177	228	260	290	207	1,292
Number passing eggs	0	0	2	25	53	107	132	119	438
Number per cent. passing eggs	—	0	3	14	23	41	46	57	34

the rate and degree of resistance developed in animals. Direct proof of the development of resistance in man is not available, and the limited and inconclusive data from two small series of human infection experiments must be supported by the mass of indirect evidence from extensive epidemiological data and from demonstrated immunological activity in man.

The two small series of human infection experiments (Fisher, 1934; Clarke, 1965), although they give some evidence of acquired resistance, are of more importance in the demonstration of natural resistance to species of parasites not usually infecting man.

The epidemiological evidence of the development of resistance is based on patterns of decreasing prevalence of infection, and on decreasing egg production, in the older age groups. It is also indicated by comparison of age prevalence relationships as assessed by specimen examinations or by immunological tests and by comparison of results of specimen examination surveys before and after periods during which transmission was partially interrupted.

The popular theory that the decrease in age prevalence of infection and in egg production in older people is the result of mechanical fibrotic obstruction of egg passage through the walls of either the bladder or the bowel is totally unacceptable. It is also unacceptable that these decreases with advancing age are the results of natural senescence of the worms, which have been shown to have a life span of over 25 years in several recorded instances. The results reported in this study, and by other workers, show that the only acceptable conclusion is that the death or the inactivation of the worms of the infection are the result of host response, which affords a protection or resistance against future infection.

Recent incomplete investigations by Gelfand *et al.* (1964) indicate that there is a transfer of detectable antibodies from mother to child during pregnancy, since antibodies have been detected by the bilharzial fluorescent antibody test in the sera of new-born infants of infected or previously infected mothers. Further investigations with more specific and reliable tests, possibly the complement fixation test, are required to confirm these reported results. If protective antibodies are also present in infants as a result of congenital passive transfer it would explain the scarcity of infections in young infants who, under conditions currently prevailing in Rhodesia, are often exposed to infection from a very early age when they are bathed in natural water.

Reference has been made in this work to records of individuals in whom resistance apparently may persist after chemotherapeutic treatment. These records and the data from the epidemiological surveys indicate that the development of resistance in man may be in two phases. In the early stages of infection the resistance is probably in the form of a premunition, where the protection conferred on the host is dependent on the presence of a living infection. At this stage the death of the worms after chemotherapy would result in the loss of resistance and the host would soon be susceptible to re-infection. However, it appears that in time the premunition is replaced by a true immunity, where the resistance of the host is a true host response which is no longer dependent on the continued presence of living worms or of antigenic material. This immunity would depend on the very rapid production of antibodies when the host is exposed to re-infection. The development of such immunity is shown by the persistence of protection after chemotherapy reported by Vogel and Minning (1953) in rhesus monkeys, and by observations of non-recurrence of infection, despite almost certain re-exposure, in people treated for long-standing infections.

From the available data of the human infection experiments, and from the mass of evidence from epidemiological surveys and from demonstrated immunological activity in man, it is possible to draw the firm conclusion that man is capable of developing resistance to infection of *Schistosoma* spp.

Once this conclusion is reached, further conclusions on the development of resistance in man can be made.

Conclusions from Epidemiological Data

The epidemiological surveys have afforded evidence to support three important assumptions relating to the development of resistance in man. These assumptions are that there are racial differences in susceptibility and the ability to acquire resistance, that acquired resistance may be species specific, and that the rate and degree of resistance developed are influenced by the patterns of transmission to which the people are exposed.

There is some evidence that resistance, both natural and acquired, is more active in Africans than it is in Europeans. The majority of clinical observers agree that bilharziasis is more severe in Europeans, in whom even apparently light infections produce clinical disease. This difference in susceptibility and resistance must be considered in determining the policies and priorities of control programmes.

As in laboratory animals, it is clear that in man there are pronounced individual variations in susceptibility to infection and in the host response and the subsequent degree of resistance which follows the infection. It is probable that the acquired resistance in an individual is in any case influenced by a number of other factors; it may be weakened by other concurrent illness or, as reported by Vogel (1958) in rhesus monkeys, by parturition, or it may be dependent on nutritional status.

The evidence of species specificity of resistance in man is at present limited. It has been shown that resistance to *S. haematobium* does not protect against *S. mansoni* infection. There is no evidence on the influence of *S. mansoni* resistance on *S. haematobium* infection, and similarly there is no knowledge on possible interspecies resistance with other species of *Schistosoma*. The lack of protection against *S. mansoni* in people who are resistant to *S. haematobium* infections could be of importance in many countries of Africa, where the development of irrigation is leading to an increase in the prevalence of *S. mansoni* in people previously exposed to heavy infections only of *S. haematobium*.

