stitutional reactions lasting three days have been produced after an intradermal test containing not more than 0.1 grain of acetylsalicylic acid. The onset of symptoms in these cases is almost immediate. Positive cutaneous reactions by testing are not obtained except in those cases in which there is a clinical history of urticaria. In other words, skin hypersensitiveness as a rule does not exist.

In some cases, the allergic reactions are delayed. In the literature are reported instances of allergic drug reactions appearing from five to twenty days after the primary injection.

Specificity.—The reactions seem to depend in most cases on the chemical molecule as a whole; in a few cases, on some fraction of the molecule. Three of the cases that showed a bronchial reaction to acetylsalicylic acid gave no reaction to salicylic acid, benzoic acid, antipyrin, sodium acetate or methyl salicylate. On the other hand, many of the instances of drug reactions reported in the literature are shown to be due to fractions of the molecule. For example, iodoform hypersensitiveness has been shown to be due to the CH_3 group, and not to iodine or iodide.

No attempt is made here to give a complete summary of the subject of drug allergy. I merely wish to emphasize the conception that such a condition exists, and that it should not be confused with what are ordinarily and properly classified as idiosyncrasies. In order to clarify the ideas on drug action, it seems possible to make tentatively some such classification as the following:

1. Normal action—side action and toxic action.
2. Idiosyncratic action—(a) exaggerated normal action; (b) exaggerated side action; (c) lessened normal action (tolerance).
3. Allergic action—abnormal action.

No attempt is made in this classification to include racial variations, which are not idiosyncratic except when comparing one species with another which has an entirely different organic or functional mechanism.

ABSTRACT OF DISCUSSION

DR. LAMBERT OTT, Baltimore: I was interested in hearing Dr. Cooke's report in regard to the sensations following the injections of acetylsalicylic acid. It must be interesting to know this condition. Some years ago I reported such a case which I called an idiosyncrasy; for after all, these conditions are produced by some chemical. I saw a patient, 37 years of age, who took acetylsalicylic acid and developed bronchial spasms. Sometimes he was advised what he was taking and sometimes not. The drug was administered in capsules and in powders, and in every instance the man developed bronchial spasms.

The Record of Vaccination.—In the Municipal Hospital of Philadelphia, during thirty-four years, in which time over 9,000 cases of smallpox have been treated, no physician, nurse or attendant who has been successfully vaccinated or revaccinated prior to going on duty has contracted the disease. On the other hand, in the Fever Hospitals of London, according to Ernest Hart, in 1893, of 2,484 persons employed, 130 became infected and two died; seventy-three had scarlet fever and twenty-three contracted diphtheria. The deaths from smallpox, in England, are thirteen per million for medical men (who are well vaccinated) as against seventy-three per million of the general population; whereas fifty-nine medical men per million die of scarlet fever as against sixteen per million of the general population. Welch and Schamberg, *Acute Contagious Diseases*.

FILARIAL PERIODICITY*

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A most interesting phenomenon in blood parasitology and one of practical importance in the question of transmission of the parasite, is the periodicity of filariae. This term has come to mean a periodic increase in numbers in peripheral capillary blood of the embryos of filariae. This, in the case of *Filaria bancrofti*, occurs during the hours of sleep, and of *Filaria loa*, during the hours of activity. Until Smith and Rivas¹ developed the acetic acid concentration method of counting the number of microfilariae in a given amount of blood, "filarial periodicity" signified the periodic appearance and disappearance of microfilariae in the peripheral blood. This acetic acid concentration method of examining for microfilariae has brought about important changes in our conception of the phenomenon, and has opened a new avenue of approach to the problem.

Smith and Rivas have thus been enabled to show that filaria embryos are to be found in the peripheral blood at all times of the day and night, and that the periodicity is a matter of a relative number of embryos circulating in the blood. They² have given a method of making an exact count, and they have been led to formulate a new theory as explaining the phenomenon.

They have shown that the period of cutaneous prevalence of *Microfilaria bancrofti* is from midnight to 8 a. m., the maximum being about 2 a. m.; that the period of cutaneous prevalence of *Microfilaria loa* is from 8 a. m. to 4 p. m., the maximum being about noon, and that from 4 p. m. to midnight is a period of cutaneous paucity of both.

