

## THE DISTRIBUTION OF CHLOROFORM IN THE BLOOD.

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Buckmaster and Gardner<sup>1</sup> have shown that in chloroform anæsthesia the bulk of the chloroform is carried by the red corpuscles. Pohl<sup>6</sup> estimated the proportion in the corpuscles as two to four times that present in the serum. Nicloux<sup>4</sup> by a more accurate method estimated the amount in corpuscles as about 88 and in the plasma 12 per 100 parts of chloroform. The enormous difference in time of absorption and of elimination, and the very much more marked effects on the tissues of chloroform when given subcutaneously, suggested to us that the chloroform might be differently combined in the two cases. By inhalation the greater part of the chloroform combines loosely with the corpuscles and is rapidly absorbed and rapidly eliminated. A small moiety is sometimes found according to Noel Paton and Miss Lindsay<sup>5</sup> still present in the blood some hours after the anæsthetic, particularly when the animal anæsthetised has been confined in a cage after the administration. This might represent a remnant of the 12 per cent. in the plasma. When given subcutaneously the much slower absorption and elimination, and the consequent greater effect on the tissues, might be due to a firmer combination of the chloroform with some part of the serum—say, the proteins, as suggested by Moore and Roaf.<sup>2</sup> That the drug is differently fixed in the two cases is further suggested by the fact that a prolonged administration of chloroform by inhalation has very little effect on the liver and kidney tissues, whereas the administration of a very small amount hypodermically causes injury to the cells of these organs.

In carrying out the experiments the same procedure was observed in all cases. The rabbits were weighed, and then where they were anæsthetised by inhalation they were kept just under for one hour. They were then killed and rapidly bled an amount of 15 per cent. solution of potassium oxalate sufficient to prevent coagulation of the blood. The blood mixture was then centrifugalised for three hours, and the corpuscles and plasma were separately estimated for chloroform. The method of Nicloux<sup>3</sup> was used throughout the estimation.

The time taken for centrifugalising—three hours—is the same as was adopted by Nicloux, and yielded more constant results than any shorter time. As an objection against such a lengthy separation may be argued that both corpuscles and chloroform would be driven to the bottom of the tube, and thus the proportion in corpuscles would rise with prolonged separation. This, as a matter of fact, is the case, but may also be due to the separation being more complete. Where the centrifugalising has gone on for one hour the corpuscles plus chloroform are mixed with a certain amount of plasma plus its chloroform; in the latter case the chloroform content is small and tends to reduce the proportion of chloroform in the mass. At the end of three hours the amount of plasma and chloroform with the corpuscles is very small indeed, and is negligible. In any case, the same procedure was adopted with both inhalation and injection specimens, so that the results are comparable.

Where chloroform was given subcutaneously amounts varying from 1 c.c. to 3 c.c. were given, and the animals were killed and bled as above two to three hours later. The amount of chloroform in the blood approaches a maximum two to four hours after the administration.<sup>5</sup> The results are:—

### 1. By Inhalation.

*Rabbit D.*—Weight, 1800 gm. Chloroform inhaled for one hour. 35 c.c. of blood taken with 1 c.c. of 15 per cent. potassium oxalate; centrifugalised for three hours. Total amount recovered, 18.13 mg. chloroform. Corpuscles, 90.8 per cent.; plasma, 9.2 per cent. of total chloroform present.

*Rabbit M.*—Weight, 2200 gm. Chloroform inhaled for 45 minutes. 58 c.c. of blood taken with 2 c.c. of 15 per cent. potassium oxalate; centrifugalised for three hours. Total amount recovered, 26.56 mg. chloroform. Corpuscles, 90.2 per cent.; plasma, 9.8 per cent. of total chloroform present.

*Rabbit P.*—Weight, 1850 gm. Chloroform inhaled for one hour. 35 c.c. blood with 5 c.c. potassium oxalate; centrifugalised for three

hours. Total amount recovered, 6.3 mg. chloroform. Corpuscles, 88.8 per cent.; plasma, 11.2 per cent. of total chloroform present.

