thought seems to be corroborated by the results of a pilot experiment carried out in collaboration with Dr. C. E. Thornton some years ago. We had the impression that a daily supplement of 40,000–50,000 i.u. of vitamin A given to rheumatic children during the phase of relapse was beneficial (Thornton, 1946).

Only scanty information exists regarding the effect of fever on the vitamin-A level in pregnancy. Bicknell (1950) suggested that in those cases of pregnant women suffering from German measles in which the termination of pregnancy was not considered vitamin A should be given. I extended this suggestion, proposing that vitamin A should be administered in every case of pregnancy complicated by infection or fever, especially during the first trimester, which approximately corresponds to the organogenic period (Leitner, 1950, 1951).

Conclusion

The work briefly reported here demonstrates the importance of an adequate plasma vitamin-A level during the embryonal development and in some clinical conditions such as ocular, dermatological, hepatic, and febrile diseases.

I should like to conclude this report with two suggestions which seem to be justified by the present state of vitamin-A research, though their strict therapeutic necessity cannot yet be substantiated. I would advocate supplementing the routine treatment in the acute stage of rheumatic fever with 40,000–50,000 i.u. of vitamin A daily. The same dose of vitamin A should be administered in pregnancy complicated by infection or fever, especially during the first trimester. No special claims are attached to these, as yet tentative, suggestions, and it is hoped that further research will support and possibly amplify them.

It is a great pleasure to acknowledge the collaboration or the generous help given by so many colleagues during the long course of these investigations. My grateful thanks are due particularly to Sir Allen Daley, Drs. H. W. Barber, F. J. Bentley, E. B. Ford, L. J. Harris, A. L. Jacobs, I. M. Sharman, G. B. Mitchell Heggs, and C. E. Thornton. I am especially indebted to Dr. T. Moore for his valuable help, friendly advice, constructive criticism, and continuous encouragement.

