A REPORT

ON

THE BILIARY SECRETION OF THE DOG:
WITH REFERENCE TO THE ACTION
OF CHOLAGOGUES:*Presented to the Scientific Grants Committee of the
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ASSISTED BY

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THIRD SERIES.

IN the first series of these experiments, published in this JOURNAL in 1875, an account was given of the action of podophyllin, colchicum, rhubarb, aloes, scammony, calomel, taraxacum, senna, gamboge, croton, and castor-oil, on the biliary secretion of the dog. The account of the second series, published in this JOURNAL in 1877, contained the results of similar experiments with euonymin, sanguinarin, iridin, leptandria, ipecacuan, colocynth, jalap, sodium sulphate, magnesium sulphate, potassium sulphate, sodium phosphate, Rochelle salt, ammonium chloride, nitrohydrochloric acid, corrosive sublimate, and calomel. In the third and concluding series, now to be detailed, precisely the same method of experiment has been had recourse to, it having been abundantly proved by us, that our method is admirably fitted to yield results of a precise, and therefore reliable, character in this important inquiry. The method of experiment, although fully detailed in the introduction to the first series (BRITISH MEDICAL JOURNAL, 1875), may here be briefly recapitulated. All the experiments were performed on dogs, because of the suitable size of that animal, and for the reason that we have abundantly shown that the liver of that animal is influenced in the same sense, although it may not be in like degree, by the agents that excite the biliary secretion in man; in addition, we have felt it to be essential for the purpose of comparing the results, to have a complete series of experiments on animals belonging to the same species. Each animal had a full meal of flesh at three or four o'clock in the afternoon; and at nine o'clock on the following morning, the experiment was begun, when of course the absorption of the food had ceased: a condition essential for a constant secretion of bile. In every case, irregular muscular movements were prevented by repeated small doses of curara, it having been ascertained that these have no influence on the biliary secretion, nor do they prevent the manifestation of the effects of hepatic stimulants. Artificial respiration was had recourse to, in consequence of the curara paralysis. Through an opening in the linea alba, a glass cannula was inserted into the common bile-duct, the cystic duct was clamped, and all the bile thereby compelled to flow through the cannula as fast as it was secreted. The bile dropped into a finely graduated cubic centimetre measure, where it was constantly collected, and a record was made of the amount secreted every fifteen minutes. Each experiment lasted the greater part of a day, at the close of which the animal was killed, and its alimentary canal opened for the purpose of observing the effects of the various substances thereon. The various drugs were not injected into the stomach, because of its containing a very considerable quantity of viscid saliva in the fasting dog, the mucin of which is apt to envelope various medicinal agents, and thus to retard their absorption. The substances were injected into the duodenum for the above reason, and also for the purpose of allowing them a fair opportunity of exciting its mucous membrane, and of thus reflexly stimulating the liver, did they possess any power of so doing.

It having been shown, in the first series of experiments, that resinous matters, such as podophyllin, are absorbed with difficulty in the absence of bile from the duodenum, a small quantity of bile (2 cc. or 3 cc.) and a similar quantity of water were injected into the duodenum, their effects observed, and then the resinous matter was mingled with the same quantity of bile and water, and injected. Having repeatedly ascertained, however, that the biliary secretion is not appreciably affected by the presence of so small a quantity of bile and water, in many of the subsequent experiments, the preliminary injection of bile and water was discarded. At the beginning of the first series, experiments were detailed which showed the normal secretion of bile in a fasting curarised dog, and it was pointed out that the secretion remains

tolerably constant for the first five or six hours of the experiment, and then falls somewhat, probably from want of food and exhaustion. One of the experiments to be subsequently reported in the present series may be taken as showing the normal secretion; for the menispermis administered in that instance had apparently no effect whatever on the secretion.

In all the charts, the numerals at the side indicate cubic centimetres of bile, those at the base indicate hours. Each dot in the curves indicates the amount of bile secreted during the previous fifteen minutes. Although the comparative results before and after the administration of any substance are obvious from the charts, yet it is impossible thus to learn the absolute effect of any substance. This can only be done by ascertaining the coefficient of secretion; that is, the amount of bile secreted in an unit of time for every unit of the body-weight of the animal; e.g., the cubic centimetres of bile secreted in an hour per kilogramme of body-weight. Obviously, the disturbing factor of size—a large animal secreting more than a small one—is thereby eliminated. By comparing the coefficients of secretion after the administration of various substances, an approximate estimate of their powers as hepatic stimulants may be arrived at; and in most cases it will be found that if a drug raise the bile secreted per hour, per kilogramme of body-weight, to 0.4 cubic centimetres, that substance is a powerful hepatic stimulant. The rule is, however, not absolute, because the livers of young dogs secrete proportionally more bile than those of more advanced ages, because of the difficulty of ascertaining what should, in the case of any of the dogs employed, be regarded as a moderate dose. Yet, though the coefficients yield only approximative results, they are nevertheless of much value; for their indications harmonise with the results of observations on the human subject.