*Rabbit R.*—Weight, 1900 gm. Chloroform inhaled for one hour. 38 c.c. of blood with 5 c.c. of potassium oxalate; centrifugalised for two and a half hours. Total chloroform recovered, 16.45 mg. Corpuscles, 88.9 per cent.; plasma, 11.1 per cent. of total chloroform present.

*Rabbit S.*—Weight, 2400 gm. Chloroform inhaled for one hour. 45 c.c. of blood with 5 c.c. of potassium oxalate; centrifugalised three hours. Total amount recovered, 14.84 mg. chloroform. Corpuscles, 87.6 per cent.; plasma, 12.4 per cent. of total chloroform present.

*Rabbit Z.*—Weight, 1800 gm. Chloroform inhaled for one hour. 40 c.c. of blood with 5 c.c. of potassium oxalate; centrifugalised for two hours. Total amount recovered, 14.84 mg. chloroform. Corpuscles, 85.2 per cent.; plasma, 14.8 per cent. of total chloroform present.

Average distribution in six rabbits: Corpuscles, 88.6 per cent.; plasma, 11.4 per cent. of total chloroform present.

### 2. By Injection.

*Rabbit C.*—Weight, 2400 gm. 1 c.c. injected; animal killed four hours later. 40 c.c. blood taken with 1 c.c. of potassium oxalate; centrifugalised three hours. Total amount recovered 7.9 mg. chloroform. Corpuscles, 81.6 per cent.; plasma, 18.4 per cent. of total chloroform recovered.

*Rabbit G.*—Weight, 2975 gm. 2 c.c. injected; animal killed two and a half hours later. 42 c.c. blood with 1 c.c. potassium oxalate; centrifugalised for three hours. Total amount recovered, 6.21 mg. chloroform. Corpuscles, 76.4 per cent.; plasma, 23.6 per cent. of total chloroform present.

*Rabbit H.*—Weight, 1450 gm. 1.5 c.c. injected and repeated in 15 minutes. 30 c.c. blood and 1 c.c. potassium oxalate; animal killed two hours later; centrifugalised three hours. Total amount recovered, 8.25 mg. chloroform. Corpuscles, 78 per cent.; plasma 22 per cent. of total chloroform present.

*Rabbit Q.*—Weight, 2300 gm. 3 c.c. injected and rabbit killed three hours later. 40 c.c. blood and 5 c.c. potassium oxalate; centrifugalised three hours. Total amount recovered, 5.88 mg. chloroform. Corpuscles, 74.8 per cent.; plasma, 25.2 per cent. of total chloroform present.

*Rabbit T.*—Weight, 2200 gm. 3 c.c. injected. 40 c.c. blood taken with 5 c.c. oxalate. Total amount recovered, 9.38 mg. chloroform. Corpuscles, 79.9 per cent.; plasma, 20.1 per cent. of total chloroform present.

*Rabbit Y.*—Weight 2050 gm. 3 c.c. injected. Animal killed two hours later. 40 c.c. blood taken with 10 c.c. oxalate; centrifugalised three hours. Total amount recovered, 10.84 mg. chloroform. Corpuscles, 72.4 per cent.; plasma, 27.6 per cent. of total chloroform present.

Average distribution in six rabbits:—Corpuscles, 77.2 per cent.; plasma, 22.8 per cent. of total chloroform present.

### Consideration of Results.

Where the chloroform was inhaled the amount found in the plasma varied from 9.2 to 14.8 per cent. of the total amount recovered from the blood. Where the chloroform was injected the amount found in the plasma varied from 18.4 to 27.6 per cent. of the total amount recovered from the blood. Thus in all cases where the chloroform was given subcutaneously the amount recovered from the plasma was much more than where the anæsthetic was inhaled. The delayed elimination therefore appears to be due to the different fixation of the drug in these cases.

The corpuscles appear to part with the chloroform rapidly, and after anæsthesia by inhalation the proportion held by the corpuscles is rapidly eliminated. Probably this is also the case with the proportion of chloroform held by the corpuscles after injection, but the difficulty of getting rid of the amount in the plasma seems to account for the delay in elimination and the injury to kidney and liver tissue.