Regarding these periods as those respectively of (a) greatest peripheral relaxation from fatigue and sound sleep; (b) of recovery from fatigue and the resumption of capillary tone in the periphery, and (c) of capillary constriction from the combined influences of tone and of compression from muscular activity, and believing that both microfilariae are restricted (but not prevented) in their motility by their ensheathment, *Microfilaria loa* evincing greater motile effort than *Microfilaria bancrofti*, Smith and Rivas advance a theory in which the mechanics of the capillary circulation plays the main rôle, with the restricted motility of the parasite playing a minor part. In brief, the theory considers that the parasites are both in smallest numbers when they have the easiest progress through relaxed capillaries (the period of relaxation, 4 p. m. to midnight), that *Microfilaria bancrofti* is caught by the first resumption of capillary tone (from midnight to 8 a. m.), that the parasites get through, finally, by the end of this time, and are then held up again in the pulmonary capillaries, and that *Microfilaria loa*, because of greater motile effectiveness is enabled to pass this moderate opposition; but when the capillaries are markedly diminished from tonic contraction and muscular compression (8 a. m. to 4 p. m.), the parasites are no longer able to progress easily, and therefore accumulate.

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* Read before the Section on Pathology and Physiology at the Seventieth Annual Session of the American Medical Association, Atlantic City, N. J., June, 1919.

1. Smith, A. J., and Rivas, Damaso: The Early Diagnosis of Filariasis, South. M. J., 5: 631, 1912.

2. Smith, A. J., and Rivas, Damaso: Notes Upon Human Filariasis, Am. J. Trop. Dis. & Prev. M. 2: 361, 1914-1915.

Supporting the mechanical part played in this theory, Smith and Rivas have performed some experiments aiming at altering circulatory conditions and capillary caliber. They succeeded, at one time, in increasing the number of *Microfilaria loa* by giving a half ounce of brandy; at another, by a half hour's general exercise, and by compressing the hand in a glove, and placing the hand in warm water. They also determined that the venous drainage of an extremity showed fewer parasites than did the capillary circulation.

Manson³ considers broadly that the periodic peripheral swarming of microfilariae is an adaptation on the part of the parasite to the biting habits of the intermediate host. Undoubtedly, the large numbers of *Microfilaria bancrofti* in the peripheral blood at night favor its entrance into the night biting *Culex fatigans*, but this does not explain the problem. Manson would believe that there is some physiologic product, the outcome of the activities of waking life, which either drives *Filaria nocturna* from the surface of the body during the day, or attracts it to certain internal organs, particularly to the lungs and large arteries.

Feeling that this chemotropic theory is rather unreasonable and that the demonstration of these embryos constantly in the peripheral blood has rendered it untenable, I have instituted a series of experiments in the human infection by *Filaria bancrofti*, and the dog infection by *Filaria immitis*, attempting to influence the number of embryos in capillary blood by circulatory alteration.

In all of these counts I have used the acetic acid method of concentration, taking 1 c.c. of blood in 10 c.c. of 2 per cent. acetic acid solution, centrifuging, washing and recentrifuging several times, spreading the sediment on a slide, and counting the whole number in the sediment.

NITROGLYCERIN EXPERIMENTS

EXPERIMENT 1.—*Human case of Filaria bancrofti*.—In J. S., an aged colored man with extreme arteriosclerosis, poor mentality, motor nervous disturbance, markedly enlarged right inguinal glands, hydrocele and general lymph gland enlargement, microfilariae were found in a drop of blood from the finger tip at 11 p. m.; none in the day time. Dec. 11, 1916, at 11 a. m. 245 microfilariae in 1 c.c. of blood from the finger tip were counted. I gave $\frac{1}{100}$ grain of nitroglycerin hypodermically. At 11:30 a. m. 171 microfilariae were found in 1 c.c. of blood from the finger tip, a decrease of seventy-four, or 30 per cent. Dec. 13, 1916, at 11 a. m., I repeated the experiment and counted 201 per cubic centimeter before the administration of the nitroglycerin, and seventy-four per cubic centimeter twenty minutes after the administration, a decrease of 127, or 63 per cent. Dec. 19, 1916, at 11 p. m., I repeated the experiment, and counted 615 microfilariae per cubic centimeter before, and 615 per cubic centimeter twenty minutes after the administration of nitroglycerin.