REFERENCES

- Aron, H. C. S. (1949). *Amer. J. Dis. Child.*, **77**, 763.
 — Craig, R. M., Farmer, C. J., Kendall, H. W., and Schwemlein, G. X. (1946). *Proc. Soc. exp. Biol.*, N.Y., **61**, 271.
 Barber, H. W., and Leitner, Z. A. (1951). In preparation.
 — and Tatz, K. (1946). *Proc. roy. Soc. Med.*, **39**, 223.
 Bicknell, F. (1950). *British Medical Journal*, **2**, 576.
 Bradley, W. H. (1951). *Proc. roy. Soc. Med.* In press.
 Breese, B. B., and McCoord, A. B. (1940). *J. Pediat.*, **16**, 139.
 Carleton, A., and Steven, D. (1943). *Arch. Derm. Syph.*, Chicago, **48**, 143.
 Cornbleet, T., and Popper, H. (1942). *Ibid.*, **46**, 59.
 Gray, C. H. (1950). *Quart. J. Med.*, **19**, 263.
 Haig, C., and Patek, A. J., jun. (1942). *J. clin. Invest.*, **21**, 309.
 Hansen, A. E. (1937). *Amer. J. Dis. Child.*, **53**, 933.
 Harris, A. D., and Moore, T. (1947). *British Medical Journal*, **1**, 553.
 Hyams, M. N., and Bloom, O. H. (1947). *Amer. J. Obstet. Gynec.*, **53**, 214.
 Irving, J. T., and Richards, M. B. (1940). *Biochem. J.*, **34**, 198.
 Jacobs, A. L., Leitner, Z. A., Moore, T., and Sharman, I. M. (1951). In preparation.
 Leitner, Z. A. (1945). *Proc. roy. Soc. Med.*, **38**, 341.
 — (1946a). *Ibid.*, **39**, 224.
 — (1946b). *Brit. J. Derm.*, **58**, 11.
 — (1948a). *Proc. roy. Soc. Med.*, **41**, 326.
 — (1948b). *British Medical Journal*, **1**, 917.
 — (1950). *Ibid.*, **2**, 730.
 — (1951). *Brit. J. Nutrit.* In press.
 — and Ford, E. B. (1947). *Brit. J. Derm. Syph.*, **59**, 407.
 — and Moore, T. (1946). *Lancet*, **2**, 262.
 — (1948). *Brit. J. Derm. Syph.*, **60**, 41.
 — and Sharman, I. M. (1947). *Brit. J. Nutrit.*, **1**, v.
 Lindqvist, T. (1938). *Acta med. scand.*, Suppl. No. 97.
 Medical Research Council (1949). *Spec. Rep. Ser.*, No. 264. London.
 Mellanby, E. (1938). *J. Physiol.*, **94**, 380.
 — (1939). *Ibid.*, **96**, 36P.
 — (1941). *Ibid.*, **99**, 467.
 — (1943). *Ibid.*, **101**, 408.
 Moore, T. (1929). *Lancet*, **2**, 380.
 — (1931). *Biochem. J.*, **25**, 275.
 — (1937). *Ibid.*, **31**, 155.
 — (1951). *Brit. J. Nutrit.* In press.
 Moul, F. H. (1943). *Arch. Derm. Syph.*, Chicago, **47**, 768.
 Nicholls, L. (1933). *Indian med. Gaz.*, **68**, 681.
 Peck, S. M., Glick, A. W., Sobotka, H. H., and Chargin, L. (1943). *Arch. Derm. Syph.*, Chicago, **48**, 17.
 Popper, H. (1941). *Arch. Path.*, **31**, 766.
 — Steigmann, F., and Zevin, S. (1943). *J. clin. Invest.*, **22**, 775.
 Porter, A., and Brunauer, S. R. (1949). *Brit. J. Derm. Syph.*, **61**, 277.
 — and Godding, E. W. (1947). *Arch. Derm. Syph.*, Chicago, **56**, 306.
 Rapaport, H. G., Herman, H., and Lehman, E. (1942). *J. Pediat.*, **21**, 733.
 Reid, J., Watson, R. D., and Sproull, D. H. (1950). *Quart. J. Med.*, **19**, 1.
 Shank, R. E., Coburn, A. F., Moore, L. V., and Hoagland, C. L. (1944). *J. clin. Invest.*, **23**, 289.
 Siskind, W. M. (1947). *Arch. Derm. Syph.*, Chicago, **56**, 540.
 Stannus, H. S. (1945). *Proc. roy. Soc. Med.*, **38**, 337.
 Straumfjord, J. V. (1943). *Northw. Med.*, Seattle, **42**, 219.
 Thornton, C. E. (1946). In *Rep. L.C.C. Med. Officer of Health*, p. 77.
 Warkany, J. (1947). *Advances in Pediatrics*, **2**, 1.
 — and Schraffenberger, E. (1946). *Arch. Ophthalm.*, Chicago, **35**, 150.
 Williamson-Noble, F. A. (1942). *Trans. ophthalm. Soc. U.K.*, **62**, 53.
 Wilson, J. G., and Warkany, J. (1947). *Proc. Soc. exp. Biol.*, N.Y., **64**, 419.
 — (1948). *Amer. J. Anat.*, **83**, 357.
 — (1950). *Pediatrics*, **5**, 708.
 Wolbach, S. B., and Bessey, O. A. (1942). *Physiol. Rev.*, **22**, 233.
 — and Howe, P. R. (1925). *J. exp. Med.*, **42**, 753.

THE DISTRIBUTION OF ANOPHELINE MOSQUITO BITES AMONG DIFFERENT AGE GROUPS

A NEW FACTOR IN MALARIA EPIDEMIOLOGY

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While it has been known for a long time in a general sort of way that some individuals are more attractive to mosquitoes than others, little attempt has been made to follow up the wider implications of this and see whether any particular age group is more attractive than others. Nothing whatever was known about whether children were bitten more by anopheline mosquitoes than adults, or whether, say, babies were more attractive than their mothers. There was really nothing to give us any idea of what happens when an anopheline mosquito enters a native house and is faced with a choice of biting babies, children, or adults. In the absence of such information it has been necessary in discussing problems of malaria transmission and epidemiology to assume a random distribution of bites among an equally accessible human population, an assumption which, however, has given rise to many inconsistencies.