It has been established that the rate of the development of resistance and the degree of resistance developed in man are dependent on the nature and extent of exposure to infection. There is, therefore, a relationship between the rate and degree of the development of acquired resistance and the extent and conditions of transmission to which the people are exposed.

The Relationship Between Acquired Resistance and Transmission

The epidemiological data show that the extent of resistance developed in the people of a community is influenced by the patterns of transmission to which they are exposed. In the communities examined, the strongest resistance to *S. haematobium* infections was apparently developed in the people of the Arcturus and Iron Duke mines where, after the ages at which the peaks of prevalence and of average egg production occurred, both the prevalence and the egg production decreased rapidly. Both these mining communities are in areas where transmission would be expected to be intense during two relatively short seasons, but low during the remainder of the year. This conforms with the opinions of Gerber (1952) that maximum resistance develops when a moderate initial exposure is followed after an appreciable period of time by regular re-exposures to infection. He suggested that the intervals between the initial and subsequent exposure to infection should extend to cover whole seasons of very low transmission. Weak resistance was shown by the people of the Turk mine, where the fall in prevalence and egg production was less rapid. In this community, where the expected pattern of infection is one of seasonal low-level exposures, it is presumed that the original infections are too light to develop full resistance. However, in the community of the Chipoli Estate, where the people are exposed to intense perennial transmission, it is apparent that resistance is again weak. In this case it is probable that the development of immunity is prevented by the very heavy exposures to infection in early childhood.

In bacterial or virus disease it is known that it is in the early years of life that immogenic processes are most active, and it is probable that the same is true for parasitic infections. If these processes are prevented by the heavy infections, the resulting "immunological paralysis" would persist for life and resistance, if any, would be weak. As a result, a large proportion of the people, even of the older adults, were found to be passing eggs. It is apparent that the most effective resistance is developed in communities exposed at intervals or seasons to moderately heavy infections. Too low or too high a level of transmission will limit the development of resistance in the people.

Patterns of Transmission

The patterns of transmission are governed by the interaction of a number of different factors. The most important of these are the stability and permanence of the waterbody, the water temperature and the density of the human population having contact with the waterbody.

Dense snail populations are usually found only in stable waterbodies. Even if all other conditions are suitable, snails will seldom be found in large numbers in waterbodies liable to excessive flooding during the rains, or to drying out during the winter and early summer. Shiff (1964a, 1964b) observed that this is particularly true for the snail host of *S. mansoni*, *Biomphalaria pfeifferi*, which can only survive in permanent water. *Bulinus (Physopsis) globosus*, the main host snail of *S. haematobium* in Rhodesia, is able to withstand desiccation, but nevertheless dense populations of this snail are seldom found in temporary waters.

Temperature has a pronounced effect on the infectivity of any waterbody and on the level of transmission. High water temperatures lead to rapid reproduction by snails, and the proportion of young, susceptible snails will be high (Shiff, 1964a, 1964b). Water temperature also influences the rate of sporocyst development, the abundance of algal food for the snails and the extent of human contact with the water. All these result in a high infectivity of the waterbody when temperatures are high. Pitchford and Visser (1962) demonstrated seasonal differences in the transmission of *S. mansoni* by recovering schistosome worms from groups of mice which had been immersed in naturally infected water in a highly endemic area. Although they did not correlate the seasons of transmission with the temperature of the water, they did find the highest transmission occurring during summer. During the winter few if any of the mice became infected.

The density of the human population dependent on the water for domestic or recreational purposes will also affect the level of transmission. This was shown for *S. mansoni* infections by Pitchford (1958) when he demonstrated that prevalence of these infections increased with the human population concentration.

Four distinct patterns of transmission can be found in Rhodesia.

In areas more than 1,000 m. above sea level transmission is limited or absent during the winter months when the water temperatures are low. Transmission is therefore seasonal and limited to the summer. In some parts of the high plateau, where these seasonal conditions of transmission occur, the transmission in summer is at a high level. In other parts, particularly in the south-west of the country, the unstable waterbodies and the low density of human settlement prevent high summer transmission.

