diabetes do not differ materially from normal subjects;

(2) in moderately severe cases of diabetes, the sugar content in the venous blood exceeds that of the arterial blood, thereby creating a negative arterio-venous difference;

(3) the difference between the moderate and the severe cases of diabetes is a matter of the degree of arterio-venous sugar difference obtained, notwithstanding the height of the fasting level of sugar.

Though the determination of the arterio-venous sugar difference in *severe* cases of diabetes in the fasting state may give us some idea of the severity of the disease, a much more definite and clear idea is obtainable by studying the arterio-venous sugar difference after a glucose meal.

Effect of ingestion of glucose on the arterio-venous sugar difference

The data which have been obtained as regards the effect of ingestion of glucose on the arterio-venous sugar difference in healthy normal individuals and in diabetic subjects may be summarized as follows :—

In normal healthy subjects—

(*a*) the arterio-venous sugar difference is negligible in the fasting stage, the average being +3 mgm. per 100 c.cm.;

(*b*) after the glucose meal, the arterio-venous difference rises, the maximum being obtained at the end of one hour after the meal. In five cases, the peak was obtained in a half hour's time;

(*c*) the average arterio-venous difference obtained in the one-hour period was +35 mgm., the variations ranging from a minimum of +26 mgm. to a maximum of +45 mgm. per 100 c.cm. of blood;

(*d*) the arterio-venous difference rapidly decreases one hour after the glucose meal, coming almost to the post-absorption level at the end of two and a half hours.

In mild cases of diabetes—

(*a*) the fasting arterio-venous difference did not differ materially from the normal cases;

(*b*) after the glucose meal, the arterio-venous difference was much less marked than in the normal case, the greatest difference (+13 to +20 mgm. per 100 c.cm. instead of +26 to +45 mgm. as in normal cases) occurring at the end of one hour after the meal;

(*c*) the fall in the sugar content of both the arterial and the venous blood began at the end of one and a half hours (instead of one hour as in normal cases);

(*d*) the arterio-venous difference regained the original level at the end of two and a half hours.

In severe cases—

(*a*) the fasting arterio-venous difference was almost always on the negative side;

(*Continued at foot of next column*)

TEBETREN IN INDIAN STRAINS OF MALARIA

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ALTHOUGH for the last three hundred years quinine has enjoyed the reputation of being the best remedy for malaria, its administration is attended with certain drawbacks: (*i*) It has to be administered in large doses and for a prolonged period (10 grains twice daily for 10

(*Continued from previous column*)

(*b*) after the glucose meal, there were at least five cases in which the rise in the sugar content of the arterial blood exceeded that of the venous blood, thus converting the initial negative arterio-venous difference into a positive one, though of a small degree. The other cases retained the negative difference throughout the test.

From the above, it is reasonable to conclude that the magnitude of the difference between the sugar content of the arterial blood and the venous (positive arterio-venous difference) after glucose ingestion is the best indication of the rate of glucose utilization in the tissues. In diabetes, it should be remembered, the power of glucose utilization in the tissues is defective according to the degree of the severity of the disease. That explains why the degree of positive arterio-venous difference becomes less and less as the severity of the disease increases and, in the severe cases, even a negative arterio-venous difference is obtained, *i.e.*, the venous sugar level rises higher than the arterial sugar. The reason for this is probably that there are times when the tissues are discharging more sugar into the venous blood than they are receiving from the capillary blood. The tissues lose the power of retaining the sugar that is stored in them and under the stress of the sudden flooding by extra sugar brought to them by the arterial blood, after a glucose meal, not only let it flow through without change but actually give up to the venous blood a little or a good deal of the sugar retained by them.

The above explanation receives some corroboration from the results of some of the experiments which the author is carrying out at present, *viz*, the action of insulin on the arterio-venous sugar difference in normal and diabetic subjects. It has been found, for example, that insulin not only helps the tissues to retain the sugar stored therein but often gives its aid in abstracting some of the sugar from the arterial blood, thus converting a negative arterio-venous difference into a positive one.

consecutive days), (*ii*) it is comparatively less effective in curing benign tertian infection, (*iii*) it has no effect on the crescentic gametocytes of *P. falciparum*, and (*iv*) it produces certain nervous symptoms and hæmoglobinuria in a small number of cases. Acton, Curjel and Dewey (1921) and Rennie, Acton and others (1921) observed that the alkaloids of cinchona bark other than quinine possess antimalarial properties and showed that 10 grains of cinchona febrifuge (a mixture of all alkaloids), given twice daily for ten consecutive days with a dose of an alkaline mixture half an hour before, cured fifty per cent of benign tertian infections, whereas with quinine the cure rate was never above thirty per cent.