For some time now I have been concerned with this serious gap in our knowledge, without, however, being able to overcome the technical difficulties. In many tropical countries, particularly in Asia and Africa, the

anopheline vectors of malaria bite mainly indoors at inconvenient hours of the night. Biting is often so intermittent that prolonged observation inside native village houses would be necessary to give conclusive results. In these circumstances there are obvious limits to the amount of co-operation one might expect from the householders and their families. The indirect approach has been considered in which members of the family might be treated with different drugs in such a way that the minute quantity of blood extracted by the mosquito would show the presence or absence of the drug among engorged mosquitoes found in that house, thus indicating which members of the family had provided the blood meal. Although attempts on these lines have met with no success, there is a distinct possibility that a satisfactory technique will be worked out in time.

In contrast to the anophelines of the Old World, the habits of *Anopheles albimanus*, a widespread vector in Central America and the Greater Antilles, lend themselves particularly well to the investigation of this problem by direct observation. In Jamaica, *A. albimanus* bites man actively outdoors as well as indoors. There is a sharp peak of biting at sundown, when most village people are sitting or moving about out of doors: and there is another sharp peak of biting at dawn, when many people, particularly the children, are still asleep in bed. During these peaks the numbers of *A. albimanus* attempting to bite are often large enough to give significant figures in quite a short time.

Present Investigation

A few random observations on mothers and their babies soon revealed a striking difference in that for each bite or attempted bite on the baby about 20-30 mosquitoes could be taken attacking the mother, most babies remaining completely free of bites during this peak at dusk. In this mosquito-infested area the co-operation of a Jamaican negro family was obtained, and routine observations were made on the whole family seated out of doors at sundown. The observations extended over several months and covered a wide range of climatic conditions and mosquito abundance. Mosquitoes settling on each person and attempting to bite were picked off by means of a sucking tube and recorded as "bites." Whether these bites would normally be followed by blood feeds is quite a different matter; this is discussed later. The youngest members of the family were soon trained to sit quietly during the 20-30 minutes that the catches were made, and we could be reasonably sure that the figures obtained were a good indication of the individual's attraction. The results of five collections in the hot summer weather—low mosquito population—and one collection in the rainy season, when anophelines were very abundant, are recorded in Table I.

TABLE I.—Distribution of *A. albimanus* Bites Among a Jamaican Negro Family at Ferry, Near Kingston, Jamaica

	Sex and Age	Number of Bites Recorded	
		Summer Weather (5 Collections)	Rainy Season (1 Collection)
Mr. Bailey	M 36	103	199
Mrs. Bailey	F 30	25	49
Marjorie	F 9	23	40
Donald	M 8	45	61
George	M 5½	8	13
Thelma	F 5½	18	15
Malcolm	M 2½	18	15
Linette	F 1	0	2

These figures show that at this period the baby—Linette—remained almost completely free of bites, in striking contrast to the very great attraction of her father. Mr. Bailey attracted nearly three times as many mosquitoes as the eldest boy, over four times as many as his wife or eldest girl, over ten times as many as each of the three younger children, and over 150 times as many as the baby. The single catch in the rainy season—the period of greatest anopheline abundance—suggests also that at these high figures the adult male attracts a proportionately higher number of mosquitoes.

These observations were repeated on two Jamaican East Indian families in the same neighbourhood. The results are shown in Table II.

TABLE II.—Distribution of *A. albimanus* Bites Among Members of Two Jamaican East Indian Families Near Kingston, Jamaica

	Sex and Age	Bites Recorded (2 Collections)		Sex and Age	Bites Recorded (1 Collection)
Mr. Anderson	M 45	58	Mr. Williams	M 36	110
Mrs. Anderson	F 36	21	Mrs. Williams	F 24	43
Dorothy ..	F 15	13	Livette ..	F 7	6
Austen ..	M 6	6	Wilfred ..	M 4	13
Melvina ..	F 2	0	Marilyn ..	F 3	10
			Alphonse ..	M 14 mths.	2

These figures show the same general trend, the scarcity of bites on the two youngest members contrasting with the great attraction of the adult males. In both families, as with the Baileys, the adult women attracted less than half as many mosquitoes as their husbands.