In the hot low-lying areas of Rhodesia the water temperatures, even during the winter, are sufficiently high for continued transmission. Where waterbodies are not stable, and where human settlement is sparse, this perennial transmission is maintained only at a low level. Where the waterbodies are stable and the human settlement is dense, as on the irrigation estates, perennial intense transmission will occur.

The pattern of high summer transmission alternating with winter seasons of little or no transmission results in strong resistance in the community. Examples of this are found in the communities of the Iron Duke, the R.A.N. and the Arcturus mines.

Where a community such as the Turk mine is exposed to a low level of transmission which is even then limited to the summer months, the resistance acquired by the community is weak.

Perennial transmission at a high level is found in the irrigation systems of the hot low-lying areas of the country. An example is the Chipoli Estate. In these areas the prevalence of infections of both *S. mansoni* and *S. haematobium* is high and the resistance acquired by the communities is weak. The Triangle and Hippo Valley estates also have conditions suitable for intense perennial transmission. However, because they are newly developed estates, and because many of the people tested are new to the area, the results of the epidemiological surveys do not reflect the expected conditions of transmission.

Probable Future Developments

It is possible to predict the future development of bilharziasis in Rhodesia if no control measures are initiated.

On the high central plateau, where most of the European community is concentrated, the continuing programme of water conservation can only result in increasing intensity of transmission in the summer months. In the north-eastern regions of this plateau, where summer transmission is already high, it will become more intense. In the south-western regions, where transmission is at present low, even during the summer transmission season, the water conservation measures are creating stable waterbodies. With the increased human population densities resulting from the intensification of agriculture, the summer transmission must increase. In the African population the prevalence of infection in the children will be high, but the effective resistance developed will result in a decreased prevalence in older people. The European population will be exposed to infections of increasing intensity without the protection of effective resistance. It must be expected that the morbidity due to the disease will increase in all sections of the community, but particularly in the Europeans. Infections of both species will increase in prevalence.

In the hot low-lying areas of the country human population density is generally low. Except in irrigation settlements, it is likely that incidence and prevalence of the disease will remain low. However, in irrigation settlements the only logical expectation must be that incidence, prevalence and intensity of infections of both *S. mansoni* and *S. haematobium* will increase dramatically. This will result from the combination of three factors: the stability and permanence of the waterbodies, the high temperatures which are maintained throughout the year and the dense human settlement. As stated previously, these factors have been shown by Pitchford (1958), Pitchford and Visser (1962) and Shiff (1964a, 1964b) to be important in maintaining a high level of transmission. Resistance acquired under these conditions of transmission will be weak. It must be expected that morbidity or even mortality will increase both in Europeans and in Africans.

The present policy of recruiting labour for the irrigation projects from the low prevalence areas of the western half of the country, where community resistance is low, must result in intense infections. These infections will occur in the economically productive adults as well as in the children. The resulting morbidity in adults could have an adverse effect on the economy of the irrigation programmes.

Eventual control of the disease will require a combination of all available methods to break the cycle of the disease or to limit the extent of transmission.

This study has emphasised the need for detailed research prior to control. The importance of the influence of acquired resistance on the epidemiology of the disease has been overlooked in the past. On available knowledge it would appear that control should be limited to those areas where transmission of the disease is too high to allow the development of resistance. This would apply only where control is designed to protect the African community; where Europeans require protection, all transmission must be stopped. Epidemiological investigations therefore determine the priorities of control, and the policies of control can only be determined on a sound knowledge of the seasonal patterns of transmission of the disease.

If control is aimed at limiting or eliminating the clinical disease in a community, and not at protecting the individual, there are a number of investigations which are required.

It is necessary to determine the mechanism of the development of resistance. If, in fact, there is developed in man a true immunity which is preceded by a stage of premunition, attempted control by mass chemotherapy could do more harm than good. This would happen if the protection due to premunition was destroyed by the drug treatment, and the individuals were subsequently exposed to heavier infection. The mass treatment of all Africans, a common practice on many Rhodesian farms, cannot be justified.

This study has demonstrated that the patterns of transmission to which the people are exposed influence the levels of acquired resistance developed in the people. More detailed investigations on these influences are required. Such information will be available from surveys to assess the prevalence patterns in communities exposed to all the different patterns of transmission. Regular surveys in the labourers and their families forming the new communities of the irrigation estates will provide information on the development of resistance in unprotected communities.

The answers to the control and eventual elimination of bilharziasis cannot be expected from laboratory research in non-endemic countries. Laboratory and field investigations in endemic areas must be intensified if the disease is to be controlled, but there is an urgency for these investigations which is not fully appreciated.

