A REPORT ON THE BILIARY SECRETION OF THE DOG: WITH REFERENCE TO THE ACTION OF CHOLAGOGUES:

*Presented to the Scientific Grants Committee of the
British Medical Association.**

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ACTION OF BENZOIC ACID AND ITS COMPOUNDS.

Benzoic acid is said to act as a stimulant of the system generally, and particularly of the kidneys, mucous membrane of the bladder, and bronchial glands. It is nowhere stated to be a cholagogue. Yet it is sometimes used empirically in hepatic affections. Tanner, in his *Practice of Medicine*, recommends ammonium-benzoate in hepatic congestion with deficient urine, and benzoic acid in suppressed action of the liver and uræmia. Dr. Wade of Birmingham employs benzoic acid in cases of catarrh of the bile-ducts; and we owe to the deep interest which he has taken in this research the valuable suggestion that we should endeavour to furnish a rational theory for the use of this agent in hepatic affections, by ascertaining whether or not it has the power of stimulating the liver. For a man, the dose of benzoic acid is from ten to thirty grains; that of benzoate of ammonia, from ten to twenty grains. Benzoate of soda has been employed by Socquet and Bonjean (Wood and Bache, *United States Dispensatory*, 1869, p. 1471) as a remedy for gout and rheumatism; but we have not been able to ascertain the dose given. Probably the dose of the sodium is similar to that of the ammonium-salt.

Experiment 15.—Dog that had fasted seventeen hours. Weight,

Fig. 15.

Secretion of bile before and after benzoic acid and sodium benzoate. 15 grains of benzoic acid in 20 cc. of water injected into the duodenum at *b*; 50 grains of sodium benzoate in 10 cc. of water injected at *bs*.

14.3 kilogrammes. (Fig. 15.) Fifteen grains of benzoic acid, partially dissolved in 20 cc. of water, were injected into the duodenum at *b*. A

slight increase of the bile-secretion ensued; but it was not thought judicious to repeat the benzoic acid, owing to the fallacy that would have arisen from the effect of the large quantity of water required for its solution. Accordingly, twenty grains of sodium-benzoate—an extremely soluble substance—dissolved in 10 cc. of water, were injected at *bs*, and a very powerful stimulation of the liver was the result, the coefficient of secretion rising as high as 0.646 cc. of bile per kilogramme of body-weight per hour.

NECROPSY.—Very slight increase of redness of the duodenal mucous membrane. No purgation.

Experiment 16.—Dog that had fasted eighteen hours. Weight, 27.1 kilogrammes. (Fig. 16.) Twenty grains of ammonium-benzoate, dissolved in 25 cc. of water, were injected into the duodenum at *b*. Within half an hour, a powerful stimulation of the liver ensued that lasted five hours, and would probably have continued still longer had the experiment been continued. One-fifth of a grain of atropia-sulphate, injected into the jugular vein at *a*, *u*, and *a'*—three-fifths of a grain in all—did not antagonise the action of the benzoate. A repetition of experiments so entirely satisfactory was unnecessary; nevertheless, in Experiment 24 there was a reason for giving sodium-benzoate, and hepatic excitement again resulted from it.

NECROPSY.—There was no purgation, the intestine being perfectly dry; but the mucous membrane of the small intestine was considerably reddened to the extent of three feet below the pylorus.

TABLE V.

	Total Dose in Grains.	Grains per Kilogramme of Body-Weight.	Secretion of Bile per Kilogramme of Body-Weight: per Hour.	
			Before.	After.
Sod. benzoate.—Ex. 15	20	1.320	0.223 cc.	0.646 cc.
Ammon. „ „ 16	20	0.737	0.247 cc.	0.544 cc.