EXPERIMENT 2.—*Human case of Filaria bancrofti*.—In T. R., a middle aged mulatto, showing chyluria, there were counted, Dec. 13, 1916, at 11 a. m., three microfilariae per cubic centimeter in the blood of the finger. I gave $\frac{1}{100}$ grain of nitroglycerin hypodermically and, at 11:20 a. m., counted one microfilaria per cubic centimeter of blood from the finger. Dec. 19, 1916, at 11 p. m., I repeated the experiment and counted 382 microfilariae per cubic centimeter before, and 300 per cubic centimeter twenty minutes after the administration of the nitroglycerin, a decrease of eighty-two, or 21 per cent. Jan. 5, 1917, at 11 p. m., I repeated the experiment and counted 353 microfilariae per cubic centimeter before, and 259 per cubic centimeter after the administration, a decrease of ninety-four, or 26 per cent.

EXPERIMENT 3.—*Dog, infected with Filaria immitis*.—Dec. 17, 1917, at 11 a. m., there were counted 2,706 microfilariae per cubic centimeter in the blood from the ear. One one-hundredth grain of nitroglycerin was given hypodermically. At 11:15 a. m. there were 972 microfilariae per cubic centimeter in the blood from the ear, a decrease of 1,734, or 64 per cent. Dec. 19, 1917, at 11 a. m. the experiment was repeated, and 3,264 microfilariae were found per cubic centimeter before, and 3,264 per cubic centimeter five minutes after administration of nitroglycerin.

Jan. 5, 1917, at 11 a. m., the experiment was repeated. There were counted 3,172 before, and 1,620 after administration of the nitroglycerin, a decrease of 1,552, or 50 per cent.

Thus, after the administration of nitroglycerin, there resulted decreases in the number of both *Microfilaria bancrofti* and *Microfilaria immitis* in the peripheral capillary blood, varying from 21 per cent. to 64 per cent. In two experiments, one with *Microfilaria bancrofti* and one with *Microfilaria immitis*, the number remained the same in twenty and five minutes, respectively. I have recorded in my notes that the product used in these was old and its potency doubtful. It was not tested, but a fresh product was substituted. I interpret these results to indicate that relaxation of the vascular system, whether during the period of cutaneous prevalence or paucity, allows these parasites to pass more freely, and consequently their number in a given volume of blood decreases.

PITUITARY EXTRACT AND EPINEPHRIN EXPERIMENTS

EXPERIMENT 4.—*Human case*.—In J. S., Dec. 17, 1916, at 11 p. m., there were counted 531 microfilariae per cubic centimeter in blood from the finger. He was given pituitary extract hypodermically, and there were counted 665 microfilariae per cubic centimeter in the finger's blood at 11:10 p. m., an increase of 134, or 25 per cent.

EXPERIMENT 5.—*Human case*.—In T. R., Dec. 15, 1916, at 11 p. m., there were counted 227 microfilariae per cubic centimeter in the finger's blood before, and 334 ten minutes after the administration of pituitary extract, an increase of 107, or 47 per cent. Dec. 17, 1916, the experiment was repeated, and there were counted 138 per cubic centimeter before, and 364 per cubic centimeter twenty minutes after the administration of pituitary extract, an increase of 226, or 164 per cent.

EXPERIMENT 6.—*Dog, Filaria immitis*.—Oct. 29, 1917, at 11:55 a. m., 1,360 microfilariae were found per cubic centimeter in blood from the ear before, and 1,620 microfilariae per cubic centimeter in blood from the ear ten minutes after the administration of 1 c.c. of pituitary extract hypodermically, an increase of 260, or 20 per cent. At the same time, 1,056 per cubic centimeter were found in blood taken directly from a large ear vein. This confirms the observation of Smith and Rivas in *Filaria bancrofti* infection. The experiment was repeated, Oct. 31, 1917, at 12:30 p. m., and 1,294 microfilariae per cubic centimeter were found before, and 2,678 per cubic centimeter of ear's blood ten minutes after the administration of pituitary extract, an increase of 1,384, or 107 per cent.