APPENDIX I

Methods and Techniques

The methods and techniques employed in the course of this study have been followed with rigid attention to detail and, because small variations in technique would be reflected in the results, full details of the methods and techniques are given.

1. Urine Examination

A. Collection of Specimens:

Bennie (1949) and Jordan (1963) have both reported on the diurnal variations in the output of *S. haematobium* eggs in urines from infected individuals. Bennie used a sedimentation technique by which she obtained an estimate of the number of eggs in the whole urine specimen; Jordan counted the eggs present in 10 ml. of the urine. Both demonstrated that maximum egg release took place at the middle of the day. Jordan showed that there was a regular increase in egg release from relatively small numbers in the early morning to a peak occurring between noon and 2 p.m. For practical reasons in this investigation, it was not possible for urine samples to be collected at the period of peak egg output, and it was necessary to limit the time of collecting of specimens to the period between 9 a.m. and 2 p.m.

In all the cases the name, sex, age, length of residence in the area, and the history of previous treatment for bilharziasis were recorded for each person examined. Great difficulty was experienced in assessing the ages, particularly of the children, because it is rare for an African to be sure of his age.

Throughout all the surveys, results of the examination of persons having had treatment for the disease, within a period of three months prior to the survey, were disregarded in the analysis of results.

A commonly occurring fault in reported urine examination surveys has been the lack of standardisation of the methods of taking samples. Most reports refer to the number of eggs in 10 ml. of urine, without reference to the total volume of urine or the time the urine was retained in the bladder. Since egg counting should attempt to measure the rate at which eggs are passing through the bladder, it appears more logical to relate the number of eggs counted to the time they have taken to pass into the bladder, rather than to a standard volume of urine. This argument becomes more acceptable when it is realised that marked variations in renal activity occur in individuals, the results of surveys showing that the volume of urine passed in one hour varies from below 10 ml. to over 100 ml. For this reason, in the majority of surveys undertaken in the course of the present study, the total egg output was estimated from a urine sample representing exactly one hour of urine collection in the bladder, and therefore to one hour of egg passage into the bladder.

The subjects to be examined were first made to empty their bladders into large, wide-mouthed, screw-capped bottles. These bottles were collected as evidence that the bladders had been emptied. After exactly one hour a second specimen was collected in a 200 ml., wide-mouthed, screw-capped bottle.

When these urine samples were collected they were immediately preserved by the addition of one ml. of an aqueous solution of merthiolate to give a final concentration of not less than 0.01%, and the preserved specimens were returned to the laboratory for examination.

In the laboratory the whole specimen was allowed to stand in its bottle for 30 minutes to allow the sediment, including the eggs, to be deposited; it was then decanted slowly and steadily to prevent the disturbance of the sediment, to leave 11 to 14 ml. of urine containing the sediment in the bottle. The bottle was vigorously shaken and the contents transferred to a 15 ml. conical centrifuge tube and centrifuged for one minute at approximately 1,500 r.p.m. The supernatant urine in the centrifuge tube was carefully decanted to leave 0.5 ml. of the urine, with the sediment, in the tube. This particular operation proved difficult and it was impossible to ensure that exactly 0.5 ml. was left since expense precluded the use of graduated tubes for surveys of this magnitude. The tube was then flicked several times with the fingers to bring the sediment into suspension, and 0.05 ml. of the suspension was removed with a pipette for microscopic examination.

Where eggs were present they were counted. If no eggs were found the tube was again agitated and a large drop was poured on to a slide for further examination. The number of eggs on the slide was accepted as representing one tenth of the total number of eggs present in the whole specimen of the urine. If no eggs were found in the initial measured 0.05 ml. sample, but were present in the second examination, no count was made, the result being recorded simply as nought. This was necessary for statistical analysis of results.

2. Stool Examination:

The collection of stool specimens for surveys follows a similar pattern to the collection of urine specimens and the name, sex, age, length of residence in the area, and the history of previous treatment for bilharziasis was recorded for each person examined. Waxed paper cartons were issued to each person and they were asked to produce specimens on the same day. After the cartons were returned approximately 10 gm. of the faecal sample were transferred to a 200 ml. wide-mouthed, screw-capped bottle and emulsified in approximately 30 ml. of 10% formalin in one per cent. aqueous saline. The emulsified stool sample was returned to the central laboratory for examination.