The shortage of quinine during the Great War led to the synthesis of a number of antimalarial compounds and the drawbacks of the use of quinine, mentioned above, also stimulated research in this direction. Though these synthetic preparations cannot totally replace cinchona alkaloids yet, some of them have been shown to be just as effective and they undoubtedly serve as very useful adjuncts in the treatment of malaria. The synthesis of plasmochin by Schulemann in 1926 marked a distinct advance in this connection. Although further experience has shown the drug to be more toxic than was at first supposed, a total of 0.04 to 0.06 gm. spread over a period of two or three days produces a rapid and marked effect on the gametocytes of *P. falciparum* strains in India. They show signs of degeneration soon after plasmochin is started and totally disappear on the completion of the course described above. Any parasites left lose their viability and are incapable of further development in the mosquito host. Green (1929) has cured quartan malaria with plasmochin alone. Freiman (1929) as well as Stern (1929) have also treated malaria with plasmochin alone but our experience with Indian strains, however, is that the dosage necessary to produce any marked effect on these strains is large enough to produce toxic effects. Symptoms of poisoning, such as pain in the abdomen, cyanosis, cardiac irregularities, etc., have occurred with such doses, which necessitated the immediate discontinuance of the drug.

The next achievement in the chemotherapy of malaria was the synthesis of atebrin in 1929. Chemically this preparation is the dihydrochloride of an alkylamino-alkylamino-acridine derivative. Its action on malarial parasites closely resembles that of the cinchona alkaloids. Unlike plasmochin, however, it is a comparatively non-toxic drug. Certain untoward symptoms have been recorded while treating patients with atebrin but they are not serious. Comparative studies of atebrin and the cinchona alkaloids, so far as their effects on malarial parasites are concerned, have been made by various workers. The general opinion is that though atebrin can not yet totally replace the cinchona alkaloids in mass treatment of malaria in this country, it is a very effective drug. It is particularly useful in those patients who are susceptible to quinine. Some also regard it as a prophylactic against malaria as it is slowly eliminated from the system.

Malarcan is another drug which has a definite action on malarial parasites. It is said to be a compound of a stereoisomeric base of methyl-cupreine with methyl-acridinium chloride and hydrochloric acid. It therefore appears to be a derivative of quinine or quinidine. Its action in some ways resembles that of atebrin but it has to be given for a longer period. The usual dosage is 9 to 12 tablets a day up to 80 or a 100 tablets. The only toxic symptoms which were noticed during the administration of the drug were flatulence, anorexia and slight ringing in the ears which disappeared with the stoppage of the drug.

The discovery of the antimalarial properties in acridine derivatives was utilized by Howard and Company in preparing 'tebetren' which they have recently introduced as a remedy for malaria. It is a combination of acridine and quinine derivatives with a derivative of cholic acid. The idea underlying this combination was to attain the maximum effect without the untoward symptoms which are usually manifested when quinine or atebrin are administered alone. Green tried this drug on a series of patients and stated that it destroys crescents. We took up the following investigation in order to study its effect on the Indian strains of malaria.

The investigation was carried out on a small series of twenty-two patients in the Carmichael Hospital for Tropical Diseases. Adult male patients giving a history of repeated attacks of malaria were admitted into the hospital under the senior author. Except in cases showing urgent symptoms the antimalarial treatment was withheld for a few days in order, firstly, to identify the species of the infecting parasites by means of daily blood examination and, secondly, to select only those cases which did not show any tendency to spontaneous recovery. Daily estimations of the number of parasites per c.mm. of blood were made during this period. Administration of tebetren was started when the parasite count was fairly constant for two or three days. Three tablets were given thrice daily for five consecutive days. The blood was examined daily for malaria parasites while tebetren was being administered and the effect of the drug was studied on (*i*) temperature, (*ii*) the sexual and asexual forms of parasites, and (*iii*) the time taken for their disappearance from the peripheral blood. Any untoward symptoms produced were carefully recorded. The patients were kept under observation for a fortnight after the treatment was completed and, if the blood examinations were negative, a