Nov. 1, 1917, at 12:30 p. m., the experiment was repeated and there were counted 1,478 microfilariae per cubic centimeter in capillary blood from the ear, 1,272 per cubic centimeter in venous blood, and, ten minutes after the administration of pituitary extract, 2,196 in capillary and 724 in venous blood, an increase in the capillary blood of 718, or 48 per cent., and, at the same time, a decrease in the venous blood of 448, or 35 per cent., thus showing that the increase in the capillary blood was a process of accumulation or holding up, and not an additional influx.

The experiment was repeated, Nov. 2, 1917, at 11:20 a. m. One thousand nine hundred and twenty-two microfilariae per cubic centimeter were counted in the capillary blood before, and 2,160 per cubic centimeter ten minutes after the administration of epinephrin, an increase of 238, or 13 per cent. Twenty minutes after the administration, 2,460 microfilariae per cubic centimeter were found in venous blood. It seems that prob-

3. Manson, P.: On Filarial Periodicity, Brit. M. J. 2: 644, 1899.

ably by this time the parasites were being released into the veins. Unfortunately, capillary blood was not taken.

The experiment was repeated, Nov. 5, 1917, at 11:30 a. m., and 2,216 microfilariae per cubic centimeter of capillary blood were counted before, and 2,820 per cubic centimeter ten minutes after the administration of epinephrin, an increase of 603, or 27 per cent., and 3,228 per cubic centimeter twenty minutes after the administration, an increase of 1,012, or 45 per cent.

The experiment was repeated, Nov. 9, 1917, at 11 a. m. Two thousand three hundred and seventy-two per cubic centimeter of capillary blood were found before, and 3,512 thirty minutes after administration of epinephrin, an increase of 1,140, or 48 per cent., and 4,420 per cubic centimeter in capillary blood forty minutes after the administration, an increase of 2,048, or 86 per cent.

A dog was anesthetized with morphin and chlorbutanol, Jan. 12, 1918, at 11 a. m. There were counted 3,268 microfilariae per cubic centimeter in capillary blood before, and 4,738 per cubic centimeter in capillary blood ten minutes after the administration of epinephrin, an increase of 1,470, or 45 per cent.

Therefore, after the administration of epinephrin and pituitary extract, there resulted increases in the number of both *Microfilaria bancrofti* and *Microfilaria immitis* in the peripheral capillary blood, varying from 13 to 164 per cent. There occurred also a decrease of 35 per cent. in the venous drainage of an area at the same time as an increase in the capillary blood of 48 per cent. and a subsequent venous increase. I interpret these observations to indicate that an increase in the tone of the vascular system, whether during the period of peripheral prevalence or paucity, prevents the free passage of these parasites through the capillaries; that, therefore, their number in a given volume of capillary blood increases, and that during this time the number getting into the venous drainage is cut down, but increases after a time, and especially when the tone begins to wear off.

EFFECT OF SLEEP

The effect of sleep on the peripheral prevalence of *Microfilaria immitis* was shown in the following experiment:

EXPERIMENT 7.—Dog 1, was kept awake from 11:20 a. m. to 1 a. m. following, and the capillary blood showed, at 11:20 a. m., 2,851 microfilariae per cubic centimeter; at 1 p. m., 2,900; at 3:20 p. m., 3,217; at 8 p. m., 2,736; at 11 p. m., 2,352, and at 1 a. m., 2,264.

In Dog 1, awake at 1 p. m., there was a count of 2,512 in the capillary blood, and, in Dog 1, asleep at 3 p. m., a count of 4,300 in the capillary blood, an increase of 71 per cent., which is comparable to but not as large, even, as the increase brought about by pituitary extract and epinephrin administration.

It is interesting to note that when the dog was kept awake there was an increase comparable to that of *Microfilaria loa* in the afternoon, and then a decrease similar to that in *Microfilaria loa* infection in the night hours. *Microfilaria immitis* is smaller in transverse diameter than *Microfilaria bancrofti* and *Microfilaria loa* embryos. As a consequence, it gets past the capillary barrier with more ease and shows constantly more in peripheral blood. There is, however, a period of relative peripheral prevalence directly connected with sleep, whether at night or in the day, which can be altered by keeping the dog awake, and the number of microfilariae in the peripheral capillary and venous blood is subject to the same natural and artificial alterations as is that of the human parasites.