In the next stage in the preparation of the sample for examination, the emulsified specimen was diluted with a large volume of one per cent. saline solution and strained through a fine copper gauze having a pore size of 0.15 square mm. The strained suspension was repeatedly washed in saline by allowing the sediment to settle and then decanting the liquid. After the final washing the supernatant fluid was reduced to 10 to

15 ml., including the sediment; this was transferred to a 15 ml. conical centrifuge tube, shaken with 0.5 ml. of ether and centrifuged for one minute at approximately 1,500 r.p.m. The plug of fat left by the evaporated ether was removed with a needle and the tube decanted to leave approximately 0.5 ml. of the liquid and sediment. After violent agitation, a drop of the suspension was transferred to a slide and examined for eggs. It was not found necessary to stain the eggs.

Fluorescent Antibody Test Surveys

The methods used followed the indirect fluorescent antibody techniques reported by Sadun *et al.*, (1960, 1961a), Anderson *et al.*, (1961a, 1961b) and Cookson (1963).

Blood from a finger prick was collected from each person, sufficient being taken to saturate an area of five sq. cm. of Whatman No. 1 filter paper. The blood clot was reconstituted in phosphate buffered saline pH 7.1, 0.01 M.

Cercariae, previously counterstained in rhodamine confugated bovine albumen were used as the antigen source. All the cercariae were from laboratory bred and infected *Bulinus (Physopsis) globosus*, and *Biomphalaria pfeifferi*.

Purified anti-human globulin confugated with fluorescein isothiocyanate was used to visualise the antigen antibody reaction.

Intradermal Tests

Antigen for use in intradermal tests was prepared from adult worms by the methods of Melcher (1943) from worms recovered from infected mice by perfusion of the mesenteric veins, the portal vein and the liver. As well as this, antigen prepared by the same method was obtained from the World Health Organisation.

The name, sex, age, length of residence in the area, and the history of previous treatment for bilharziasis were recorded for each person examined. The scapular region of the back was cleaned with a swab soaked in alcohol and, using two 1 ml. tuberculin syringes fitted with 27 gauge, one cm. long platinum needles which could be flame sterilised, 0.05 ml. of each of the antigen and a control solution were injected intradermally, about six cm. apart in the cleaned area. The result was read after 15 minutes and the test was regarded as positive if the antigen wheal had increased in size to twice the diameter of the control wheal, or to over one square cm. in area.

A permanent record of the result of the test can be made by outlining the wheals with a ball-point pen and pressing an alcohol-moistened piece of paper against the marks, the ball-point outline being transferred to the paper.

REFERENCES

Anderson, R. I. (1960). Serologic diagnosis of *Schistosoma mansoni* infections. I. Development of cercarial antigen slide flocculation test. *Amer. J. Trop. Med. Hyg.*, **9**, 299-303.

Anderson, R. I., Sadun, E. H. & Schoenbechler, M. J. (1963). Cross absorption studies performed with *Schistosoma mansoni* and *Trichinella spiralis* antigens in sera from patients with trichinosis. *Exp. Parasit.*, **14**, 323-329.

Anderson, R. I., & Williams, J. S. (1961a). A technique for the use of minute amounts of dried blood in the fluorescent antibody test for schistosomiasis. *Exp. Parasit.*, **11**, 111-116.

Anderson, R. I. & Williams, J. S. (1961b). Preserved cercariae in the fluorescent antibody (FA) test for schistosomiasis. *Exp. Parasit.* **11**, 226-230.

Bassenes, M. S. & Pantoja, W. P. (1947). Esquistossomose.—Prevalencia de *S. mansoni* na populacao humana. *Rev. Serv. Saude publ.* (Rio de J.), **1**, 135-148.

Bennie, I. (1949). Urinary schistosomiasis: the best time to obtain specimens: the effect of specific therapy on egg output. *S. Afr. med. J.*, **23**, 97-100.

Clarke, V. de V. (1963). The control of bilharziasis by the application of molluscicides to natural waters in Southern Rhodesia. VIIth International Congresses of Tropical Medicine and Malaria, Rio de Janeiro.

Clarke, V. de V. (1966). Evidence of the development in man of acquired resistance to infections of *Schistosoma* spp. *Cent. Afr. J. Med.*, **12**, 1.

Clarke, V. de V., Shiff, C. J. & Blair, D. M. (1961). The control of snail hosts of bilharziasis and fascioliasis in Southern Rhodesia. *Bull. Wld. Hlth. Org.*, **25**, 549-558.

Cookson, L. O. C. (1963a). Some investigations with the fluorescent antibody technique: I. Schistosomiasis. *Cent. Afr. J. Med.*, **9**, 429-434.