ACTION OF PHYSOSTIGMA.

Since the well-known researches of Sir Robert Christison and Professor Fraser, the physiological actions of Calabar bean have been made the subject of extensive inquiry; its action on the liver has not, however, hitherto been investigated, owing to the want of a reliable method of experiment. As stated by Professor Fraser, this agent excites the salivary, intestinal, and lacrymal glands; and at his request we performed the following experiments on the liver. The extract of Calabar bean of the *British Pharmacopœia* was the preparation employed, the maximum dose of which for the human subject is a quarter of a grain.

Experiment 1.—Dog that had fasted eighteen hours. Weight 26.7 kilogrammes. (Fig. 1.) One grain of extract of Calabar bean triturated with half cc. of bile, half cc. of rectified spirit, and 5 cc. of water, was injected into the duodenum at *c*, and the same dose was given again at *c'*. The increased secretion of bile was decided and prolonged after the second dose. The bile and alcohol were employed merely to promote absorption of the active principle; and it may be safely assumed that none of the effect was directly due to either, for it has been already stated that 2 cc. or 3 cc. of bile introduced into the duodenum does not notably affect the biliary secretion; and it will be shown that a much larger quantity of alcohol than was given in this case has also no effect (Experiments 28 and 29).

Although the antagonism between atropia and physostigma has been abundantly proved by Fraser, Arnstein, Heidenhain, and others, it was nevertheless deemed desirable to definitely ascertain whether or not, in the case of the liver, this antagonism also obtains; accordingly, four-fifths of a grain of atropia-sulphate, dissolved in 3 cc. water, was injected into the duodenum at *a*. The effect being somewhat doubtful, six-tenths of a grain dissolved in 3 cc. of water was injected into the jugular vein. The bile-secretion speedily fell, and it is evident from the chart that within half-an-hour after the administration of the second dose the effect of the physostigma had entirely disappeared.

NECROPSY.—There was decided irritation of the duodenal mucous membrane to the extent of eight inches below the pylorus. Evidence of only slight purgative action was found in the small intestine.

Experiment 2.—Dog that had fasted eighteen hours. Weight, 13.6 kilogrammes. (Fig. 2.) Two grains of the extract of Calabar bean, triturated with 1 cc. bile and 5 cc water, were injected into the duodenum at *c* (Fig. 2). The stimulating effect on the liver was rapid and very powerful. Four-fifths of a grain of atropia sulphate, dissolved in 4 cc. water, was injected into the jugular vein at *a*. This was done just five minutes after the next reading of the bile. It is, therefore, certain that two-thirds of the bile that formed the highest reading in the experiment was secreted previous to the injection of the atropia; and, as atropia did not increase the secretion in the preceding experiment, it follows that the very high reading of the bile immediately subsequent to the atropia administration is to be attributed to the action of the physostigma not yet antagonised. Ere long, however, the atropia asserted its influence and antagonised the physostigma. At *a*, three-fifths of a grain

Experiment 1.

Secretion of bile per 15'.	Secretion of bile per kilogramme of dog : per hour.
cc.	
0.70	
0.90	
0.65	
0.55	
0.70	
0.60	
0.80	
c	
0.75	
0.55	
0.85	
1.10	
1.60	
1.30	
1.35	
0.90	
0.75	
c'	
1.95	
2.05	
2.50	
2.40	
2.15	
2.40	
2.20	
1.75	
2.00	
a	
1.90	
1.80	
1.90	
1.65	
a'	
1.20	
0.60	
0.90	
0.50	
0.70	
0.55	

} 0.093 cc.

} 0.365 cc.

} 0.098 cc.

Experiment 2.