In this connection, it would be interesting to know whether the acetic acid concentration method would not show a periodicity of the smaller human filaria embryos, *Filaria perstans* and *Filaria demarquayi*, which are to be found by old methods of examination constantly in the peripheral blood.

EFFECT OF COLLAPSE OF THE LUNG

EXPERIMENT 8.—Dog 1, anesthetized with chlorbutanol and morphin gave a count of 3,268 microfilariae in the peripheral capillary blood.

One lung was artificially collapsed by the introduction of air into the pleural sac. Five minutes later the dog died, and the thorax was opened. The uncollapsed lung showed 8,962 microfilariae in the capillary blood; the collapsed lung, 350,000 per cubic centimeter, this being a rough count as there were so many it could not be made exact; the left ventricle, 7,365, and the right ventricle, 10,778. Unfortunately, the bloods taken from various other parts were allowed to clot, and were consequently useless for counting.

This is one of the most striking of the experiments. The capillary circulation in the lungs is more of a barrier to the passage of these parasites in both *Microfilaria bancrofti* and *Microfilaria immitis* infections than is the peripheral capillary system, as is evidenced by the larger numbers in the uncollapsed lung of this dog and in Manson's case of *Microfilaria bancrofti* infection, which came to necropsy, and also in a case in which I made a postmortem examination. As shown by my necropsy, this appears to be not simply a retirement from the periphery to the lungs during the period of peripheral paucity. Apparently the lung filter is more or less constantly difficult of their passage. The collapse of the lung seems to have created a pressure on the capillaries and to have rendered them relatively impassable, even by this small worm, and to have led to an enormous accumulation, showing an increase over the number in the other lung of 3,805 per cent. in five minutes.

It is to be noted also that the number getting through the lungs and showing in the left heart was even less per cubic centimeter than in the uncollapsed lung.

I would interpret this experiment as showing what an influence on the number of these worms a purely mechanical capillary barrier may have.

HUMAN NECROPSY

Manson has reported a necropsy of a subject of *Filaria bancrofti* infection who died suddenly at 8 a. m., in whom he found prodigious numbers in the lungs, very many in the pulmonary artery and vein, large numbers in the carotid artery, a large number in clots from the left ventricle and aorta, many in the heart muscle, and a few in other places. From this he concludes that *Filaria nocturna*, during its temporary absence from the cutaneous circulation, retires to the localities in which he found large numbers.

Sept. 16, 1916, I performed a necropsy on a subject of *Filaria bancrofti* infection who died of pellagra at about 2 a. m. I was not at the time using the acetic acid method of counting, but I recorded large numbers of microfilariae in the lungs, and a few in the blood of the kidney, spleen, liver, heart, retroperitoneal lymph glands and large vessels. This confirms Manson's observation in regard to the lungs, but not in regard to the heart and large vessels. Neither of these cases furnishes positive reliable evidence of the distribution except in a rough way. I expect interesting exact data to be obtained from a repetition of postmortem exam-

inations by the use of the acetic acid method of counting. I can see no means by which the microfilaria could maintain itself against the current in the large vessels, particularly such as the aorta and carotid artery.

INTRAVITAM OBSERVATIONS ON MICROFILARIA IMMITIS

EXPERIMENT 9.—Dog 1 was anesthetized, the abdomen opened, and the omentum drawn over the stage of a microscope. Considerable injury was done and it was difficult to keep the membrane warm and moist. Consequently, the capillary circulation was largely sluggish or stopped. Three microfilariae were seen wriggling with the stream, faster than the blood was moving, in a large capillary. One was seen to progress against the stream of a small capillary. Two went slowly forward through a capillary carrying a single line of cells. These were wriggling, and the blood cells passed by them in their convolutions. This explains why even large numbers do not prevent the passage of blood in the small capillaries. The one progressing against the stream and those going forward faster than the sluggish stream appeared to push themselves against the wall. Apparently, therefore, they have some propulsive power even in the capillaries. It was planned to observe the action of drugs on the vessels, and the effect on the passage of the parasite, but the technic will have to be perfected before this can be done. I expect this measure, however, to furnish interesting information concerning the passage of microfilariae through the capillaries.