Cowper, S. G. (1953). Schistosomiasis in Mauritius. *Trans. Roy Soc. Trop. Med. Hyg.*, **47**, 564-579.

Fisher, A. C. (1934). A study of schistosomiasis of the Stanleyville district of the Belgian Congo. *Trans. Roy. Soc. Trop. Med. Hyg.*, **28**, 277-306.

Gelfand, M., Clarke, V. de V. & Turnbull, C. (1964). The detection of antibodies to *Schistosoma* spp. in newly born infants of mothers having the same antibodies. *J. trop. Med. Hyg.*, **67**, 254.

Gerber, J. H. (1952). Bilharzia in Boajibu. *J. Trop. Med Hyg.*, **55**, 52-58.

Honey, R. M. & Gelfand, M. (1960). The urological aspects of bilharziasis in Rhodesia. Parts II and IV. *Cent. Afr. J. Med.*, **6**, 58-61 & 199-212.

Jordan, P. (1963). Some quantitative aspects of bilharzia with particular reference to suppressive therapy and mollusciciding in control of *S. haematobium* in Sukumaland, Tanganyika. *E. Afr. med. J.*, **40**, 250-260.

Kagan, I. G. (1958). Contributions to the immunology and serology of schistosomiasis. *Rice Inst. Pamphl.*, **45**, 151-183.

Maclean, G., Webbe, G. & Masangi, A. S. (1958). A report on a bilharzia and molluscan survey in the Tanga district of Tanganyika. *E. Afr. Med. J.*, **35**, 7-22.

MANSON-BAHR, P. E. C. (1958). The clinical features, diagnosis and host parasite relationship of schistosomiasis in East Africa. *E. Afr. Med. J.*, **35,** 401-411.

MELCHER, L. R. (1943). An antigenic analysis of *Trichinella spiralis*. *J. Infect. Dis.*, **72,** 242-245.

MORLEY-SMITH, F. & GELFAND, M. (1960). The establishment of immunity in bilharziasis as judged by age. *Cent. Afr. J. Med.*, **6,** 447-448.

NEWSOME, J. (1956). Problems of fluke immunity: with special reference to schistosomiasis. *Trans. Roy. Soc. Trop. Med Hyg.*, **50,** 258-274.

ORPEN, L. J. J. (1915). Annual Report Public Health Dept., Salisbury, S. Rhodesia.

PESIGAN, T. P., FAROOQ, M., HAIRSTON, N. G., JAUREQUI, J. J., GRACIA, E. G., SANTOS, A. T., SANTOS, B. C. & BESA, A. A. (1958). Studies on *Schistosoma japonicum* infection in the Philippines. I. General considerations and epidemiology. *Bull. Wld. Hlth. Org.*, **18,** 345-455.

PITCHFORD, R. J. (1958). Influence of living conditions on bilharziasis infection rates in Africans in the Transvaal. *Bull. Wld. Hlth. Org.*, **18,** 1088-1091.

PITCHFORD, R. J. & VISSER, P. S. (1962). Results of exposing mice to schistosomes by immersion in natural water. *Trans. Roy. Soc. Trop. Med. Hyg.*, **56,** 294-301.

SADUN, E. H. (1963). Seminar on immunity to parasitic helminths. VII. Fluorescent antibody technique for helminth infections. *Exp. Parasit.*, **13,** 72-82.

SHIFF, C. J. (1964a). Studies on *Bulinus (Physopsis) globosus* in Rhodesia. I. The influence of temperature on the intrinsic rate of natural increase. *Ann. Trop. Med. Parasit.*, **58,** 94-105.

SHIFF, C. J. (1964b). Studies on *Bulinus (Physopsis) globosus* in Rhodesia. II. Factors influencing the relationship between age and growth. *ibid.*, **58,** 105-115.

SIEGAL, S. (1956). Non parametric statistics for the behavioural sciences. McGraw Hill London, Toronto, New York.

VOGEL, H. (1958). Acquired resistance to *Schistosoma* infection in experimental animals. *Bull. Wld. Hlth. Org.*, **18,** 1097-1103.

VOGEL, H. & MINNING, W. (1953). Uber die erworbene resistenz von Macacus rhesus gegenüber *Schistosoma japonicum*. *Z. Tropenmed. Parasit.*, **4,** 418-505.

Acknowledgment

I wish to thank Dr. M. H. Webster, Secretary for Health, Rhodesia, for permission to publish this article.