TABLE

No.	Race, sex and age	Temperature	PARASITE COUNT PER CUBIC MILLIMETRE.												Days of fever	Resultant effect on plasmodial infection
			BEFORE TREATMENT			DURING AND AFTER TREATMENT										
						2nd day		3rd day		4th day		5th day		6th day		
			Species	Asex.	Sex.	Asex.	Sex.	Asex.	Sex.	Asex.	Sex.	Asex.	Sex.	Asex.	Sex.	
1	H. M., 20 ..	99°F.	B. T. M. T. Q.	+ Sc. +	Sc. 0 Sc.	+ Sc. +	Sc. 0 Sc.	++ Sc. Sc.	Sc. Sc. Sc.	Sc. 0 Sc.	Sc. 0 Sc.	Sc. 0 Sc.	0 0 0	0 0 Sc.	0 0 0	3	Quartan persisted. (Hw. infection.)
2	H. M., 29 ..	105°F.	M. T. Q.	Sc. +	0 0	0 Sc.	0 Sc.	0 Sc.	0 Sc.	0 Sc.	0 0	0 Sc.	0 0	0 Sc.	0 0	2	Quartan persisted. (Hw. infection.)
3	H. M., 17 ..	102°F.	Q.	800	0	400	0	160	0	Sc. deg.	0	0	0	0	0	2	Cleared; relapsed on the 15th day after treatment showing B. T. (Hw. infection.)
4	E. M., 33 ..	98°F.	M. T.	Sc.	0	Sc.	Sc.	Sc.	Sc.	0	Sc.	0	Sc.	0	Sc.	..	Crescents persisted. Took atebrin and plasmochin before admission.
5	H. M., 18 ..	99.4°F.	B. T. M. T.	Sc. Sc.	0 0	Sc. Sc.	Sc. Sc.	Sc. Sc.	Sc. Sc.	Sc. Sc.	Sc. Sc.	0 0	0 Sc.	0 0	0 Sc.	2	Crescents persisted. Relapsed on the 18th day after treatment.
6	H. F., 16 ..	99°F.	M. T.	1,200	240	0	320	0	240	0	180	0	Sc.	0	Sc.	2	Crescents persisted. Relapsed on the 4th day after treatment.
7	H. M., 28 ..	100.4°F.	M. T.	3,060	0	2,250	0	Sc.	0	Sc.	Sc.	0	Sc.	0	Sc.	3	Crescents persisted.
8	H. M., 36 ..	100°F.	Q.	750	160	240	80	200	80	Sc.	0	Sc.	0	0	0	2	Cleared.
9	H. M., 20 ..	98°F.	B. T.	Sc.	Sc.	Sc.	Sc.	0	0	0	0	0	0	0	0	..	Originally B. T. and M. T. Blood showed B. T. immediately before treatment was started. M. T. found on 23rd day after treatment. Took quinine before admission.
10	H. M., 20 ..	105°F.	M. T. B. T.	5,300 1,000	700 0	1,280 160	800 80	+ +	Sc. 0	Sc. Sc.	+ 0	0 0	+ 0	0 0	+ 0	2	Crescents persisted.
11	M. M., 18 ..	102°F.	B. T.	2,800	0	1,300	0	400	0	0	0	0	0	0	0	2	Cleared.

12	H. M., 17 ..	99.4°F.	M. T.	+	Sc.	Sc.	Sc.	Sc.	Sc.	Sc.	+	0	+	0	+	..	Crescents persisted.
13	H. M., 32 ..	100°F.	M. T.	+	Sc.	Sc.	+	0	+	0	+	0	+	0	+	1	Do. Took quinine before admission.
14	H. M., 54 ..	101°F.	Q.	+	Sc.	+	Sc.	Sc.	0	Sc.	0	Sc.	0	Sc.	0	2	Persisted for a week after treatment.
15	M. F., 38 ..	101.8°F.	B. T.	7,500	160	5,000	160	1,600	0	Sc.	0	0	0	0	0	2	Cleared. Patient left on 13th day after treatment. (Indeterminate.)
16	H. M., 5½ ..	98.4°F.	M. T. B. T.	Sc. Sc.	Sc. Sc.	Sc. Sc.	Sc. Sc.	0 0	Sc. 0	0 0	Sc. 0	0 0	Sc. 0	0 0	Sc. 0	..	Crescents persisted.
17	H. M., 7 ..	102.6°F.	B. T.	5,600	0	3,600	160	200	240	800	0	0	0	0	0	..	Cleared. Helminthic infection and low fever persisted.
18	H. M., 18 ..	104°F.	Q.	+	0	+	0	Sc.	0	Sc.	0	Sc.	0	Sc.	Sc.	1	Parasites disappeared 6 days after treatment. Q. and M. T. found again 7 weeks after treatment.
19	A.-I. F., 2 ..	101°F.	B. T.	++	Sc.	+	Sc.	Sc.	Sc.	Sc.	0	Sc.	0	Sc.	0	..	Parasites and fever persisted with ½ tablet b. d. for 5 days.
20	Do. ..	100°F.	B. T.	Sc.	0	Sc.	0	Sc.	0	0	0	0	0	0	0	..	Parasites cleared. Fever persisted with 1 tablet twice a day for 5 days. Relapsed on 11th day after treatment.
21	H. M., 20 ..	106°F.	M. T.	45,000	1,000	30,000	1,600	3,800	1,200	Sc.	1,000	0	1,100	0	1,200	2	Crescents persisted. Left on risk bond 5 days after treatment. (Indeterminate.)
22	I. Ch. M. ..	101.4°F.	M. T.	Sc.	0	Sc.	0	..	..	..	..	..	..	..	..	..	Tebetren omitted after 1 day as found sensitive to it. (Indeterminate.)