Secretion of bile per 15'.	Secretion of bile per kilogramme of dog : per hour.
cc.	
0.35	
0.45	
0.50	
0.60	
c	
1.10	
2.00	
1.75	
1.90	
2.70	
a	
4.00	
3.05	
1.95	
1.45	
1.00	
0.95	
1.05	
a'	
0.65	
0.50	
0.15	
0.35	
c'	
1.35	
0.85	
0.75	
1.05	
1.10	
c''	
1.30	
1.15	
1.25	
1.10	
e	
1.35	
0.25	
0.60	

} 0.138 cc.

} 0.753 cc.

} 0.121 cc.

Fig. 1.

Secretion of bile before and after Calabar bean and atropia. 1 grain extract Calabar bean with $\frac{1}{2}$ cc. of bile, $\frac{1}{2}$ cc. of rectified spirit, and 5 cc. of water, injected into duodenum at c, and again at c'; 4.5th grain of atropia sulphate injected into duodenum at a; 6.10th grain into jugular vein at a'.

Fig. 2.

Secretion of bile before and after Calabar bean, atropia, and lead acetate. 2 grains extract of Calabar bean with 1 cc. of bile and 5 cc. of water injected into the duodenum at c; $1\frac{1}{2}$ grain extract, with same, at c'; 2 grains extract, with same, at c''; 4.5ths of a grain of atropia sulphate in 80 minims of water injected into the jugular vein at a; 3.5ths of a grain at a'; 8 grains of lead acetate in 20 cc. of water injected into the duodenum at l.

of atropia sulphate was again injected into the jugular vein, and it is evident from the chart that the physostigma was completely antagonised thereby. A continuation of the experiment was, perhaps, scarcely necessary; still a grain and a half of Calabar extract, triturated with 1 cc. bile and 5 cc. water, was injected into the duodenum at *c'*, and two grains of the extract similarly treated were injected at *c''*. The exciting effect was not very marked; nor need this be wondered at, considering how powerfully the liver had been previously stimulated, and its partial exhaustion induced not merely to the above cause, but also to the duration of the experiment.

As the action of acetate of lead on the liver was to be investigated, eight grains of that substance, dissolved in 20 cc. of water, were injected into the duodenum at *l*, and the secretion of bile soon thereafter came to a standstill. Subsequent experiments show that this effect was unusual and attributable to the depressant effect of the lead on a liver already well-nigh exhausted.

NECROPSY.—Great irritation of the mucous membrane of the small intestine to the extent of about fifteen inches below the pylorus. The viscus contained only slight evidence of purgative action.

Result of Experiments with Physostigma.—The relation of the dose to the size of the animal, and the coefficients of the secretion before and after its administration, are stated in Table I.

TABLE I.

Physostigma.	Total Dose in grains.	Grains per Kilogramme of Body-Weight.	Secretion of Bile per Kilogramme of Body-Weight per Hour.	
			Before.	After.
Experiment 1	2 with bile	0.0074	0.098 cc.	0.365 cc.
„ 2	2 „	0.0147	0.138 cc.	0.753 cc.

It is interesting to observe that in Experiment 2 the dose, which, in relation to the size of the animal, was twice as great as in Experiment 1, raised the coefficient of secretion to a little more than twice the figure attained in Experiment 1, showing forcibly the precision of the experimental method employed. The high coefficient in Experiment 2 indicates a very powerful effect; yet, since the dose employed was four times the maximum dose for a man, and seeing that one grain produced only a trifling effect in Experiment 1, it may be inferred that, in the human subject, physostigma will probably be found to have, in the relatively small doses administered, an insignificant effect on the liver; for the experiments of the first and second series have demonstrated that, when the same dose of a substance that powerfully excites the human liver is given to an average-sized dog, it powerfully excites its liver. It is an error to suppose that the dog requires much larger doses of all drugs than are necessary for the human subject. The effect of physostigma on the liver is completely antagonised by atropia sulphate.

Prevost of Geneva, in 2 communication to the Paris Academy of Sciences (August 3rd, 1874), states that muscaria increases the biliary secretion, and that atropia checks the excessive secretion due to muscaria.

[To be continued.]