These results suggest that in cases of delayed chloroform poisoning the distribution of the anæsthetic in the blood may more closely approximate to that of rabbits after injection of chloroform. The amount in the plasma varies within fairly wide limits, and this variation may be due to a variety of causes. Anything which would cause a larger proportion than usual of the chloroform in the blood to combine with the plasma constituents might cause a delayed elimination of the drug, and consequently injury to liver and kidney tissue.

It is of interest to note that in one rabbit which died just before the chloroform inhalation was stopped—after one hour inhalation—the amount of chloroform recovered was 22.24 mg. in 35 c.c. of blood, and of this the corpuscles contained 67.7 per cent. and the plasma 32.3 per cent., so that the fatal result was at least associated with a large percentage of chloroform in the plasma.

*Summary.*—Evidence is given that in rabbits the blood contains a larger proportion of chloroform in the plasma when the anæsthetic is given subcutaneously than when it is given as an inhalation. This is considered to be the reason for the delay in elimination and the consequent greater injury to the tissues which is associated with this mode of administration.

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## TWO UNUSUAL FORMS OF MENINGITIS OCCURRING IN INFANCY.

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THE two following cases of meningitis, which have come under our observation during the past year, seem worthy of record: the first on account of a curious dual and at the same time successive infection, and the second on account of the rarity of the exciting organism.

**CASE 1. Meningitis dependent on (a) a leptothrix; (b) the tubercle bacillus.**—The patient was an infant aged 10 months, who was originally brought to the Queen's Hospital for Children as an out-patient on Dec. 13th, 1911, for wasting. The diet was re-arranged and when the baby was seen again on Dec. 20th everything seemed very satisfactory, there being a gain of 7 oz. in weight. On the 23rd, however, the child appeared unwell, refused food, was sleepy, and took little or no notice of his mother. When seen again on Dec. 27th he was distinctly drowsy and very irritable on examination. The abdomen was slightly retracted, the reflexes very brisk, and the fontanelle moderately distended; the temperature was 101° F., and the child had lost 6 oz. in weight. There was, however, no rigidity of the neck, no screaming, or other positive signs of meningitis. The infant was admitted into hospital with a provisional diagnosis of meningitis. Two days later (on Dec. 29th) lumbar puncture was performed, and about 2 c.c. of purulent cerebro-spinal fluid was withdrawn. The temperature, which had ranged between 100°-103°, now dropped to normal, but rose again on the 31st to 101°. Lumbar puncture was again performed, with the same result. After the second lumbar puncture the drowsiness and irritability disappeared, the child could sit up, took its feeds well, and displayed a fair amount of interest in its rattle. In fact, except for a considerable degree of temperature, there were no indications that the child was other than a badly fed infant; there were certainly none to indicate a purulent meningitis.

An examination of the cerebro-spinal fluid withdrawn on Dec. 29th showed an intense polynuclear leucocytosis, while a culture yielded a pure growth of a very active motile bacillus. The morphological and cultural aspects of this organism were as follows. Growth occurred on all ordinary media—e.g., plain broth, plain agar, glucose and maltose agar; it also grew on gelatine at 20° without liquefaction. On solid media the colonies were smooth, raised, white and opaque, and not confluent. These colonies did not usually appear in less than 72 hours, but growth took place a little more quickly on media containing whole blood or hæmoglobin. The colonies themselves consisted of: (1) filaments up to 100 $\mu$  long, unbranched, and showing a wave-like motion in fluid media; (2) short and very actively motile bacillary forms. Both forms were Gram-negative. Repeated plating and fishing of single colonies and repeated subcultivation never succeeded in separating the two forms. This organism when grown in sugar media gave the following reactions: glucose —; lactose —; saccharose —; lævulose —; raffinose —; galactose —; salicin +; inulin —; coniferin —; dulcitol —; sorbitol —; mannitol +; glycerine —; milk —. Finally this organism (1) did not originate any change in neutral red; (2) did not form gas in any media; (3) did not form indol in peptone water; and (4) did not grow under anaerobic conditions. On these grounds this organism was considered to be a leptothrix.