Abbreviations.

Sc. .. Scanty.
Hw. .. Hookworm.
M. T. .. Malignant tertian.
B. T. .. Benign tertian.
Q. .. Quartan.
H. M. .. Hindu male.
H. F. .. Hindu female.
E. M. .. European male.
M. M. .. Mohammedan male.
M. F. .. Mohammedan female.
A.-I. F. .. Anglo-Indian female.
I. Ch. M. Indian Christian male.

cultural examination was also done. No special precautions were observed during the course of treatment except that constipation if present was relieved with a mild purgative. The results have been analysed and are given in the table.

Perusal of the table shows that in cases of infection with *P. falciparum* the asexual forms are destroyed within three to five days, but the sexual forms remain unaffected (cases nos. 1, 2, 4, 5, 6, 7, 10, 12, 13, 16 and 21). In cases of infection with *P. vivax* both the asexual and sexual forms disappeared from the peripheral blood within three to five days (cases nos. 1, 5, 9, 10, 11, 15, 16 and 17). The effect of tebetren on both the asexual and sexual forms of *P. malariæ* was much less marked and in cases nos. 1, 2, 3, 8 and 14 the parasites persisted for a comparatively longer period. In case no. 14 the plasmodia persisted for seven days after completion of treatment. The cure rates with this drug on the three species of parasites are as follows :—

P. vivax .. 6 out of 9 (66 per cent), one of whom left hospital on the 13th day after treatment.

P. falciparum .. 8 out of 12 (66 per cent), one of whom left hospital on the 5th day after treatment.

P. malariæ .. 3 out of 6 (50 per cent).

The following cases are of special interest in this investigation. Case no. 3 was admitted with quartan infection, but the relapse showed benign tertian infection instead of quartan. Case no. 18 also had quartan infection but the relapse showed both quartan and malignant tertian. In the case of no. 9, *P. vivax* and *P. falciparum* were both present on admission but only *P. falciparum* was found when treatment was started; the relapse which occurred on the 23rd day showed *P. vivax* only. The explanation appears to be that cases nos. 3 and 18 had a latent benign tertian and malignant tertian infection respectively which could not be controlled by tebetren. Similarly in case no. 9 the malignant tertian infection had become latent by the time treatment was actually started, and possibly remained unaffected. These three cases show that this drug like others does not reach the parasites in the internal organs in sufficient concentrations to destroy them completely and when relapse occurred they became active and appeared in the peripheral circulation.

The untoward effects which were met with in a certain number of patients during the course of trials with tebetren were anorexia, a sense of uneasiness in the epigastric region and flatulence. One or two patients complained of some disturbance in sleep. Case no. 22 showed

(*Continued at foot of next column*)

THE TREATMENT OF OBSTRUCTION OF LACRIMAL DUCT AND CHRONIC DACRYOCYSTITIS

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OBSTRUCTION of the lacrimal duct is generally due to chronic dacryocystitis and subsequent fibrosis, stricture or stenosis of the lacrimal duct. It is not necessary to give the pathological factors which bring about the condition, as they can be found in any textbook on ophthalmology. On the other hand I propose to discuss the treatment in some detail.

Treatment

The measures adopted to cure this condition are :—

(1) Syringing the lacrimal sac with antiseptics or astringents.

(2) Dilating the stricture by passing graduated probes through the lacrimal duct.

(3) Excision of the lacrimal sac—

(*a*) by the usual external method.

(*b*) by the intranasal method (the operation goes by the name of West intranasal dacryocystotomy).

(4) Stricturectomy by Poulard's method.

(5) Toti's or Dupuy Dutemps' operation—in other words establishing a permanent drainage of the lacrimal sac into the nasal cavity (dacryocysto-rhinostomy).

(*Continued from previous column*)

sensitiveness to tebetren and the drug had to be stopped after the first day.

Summary.—Tebetren resembles quinine and atebrin in its action on Indian strains of malaria. It destroys the asexual and sexual forms of *P. vivax* and *P. malariæ*, but only the asexual forms of *P. falciparum*. Its action on *P. malariæ* is comparatively slower and less potent. Like atebrin it is not unpleasant to take, but the drug has to be given in much larger doses than atebrin. As compared with cinchona alkaloids the drug is much more expensive and appears to have no particular advantage over them.

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