Result of Experiments with the Benzoates.—Sodium-benzoate and ammonium-benzoate are both very powerful stimulants of the liver, but are not stimulants of the intestinal glands. It appears from the above experiments that the salt of sodium is a more powerful stimulant than that of ammonium; but the experiments are inconclusive on that point, because in Experiment 15 the sodium-salt was assisted in its action by the previous administration of benzoic acid, and in addition the dose of the salt was greater in proportion to the size of the animal than in Experiment 16. Now that we have proved this action of these substances on the liver of the dog, a similar action on the human liver will doubtless be found; and probably the reason why it has hitherto escaped the attention of physicians is, that these substances, being hepatic but not intestinal stimulants, the excessive secretion of bile induced by them has not been revealed so as to attract attention. But probably, if a dose of sodium or ammonium benzoate were given at night, and a pure intestinal stimulant, such as magnesium-sulphate, given in the morning, clear evidence would be found of the increased secretion of bile. These results, therefore, furnish a rational theory for the employment of the benzoates in congestion and some other affections of the liver.

One cannot leave the subject of benzoic acid without recalling Wöhler and Keller's well-known discovery that when benzoic acid is introduced into the economy, it is eliminated by the kidneys entirely in the form of hippuric acid. The fact that the latter, when treated with boiling hydrochloric acid, splits up into benzoic acid and glycine, suggested that the hippuric acid consequent upon the ingestion of benzoic acid arises from the union of that substance with glycine. Seeing that the two bile-acids—glycocholic and taurocholic acids—are conjugates of cholalic acid with glycine and taurine respectively, the thought naturally arose that the formation of hippuric acid by the conjugation of benzoic acid with glycine probably takes place in the liver. This theory of the seat of its formation was supported by Kühne and Hallwachs (Virchow's *Archiv*, xii, p. 386); but, on the other hand, Meissner and Sheppard (*Untersuchungen über das Entstehen der Hippursäure im thierischen Organismus*, Hanover, 1866) maintained that the transformation of the benzoic acid takes place more in the kidneys than in the liver, and this opinion is supported by Schmiedeberg and Bunge (*Archiv für Experiment. Pathologie*, vi, p. 233). The evidence adduced by Kühne in favour of the liver as the exclusive seat of formation, or that by the other observers in favour of the kidney, need not here be entered into, for no light would thereby be thrown on the fact that, while benzoic acid is allying itself with glycine and carrying this substance into the urine, the hepatic cells are stimulated to produce more bile. In reviewing this subject, we have to express our regret that the bile was not analysed in the last two experiments, for the purpose of ascertaining whether or not its percentage amount of glycocholic acid

* Continued from page 32 of last number.

Experiment 16.

Secretion of bile per 15".	Secretion of bile per kilogramme of dog: per hour.
cc.	
1.40	
1.35	
1.85	
1.55	
1.55	
1.65	
1.70	
1.80	
<i>b</i>	
1.55	
3.03	
4.05	
4.00	
3.10	
3.30	
3.20	
2.90	
2.65	
2.80	
2.55	
2.55	
2.45	
2.50	
2.50	
2.50	
2.50	
2.65	
2.35	
<i>a</i>	
2.45	
<i>a'</i>	
2.25	
2.30	
<i>a''</i>	
2.40	
2.25	

} 0.247 cc.

} 0.544 cc.

} 0.37 cc.

Fig. 16.

Secretion of bile before and after ammonium benzoate and atropia. 20 grains of ammonium benzoate in 25 cc. of water injected into the duodenum at *b*; one-fifth of a grain of atropia sulphate injected into the jugular vein at *a*, *a'*, and *a''*.

Experiment 17.

Secretion of bile per 15".	Secretion of bile per kilogramme of dog: per hour.
cc.	
1.82	
1.72	
1.82	
1.72	
<i>w</i>	
1.72	
1.75	
1.80	
1.75	
<i>s</i>	
1.70	
1.70	
1.75	
1.75	
<i>s'</i>	
1.75	
1.85	
1.90	
1.90	
2.00	
1.80	
<i>s''</i>	
1.85	
2.10	
2.15	
2.20	
2.22	
2.00	
2.15	
<i>s'''</i>	
1.90	
1.90	
2.00	
1.80	

} 0.28 cc.