This experiment appears to show that the parasite does not perform simply as a foreign body but that its own activity is to some extent concerned in its passage of the finer capillaries, as was conjectured by Smith and Rivas.

FURTHER DRUG ADMINISTRATION

Incidentally, it may be mentioned that in the human experiments ergot and caffeine were administered without altering numbers, that emetin was given hypodermically with no effect on the parasite, and that while oil of chenopodium given intravenously in considerable doses in the dog killed the embryo, doses compatible with the life of the animal had no apparent effect, and neither did alimentary administration.

SUMMARY

Fully realizing the limitations to be placed on interpretations of the effect on the capillary system of the drugs used, and that these experiments need confirmation and elaboration, I believe that these observations strongly support the mechanical theory of Smith and Rivas in regard to filarial periodicity, and that the reasonable explanation of filarial periodicity is furnished by some such mechanical proposition, in which the caliber of the capillaries plays the main rôle, with the motility of the microfilariae playing a lesser part, so that the peripheral prevalence of microfilariae is largely dependent on the difficulty of passage of the peripheral capillaries during periodic tonicities and is directly related to sleep and wakefulness, but is affected to an extent varying with the size and the motility of the parasite, the pulmonary capillary system relative to these two conditions playing the part of a more or less constant barrier, but one probably more effective during the hours of the tone of activity.

CONCLUSIONS

1. The acetic acid concentration method of Smith and Rivas furnishes an exact method of counting microfilariae, and only by exact counts can the number in a given part of the body be accurately determined.

2. The administration of nitroglycerin is followed by a decrease in the number of *Microfilaria bancrofti* and of *Microfilaria immitis* in the peripheral capillary blood, during both periods of peripheral prevalence and paucity.

3. The administration of epinephrin or pituitary extract is followed by an increase in the number of *Microfilaria bancrofti* and of *Microfilaria immitis* in the peripheral capillary blood, during the periods both of cutaneous prevalence and of cutaneous paucity.

4. The period of cutaneous prevalence of *Microfilaria immitis* is directly connected with sleep.

5. In the collapsed lung, *Microfilaria immitis* accumulates in enormous numbers.

6. During the period of cutaneous paucity of both *Microfilaria bancrofti* and *Microfilaria immitis*, there are large numbers in the lungs.

7. The venous drainage of a part contains fewer microfilariae than the capillaries, there are still fewer when accumulation in the capillaries is produced by vascular stimulation, and following this capillary accumulation the venous drainage contains larger numbers.

TYPHOID, PARATYPHOID AND DYSENTERY CARRIERS AMONG RETURNING OVERSEAS TROOPS

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Circular 69, issued in February, 1919, by the chief surgeon of the American Expeditionary Forces stated that during the autumn and early winter of 1918 the incidence of typhoid and paratyphoid fevers among the American troops overseas had shown a noteworthy increase. More than 874 cases of typhoid and paratyphoid were reported between October 1 and February 1. This number, while not large in itself, represented an unexpected degree of infection among vaccinated individuals. The questions that presented themselves were: What percentage of the convalescents would become chronic carriers, and to what extent would these returning troops prove a menace to the home population?

It was therefore planned to examine the stools of a sufficient number of returning troops to include members of practically all divisions and at the same time to reduce the percentage of error. This laboratory seemed to be particularly well adapted for this purpose, not only on account of its facilities, but especially because of the fact that an intensive survey for intestinal parasites was being conducted among all homecoming men by Major C. A. Kofoed, S. C., U. S. Army.

The routine for the collection and examination of specimens was as follows:

The specimen of stool was placed in a cardboard drug can with tin bottom and top and immediately brought from the ward to the laboratory. A small portion (about the size of a pea) was thoroughly emulsified in 10 c.c. of nutrient broth and the tube placed in the incubator for two hours, during which time the larger particles settled to the bottom. A loopful of the suspension was then streaked on Endo agar and the plates were incubated over night. All colorless colonies were then fished to Russell's double sugar agar,