In order to find out how far this striking difference in the distribution of anopheline (*A. albimanus*) bites applies during the night, when the family are asleep, observations were carried out on the Bailey family indoors during the half-hour before dawn. The six children were asleep on the single bed; Mr. Bailey sat near by, and Mrs. Bailey was absent. The results were as follows: Mr. Bailey, 81; Marjorie, 3; Donald, 13; George, 0; Thelma, 3; Malcolm, 1; Linette, 3.

The very great attraction of the adult male is again evident, with the eldest boy, as before, next in order of attraction. Particular attention was paid to mosquitoes attempting to bite the baby—Linette. Observations at sundown had already shown how extremely sensitive she was to mosquitoes even settling on her skin. In the pre-dawn observations it was interesting to note that even when she was asleep she was still very sensitive to mosquitoes attempting to bite. Those mosquitoes attracted to her spent a long time probing around, and when the mouth parts were finally inserted the mosquito was shaken off in each case before actual feeding could take place. In contrast to this, mosquitoes alighting on Mr. Bailey, and to a less extent on Donald and Marjorie, bit immediately after settling and took a blood meal with great rapidity. In this respect it is worth noting that many adults are quite unaware of anophelines feeding on them.

It is possible that the interrupted biting, so marked in the case of the baby, might apply to a certain extent to the next youngest member of the family—that is, to children 2 to 3 years of age. Plans to extend these observations, however, received a severe setback when, during my absence, the Bailey family was attacked by "vomiting sickness," from which Mrs. Bailey, Malcolm, Linette, and a premature child all died within a few days of each other.

During a four-weeks visit to Trinidad it was possible, thanks to the co-operation of Dr. H. P. S. Gillette and Major Senior White, to repeat the sundown observations on *A. aquasalis* and *A. bellator*, the two vectors of malaria in that island. Arrangements with suitable family groups were not easy to make at short notice, and repeats on exactly the same group were not possible. The results with *A. aquasalis* are given in Table III.

TABLE III.—Distribution of *A. aquasalis* Bites Among East Indian Family Groups at Sundown. New La Paille, Trinidad. Three Collections

	Sex and Age	Bites Recorded		Sex and Age	Bites Recorded
Buddhu..	M Adult	16 18	Hubert Knutt ..	M Adult	21
Mrs. Sukea	F "	6 —	Corisha Mohammed	F "	2
Ramnarin	M "	18 —	Earlyn Mareth ..	F " 3½	1
Lochu ..	M 8	13 8	Chakra Mohammed	F 3	0
Sukdeo ..	M 3	1 2	Ethlina Mohammed	F 10	0
Sriprasad	M 2½	2 7		mths	

Allowing for the absence of a baby in the first group, for the low degree of biting in the second group, and for the absence of repeats, the results suggest that the general trend of biting is not unlike that of *A. albimanus*.

The observations on *A. bellator* were much more satisfactory, as both family groups included a well-behaved quiescent baby, and there was a high degree of biting. The results of two collections are given in Table IV.

TABLE IV.—Distribution of *A. bellator* Bites Among Two East Indian Family Groups. Cumuto, Trinidad

	Sex and Age	Bites		Sex and Age	Bites
Sarah Mohammed..	F Adult	12	Pancham Ramprasad	F Adult	15
Ramjng Sooknanan	M 15	12	Teresa ..	F 14	13
Ramdad Sooknanan	M 13	17	Samdaye ..	F 10	28
Said Mohammed ..	M 5½	4	Chumania ..	F 8	9
Sahidan Mohammed	F 17	1	Chandramati ..	F 10	0
	mths			mths	

Again the scarcity of bites on the babies is in striking contrast to the greater attraction of the mother and the older children (the father of each family being absent).

These observations on Trinidad anophelines, incomplete though they are compared with those made in Jamaica, nevertheless indicate roughly the same general behaviour, and suggest that the uneven distribution of bites may be common to many other anophelines besides *A. albimanus*.