} 0.306 cc.

} 0.346 cc.

Fig. 17.

Secretion of bile before and after sodium chloride. 10 cc. of water injected into the duodenum at *w*; the same with 120 grains of sodium chloride, injected at *s*; the same repeated at *s'*, *s''*, *s'''*.

was diminished, and to find out whether or not hippuric acid is excreted by the liver as well as by the kidney. The difficulty experienced in obtaining permission to perform the experiments of this series precludes the hope that this question can be determined in this country at present.

ACTION OF SODIUM-SALICYLATE.

Scarcely anything is known regarding the physiological actions of salicylic acid. Bertagnini (quoted in Husemann's *Die Pflanzenstoffe*, 1871, p. 696) took a hundred grains within two days in four-grain doses, and felt nothing but ringing in the ears and some degree of deafness. He observed that the acid was excreted in the urine in the form of salicyluric acid. It is known that this is a conjugate of salicylic acid and glycin. The formula of benzoic acid is, $C_7H_6O_2$; that of salicylic acid, $C_7H_6O_3$. Their near chemical alliance and their similar behaviour towards glycin rendered it probable that salicylic acid, like benzoic acid, excites the hepatic cells. This substance has been for some time a fashionable remedy in acute rheumatism. The dose for a man is from fifteen to twenty grains.

Experiments 3, 10, 11, 12, and 14, already detailed, furnish abundant evidence of the remarkable powers of sodium-salicylate as a stimulant of the liver, and other experiments yet to be described (Experiments 26 and 28) furnish evidence still more striking; indeed, this substance is a certain hepatic stimulant, never failing, when placed in the duodenum, to excite the liver within half-an-hour. Owing to its certain and speedy action, it has been repeatedly used in this series of experiments, merely to furnish an effect which might be readily compared with that produced by some other substance. Table 6 gives the coefficients of bile-secretion under its influence.

TABLE VI.

Sodium Salicylate.	Total Dose in Grains.	Grains per Kilogramme of Body-Weight.	Secretion of Bile per Kilogramme of Body-Weight: per Hour.	
			Before.	After.
Experiment 26....	20	1.00	0.178 cc.	0.565 cc.
" 3....	25	1.55	2.260 cc.	0.664 cc.
" 11....	20	2.15	0.329 cc.	0.890 cc.

Result of Experiments with Sodium-Salicylate.—It is a very powerful hepatic stimulant in the dog, and will probably be found to have a similar effect on the human liver, now that attention is directed to the subject. Its slight action on the intestine is probably the reason why its effect on the liver has passed unobserved by the physician. It may, however, perhaps be thought that, in the above experiments, attention has been too exclusively directed to the benzoic and salicylic acids, while the sodium with which they are combined has been lost sight of. It will therefore be important to observe the effects of other sodium-salts. In the second series of experiments (this JOURNAL, 1877), sodium-phosphate was shown to be a powerful excitant of the liver, while sodium-sulphate and Rochelle salt were found to have a similar though a feebler effect.

ACTION OF SODIUM-CHLORIDE.

Sodium-chloride is a cathartic when given in doses of 120 to 240 grains. Nothing is known regarding its action on the liver; but, as it occurs in considerable quantity in the mineral waters of Carlsbad, Ems, and Friedrichshall, that are of service in abnormal conditions of the liver, we thought it desirable to test its action on this organ.

Experiment 17.—Dog that had fasted eighteen hours. Weight 25 kilogrammes. (Fig. 17.) Ten cc. water were injected into the duodenum at ω : a needless precaution, as the bile-secretion is unaffected by so small a quantity. One hundred and twenty grains of sodium-chloride in 10 cc. water were injected at s , s' , s'' , and s''' , 480 grains being given in all. The resulting increase in the bile-secretion was very trifling.