THE CAUSE OF DEFORMITY IN FRACTURE OF THE LOWER END OF THE RADIUS.—It is a well known and generally acknowledged fact, that a fracture of the radius can often only be diagnosed by the very characteristic deformity which takes place in the lower extremity of the bone. There are, however, cases in which this deformity cannot be proved, and in consequence the diagnosis must be very uncertain. M. Schmit (*Revue Mensuelle de Médecine et de Chirurgie* for November) has tried to diminish this difficulty by showing that the age of the patient, the height from which he fell, and the amount of the injury sustained, are more or less closely connected with the absence of this deformity. The author has made many experiments, the result of which he quotes as follows. The deformity can be demonstrated in about one-half of the cases as long as the epiphysis and the bone are not yet firmly joined together. Between the age of twenty and forty, deformity is quite the rule; the exceptions are very rare, perhaps only five per cent. With advancing age, however, this tendency to deformity grows less; after sixty, it is only met with as an exception, especially in women, where it appears in eleven out of thirty. In order to discover why this very characteristic deformity does not take place in fractures of the inferior extremity of the radius in old men, and especially in women after sixty, M. Schmit has repeated the experiments performed by Nélaton, Lecomte, and Tillaux, in addition to his own. He has come to the conclusion that in all these cases deformity is prevented by the want of resistance in the radius of the aged, which is caused by the increasing thinning of the substance of the bone.

DISEASES OF THE BRONCHIAL GLANDS.

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THE study of the diseases of those lymphatic glands which are situated at the bifurcation of the trachea is of great interest and importance, not only in reference to the diseased glands themselves, but also by reason of the manner in which they, on the one hand; simulate, and, on the other hand, modify and mask the diseases of other organs in the neighbourhood. Throughout English and foreign medical literature numerous cases will be found described, in which there existed marked disease of the bronchial glands. Little notice, however, has been taken of less striking, but far more numerous, examples of disease. And it is only within a comparatively recent time that the condition has received special attention and been discussed as a disease *per se*. MM. Riillet and Barthez, in their well-known *Traité des Maladies des Enfants*, have described the disease in infants; and Dr. West, in his work on *The Diseases of Infancy and Childhood*, has fully and clearly described—under the head of “Bronchial Phthisis”—the tubercular diseases of these glands in young subjects. It is, however, to M. Noël Guéneau de Mussy, following up and widely extending the investigations of his predecessors, that we are specially indebted for our knowledge of the effects of these lesions, and to his pupil, M. Baréty, who has published an exhaustive memoir upon them, under the title *L'Adénopathie Trachéo-Bronchique*. The subject has attracted my notice since, or even before, the year 1853, and I have kept short notes of nearly sixty cases which I have seen in private practice and which will form the basis of some of the conclusions to be here stated.

Before, however, describing the pathological and clinical history of the diseases of the bronchial glands, it will be well to make a short reference to their anatomical relations. Taking the bifurcation of the trachea as a starting point, we find in the space between the right and left bronchus a group of glands. They are from ten to fifteen in number, and they vary in size from that of a small pea to that of an almond. The glands towards the right bronchus are larger than those towards the left. Glands are also situated upon the tubes; they are few in number and small. The vascular supply of the glands, which is free, is derived from the bronchial arteries, and the blood is returned to the bronchial veins. Afferent lymphatics reach these glands from the lungs, from the pleura, from the neck, and other neighbouring parts. Besides these groups of comparatively large glands, numerous minute lymphatic glands are found in connection with the primary division of the bronchi, chiefly at the back of these tubes, at their bifurcations and those of the pulmonary artery. The central group of glands is in relation in front with the pericardium, the arch of the aorta, and the pulmonary artery; behind, with the pulmonary plexus of nerves, the oesophagus, the aorta, the vena azygos, etc. The glands on the upper, the anterior, and posterior surfaces of the right bronchus are four or five in number, and smaller than those of the central group. Their situation brings them into relation with the arch of the aorta, with the innominate and subclavian arteries, with the brachio-cephalic vein, and with the vena azygos, the pneumogastric nerve, and its recurrent branch. The glands on the left bronchus are still smaller than those of the right side. Their position gives them relations with the arch of the aorta, the origin of the left carotid and subclavian arteries, the left branch of the pulmonary arteries with the large veins, with the left pneumogastric nerve, and especially with its recurrent branch. Lastly, it should be stated, as a guide in clinical examination, that the bifurcation of the trachea takes place in front of the body of the fifth dorsal vertebra, or between the fourth and fifth, and behind the lower end of the first bone of the sternum. The glands, except when diseased, are proportionately larger in children than in adult or aged persons.

The bronchial glands participate in the *pathological conditions* which affect lymphatic glands generally. In the present instance, however, those cases will not be noticed in which the bronchial glands, becoming the seat of constitutional disease in association with other glands in the neighbourhood, constitute large and manifest tumours. Nor is it intended to give prominent consideration to the state of the glands when they enlarge in acute disease—such as eruptive fevers;