Discussion

What bearing have these facts on malaria transmission and epidemiology? The findings appear to have two quite different implications. First, the fact that the younger age groups—under 2 years of age—are bitten so seldom compared with older children and adults must confer a considerable degree of protection from infection, especially with a species like *A. albimanus*, which seems to have a very low infection rate. In the Bailey family, for example, repeated blood examinations over a period of about eight months failed to reveal any sign of malarial infection in the two youngest children, Malcolm and Linette. Thelma—aged 5½—also remained free of infection, while *Plasmodium falciparum* infections were recorded in George (5½), Donald (8), and Mrs. Bailey, and a persistent quartan infection in Marjorie (9). The absence of parasites in several tests

on Mr. Bailey is presumably related to a fairly effective immunity built up over years of exposure to infection.

In this anopheline-infected district there were other families too in which some of the children appeared to have remained free of malarial infection during the first year or two of life. On the other hand, the freedom of the younger age groups from anopheline bites is relative only, and by no means absolute. With a high mosquito population these children may still be bitten many hundreds of times in the course of a year, and in this same area there were several records of *P. falciparum* infections during the first year of life. Bearing in mind the biting habits of *A. albimanus*, described above, it seems very likely that when infants do get infected it is from mosquitoes which bite them without extracting any blood, as it has been established that infection can result from the simple insertion of the proboscis (Boyd, 1949).

The second implication of these findings regarding the unequal distribution of bites and feeds in different age groups is that they may play an important part in determining which age group is mainly responsible for infecting anopheline mosquitoes with malaria parasites. A commonly accepted idea that young children form the main reservoir of malarial infection may need considerable revision, as it is strongly indicated that, other things being equal, the adult gametocyte carrier could be a much greater danger to the community because of the much greater frequency with which he is bitten; and this applies particularly to the men, who are much more attractive to anopheline mosquitoes than their womenfolk. Although the gametocyte rate of children under 5 years is usually higher than in older children or adults, not only are the youngest children bitten much less frequently but, equally important, the mosquitoes which do bite them seem to have much less opportunity of following the bite with a full blood meal.

This rather simplified interpretation of these new findings may of course require modification as new factors come to light. The direct comparison of gametocyte rates and gametocyte counts between different age groups is not necessarily an indication of the infectivity of these "carriers" to mosquitoes. Again, the tendency of the adult woman's immunity to break down during pregnancy (Walton, 1949) and to result in severe attacks of malaria (as happened with Mrs. Bailey in the family described above), might increase her importance as a potential mosquito infector.

In Jamaica several of these implications are being followed up to try to find out what part each age group of gametocyte carriers might play in maintaining transmission or initiating outbreaks, and it is hoped to communicate these results in due course.

It is tempting to speculate about the possibilities of African and Oriental anophelines showing the same biting trends as those studied in the Caribbean. Should these habits prove similar they would certainly help to explain some inconsistencies about infant infection rates in those regions. For example, malariologists in Africa have long been struck by the low rate of malarial infection in infants under 3 months, even in areas where the main vector—*A. gambiae*—is very abundant and maintains a gland infection rate of 10% or more. Explanations vary from an inherited immunity in the first few months of life to some purely mechanical protection from mosquito bites at that age. The whole subject of infant parasite rates in relation to exposure

to the bites of infected mosquitoes under these conditions has recently been discussed by Macdonald (1950), who points out that the only reasonable explanation of the discrepancy between observed and calculated figures is that the number of infective bites to which the infants are exposed must be less than that estimated.

In the great malaria epidemic of Ceylon in 1934-5 one of the most difficult features to explain was the explosive nature of the outbreak. During the early stages of the epidemic, outbreaks of sickness were mainly confined to adults, there being a remarkable absence of mortality among infants during the first four weeks at least. Gill (1938) has pointed out that if we attribute this outbreak to new infections rather than to a wave of relapses, it would be necessary to assume that at the beginning of the epidemic the main biting activities of *A. culicifacies* were directed towards adults. In the light of the observations described above this explanation now seems much more feasible.

Before these speculations about conditions in other countries carry us into deep water it will obviously be necessary to repeat these observations on their particular vector *Anopheles*. The possibility that this biting factor may also enter into problems of other insect-borne diseases can hardly be overlooked. Culicine mosquitoes appear to bite infants rather more readily than anophelines do, but no systematic observations have yet been done on them, and there should be many interesting possibilities in following up this line of inquiry.