NECROPSY.—The small intestine contained 203 cc. of liquid with numerous mucous flakes. As only 50 cc. of fluid had been injected, decided purgative action had taken place. The vascularity of the mucous membrane was slightly increased.

Result of Experiment with Sodium-Chloride.—As the foregoing experiment seemed so clearly to show that sodium-chloride is a feeble hepatic stimulant, it did not appear necessary to repeat it.

[To be continued.]

A COMMUNICATION was received by the Mayor of Exeter this week, dated from the War Department, stating that it is not the intention of the Government at present to extend the operation of the Contagious Diseases Acts in Exeter.

REMARKS

ON

HEMIANÆSTHESIA AND ITS CURE.

By SAMUEL WILKS, M.D., F.R.S.,
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THE subject of hysterical anæsthesia and its cure after the application of metals seems to have divided the profession into those who find an explanation for the result in galvanic agency and those who, discarding this as purely speculative, connect it in some way with a mental operation. Neither view, to my mind, will satisfactorily account for the phenomena; nor do I think it probable, in the present state of our knowledge, that an explanation can be looked for. We cannot unravel the mysteries of a very intricate piece of mechanism by watching it; discoveries have never been made by any such method. Researches are instituted to solve simple questions, and thus step by step, by discovering new laws, we apply these in explanation of complex conditions which had hitherto been unintelligible. No one, by looking at the brain or nerves, can tell the nature of the forces operating; and, if he conjecture that they may be electrical or of the nature of those forces which have lately been observed in the telephone or microphone, it must be remembered that we have gained a knowledge of these forces in the laboratory. It is probable that, if we could at the present moment be told the nature of nerve-force, the very terms of the expression would be foreign to us. We are, indeed, in the position of not knowing what kind of force is produced in the brain and cord, nor the mode in which it is transmitted. Our knowledge is almost limited to the facts that an act of the will can move our muscles, and that a galvanic current can do the same. We, therefore, consider that every observable change in the nervous and muscular system must be due to one or other of these causes.

In cases of hemianæsthesia, it is very clear that other substances than metals will induce a cure; but, on this account to attribute the results to the will or some mental operation, affords us no explanation of the nature of the phenomena; for, if it be granted that an effort of the will is sufficient to restore movement to a paralysed limb, and bring back not only common sensation, but the activity of the special senses, which had been previously lost, we cannot understand how any state of the will can account for the production of the original symptoms. The case is often argued as if the hysterical condition were one of shamming or feigning, so that, if a woman have paralysis of a limb, it is the same thing as if she did not choose to move it; but a mere unwillingness or negative state of mind is certainly not the same as hysteria. Any of us may declare that we cannot move an arm or leg, and at the next moment change our mind and move them; but, in the hysterical condition, this is rarely possible; for the will has gone. Sir James Paget says rightly that the very essence of the disease consists in the patient not being able to "will". To rouse the will constitutes the cure. Thus it happens that an hysterical woman will ask the doctor to aid her in making the effort; and, if she cannot accomplish it herself, a sudden shock or fright will rouse her nerve-centres sufficiently for her to throw the requisite force into the limb. If there were any doubt as to the hysterical condition being much more intricate than that dependent upon a want of volition, the accompanying hemianæsthesia and loss of the special senses would show it; for the latter could scarcely be due to any effort or want of effort on the part of the patient. She can deceive and declare she is blind when she is not so; but she cannot produce the hysterical amblyopia.

To me it seems clear that, in these cases, the brain, as a whole or in part, has ceased to act or perform its function; no other explanation appears to me at present sufficient to include all the phenomena; for we notice that there is paralysis of motion, sensation, and of all the special senses, and therefore the function of the brain must be in abeyance, somewhat after the manner of sleep.

My principal object in the present communication is to draw attention more especially to the fact that an injury or blow is often the starting-point of the attack; this is an additional factor to be considered in discussing the nature of hysterical paralysis, and is of great interest in connection with the subject of localised lesions of the brain. Thus a patient who lately left Guy's Hospital attributed her symptoms to a fall.