On Jan. 1st, after lumbar puncture, the cerebro-spinal fluid proved much clearer than on previous occasions and the cultures were sterile. On the 3rd, except for a temperature, the child seemed very much better and appeared well on the

road to recovery. On the 8th, as the temperature still rose of an evening to 103° or 104°, lumbar puncture was again performed. The fluid was again very turbid, and cultures from it yielded a pure growth of the original organism. From the 8th to the 14th there was practically no change in the infant's condition, the weight was stationary, and the temperature was descending by lysis. From all points of view the infant was holding his own.

On Jan. 15th, however, the child was sick and on the 16th he was noticed to squint. On the 17th there was repeated vomiting. On the 19th the head and abdomen became retracted and the infant began to waste rapidly. On the 19th and 22nd doses of vaccine were given and a few days later the temperature became normal. On the 27th wasting was extreme, rigidity was general, and there was well-marked opisthotonos. Lumbar puncture at this date yielded a fluid identical in opacity and constituents with the preceding. On the 30th a third dose of vaccine was given. The temperature was still normal. On Feb. 6th the general symptoms remained the same, but there was a sudden rise of temperature, which now maintained an irregular course until the day of death. On the 13th a fourth dose of vaccine was administered, and five days later lumbar puncture was again resorted to. The cerebro-spinal fluid now proved to be clear save for a small coagulum. Albumin was present (0.25 per cent., Aufrecht). Cultures made from the fluid were sterile, but the films made from the coagulum showed tubercle bacilli in fair numbers. Progress from this date was steadily downhill. Rosenbach's tuberculin (0.01 c.c.) was given on the 21st and on succeeding dates, but without any influence on the usual termination. Death, however, was postponed until as long as March 28th.

The post-mortem examination in this case showed the usual typical pathological changes associated as a rule with tuberculous meningitis, and in addition a slight tuberculous deposit in the bronchial glands.

The interesting features of this case are, we think: (1) The long duration of the case—viz., 14 weeks; (2) the appearance in the first instance of a suppurative meningitis due apparently to a leptothrix alone; (3) the slight initial symptoms associated with this form of suppurative meningitis; and (4) the apparent tendency to recovery from this infection which was prevented by the very unusual sequence of a secondary infection of the meninges by the tubercle bacillus. It may be said that this was really all the time a double synchronous infection and not a successive condition; to that we would say that the sudden onset, the preliminary stages, the appearance and contents of the cerebro-spinal fluid, and especially the long duration of the illness, were all against an original tuberculous infection.

**CASE 2. Meningitis dependent on bacillus coli communis.**—The patient was an infant aged 5 months, whose history is as follows. On the night of March 2nd the child woke and commenced to scream. She was sick once. The attacks of screaming and irritability continued until the 6th, when the infant had a convulsion, and was then admitted into hospital with a provisional diagnosis of meningitis. On admission the child was found to be well nourished, and no disease of the circulatory or respiratory systems could be detected, nor was there any evidence of any gastro-intestinal disturbance. All four limbs were, however, spastic, the deep reflexes were increased, and Kernig's sign was well marked. There were slight drowsiness and distinct irritability on interference, while the fontanelle was full but not tense. On the 9th the spasticity was more marked, the head was slightly retracted, and there was pain in the neck on movement; a convergent strabismus had appeared and the fontanelle was now distinctly bulging. The child had vomited once or twice and the temperature was raised at night to 103°, being two or three degrees lower in the mornings. Consciousness and mental irritability were less marked and drowsiness was the more prominent feature. An examination of the fundus showed no pathological changes. Lumbar puncture was performed on the 9th, and a quantity of opalescent fluid flowed freely into the receiver. This fluid was found to contain a quantity of albumin, a trace of globulin, and no reducing bodies. Films made from the fluid revealed a large number of mono- and poly-morpho-nuclear leucocytes in about equal proportions. In addition to these changes a large number of Gram-negative motile bacilli were present. Cultures from this fluid gave a pure