Summary

Observations on the biting habits of *A. albimanus* on family groups in Jamaica have shown that babies are bitten much less frequently than older children or adults. Similar behaviour has been seen in *A. aquasalis* and *A. bellator* in Trinidad. This uneven distribution of bites and feeds has been discussed in relation to general problems of malaria transmission and epidemiology.

REFERENCES

- Boyd, M. F. (1949). *Malaria*, vols. 1 and 2. Saunders, Philadelphia and London.
Gill, C. A. (1938). *Seasonal Periodicity of Malaria*. Churchill, London.
Macdonald, G. (1950). *Trop. Dis. Bull.*, **47**, 907.
Walton, G. A. (1949). *Ann. trop. Med. Parasit.*, **43**, 117.

Research on "agenized" flour is carried a step further by a note from a Nottingham group of research workers (*Nature*, May 12, p. 773) which describes how they were at first unable to produce convulsions in rabbits and traced this to the presence in the animal's diet of greenstuff, which seemed to protect against convulsive doses of the toxic substance. It will be recalled that flour is improved in keeping and baking quality by treatment with "agene" (nitrogen trichloride), and some time ago it was shown that flour treated in this way and fed to dogs and rabbits gave them fits. Medical Research Council workers were unable to produce any abnormal symptoms or signs in human beings given large amounts of the treated flour. The toxic substance was identified by chemists as a derivative of methionine, an amino-acid occurring naturally in the protein of the flour, and as little as 2 mg. would cause convulsions in a normal rabbit. A rabbit getting 150 g. of fresh greens a day, however, would be protected, or almost completely so. The reason for this is so far unknown. The toxic substance has been studied in the laboratory for its inhibitory effect on the growth of the bacterium *Leuconostoc mesenteroides*, an effect abolished by glutamine. Fresh greenstuff is often rich in glutamine, and it may be this which protects the rabbit.

BLACKWATER FEVER IN AFRICAN CHILDREN

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The rarity of blackwater fever among indigenous African adults is well recognized (Fairley, 1946; Joyeux and Sicé, 1950; etc.). Sporadic cases do, however, occur, and larger numbers have been reported under special circumstances, as, for example, when adult Africans have migrated from non-malarial hill country to an endemic malarial area. This has been recorded in the Cameroons (Strong, 1944). Again, blackwater fever cases have been observed among groups of Africans who have been using either anti-malarial suppressive drugs or mosquito-nets. Thus, Findlay (1949) noted a definite increase in cases among West African soldiers, who were taking no quinine, but who were being partially protected by mosquito-nets and mosquito control.

In addition, there would seem to be some unexplained geographical factor to be considered. Gelfand (1944) records that he has never seen a case of blackwater fever in an African, presumably referring to experience in S.E. Africa, and more particularly Southern Rhodesia. Shelley (1931), in a review of cases seen in Nyasaland between 1921 and 1930, makes no reference to the disease having occurred in Africans during this period. In contrast to this, cases occurring sporadically are noted occasionally in West African adults.

In normal circumstances blackwater fever is extremely unusual amongst indigenous African children, despite the fact that, during childhood and more especially infancy, severe attacks of subtertian malaria occur frequently, at least in Nigeria. However, as is mentioned by several authorities (Manson-Bahr, 1945; Maegraith, 1948), if the development of malarial immunity ("premunition") is interfered with—as, for example, by the repeated inadequate quinine treatment of malaria in childhood—blackwater fever can occur. Thus, Chesterman (1935) observed a case of blackwater fever in an African child aged 2½ years. There was a past history of occasional dosage with quinine for attacks of fever. The blood film showed *Plasmodium falciparum*. The illness was precipitated by the taking of quinine, and consisted of a single mild bout of haemoglobinuria, lasting only a day. Mackey (1928) recorded a case in Nigeria. This occurred in an Ibo child aged 2½ years. Again there was the same background of occasional treatment with quinine over a number of years. The blood film showed *P. falciparum* to be present. In this case a severe bout of haemolysis, with typical urine changes, was followed by increasing jaundice, unconsciousness, and death.

In contrast to these two reports, Jackson (1935) has described a case in an infant of 16 months in the Plateau Province of Northern Nigeria. The blood film showed *P. falciparum*. The onset of the illness was associated with the taking of quinine, but there was no definite history of previous quinine therapy.