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

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British Medical Association.**

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SUMMARY OF RESULTS.—(Continued.)

HEPATIC DEPRESSANTS.

It cannot fail to strike the reader as a remarkable fact, that while, in the long list of drugs whose hepatic effects we have investigated, we have found many that stimulate the liver, there is only one—acetate of lead—which appears to have a directly depressant effect. We have, however, found several drugs that have an indirectly depressant action; thus, when the intestinal glands are excited to secrete, there is an indirectly depressant effect on the liver, whereby the secretion of bile is lessened. This we have seen to happen when magnesium-sulphate, castor-oil, gamboge, and calomel are given, and doubtless other purely intestinal irritants have a similar effect. We invariably observed that, while slight purgation—by a purely intestinal irritant—scarcely, if at all, depressed the secretion of bile, powerful purgation produced a very marked effect. Why is the action of the liver thus depressed? In our experiments, we had to deal with fasting animals, whose intestinal canals contained neither bile nor food. Under such conditions, magnesium-sulphate could not depress the bile-secretion by diminishing the absorption of substances that augment the formation of bile. Its depressant effect seems, therefore, attributable either to a drain from the portal blood of bile-forming substances, or to an excessive lowering of the blood-pressure in the liver, as in the system generally, by a large dilatation of intestinal and mesenteric vessels. But when such a purely intestinal stimulant as magnesium-sulphate is given to an individual under ordinary circumstances, it doubtless depresses the secretion of bile, not only in the manner just indicated, but also by hurrying out of the intestinal canal substances which would otherwise have been absorbed and would have assisted in the formation of bile. Thus it cannot be doubted that, when the bile is prevented from entering the intestinal canal, less bile is secreted by the liver; and there is ample reason for believing that about seven-eighths of the sulphur daily secreted by the liver is reabsorbed from the intestinal canal by the portal vessels—in the form of some sulphur-containing substance derived from the decomposition of taurocholic acid, the sulphur-containing acid of the bile. And it may be that, in abnormal states of the intestinal contents, various deleterious matters may be absorbed, and hamper hepatic action. Therefore, it is reasonable to suppose, that a pure intestinal stimulant, such as magnesium-sulphate, although it does not stimulate the liver, may, nevertheless, in some abnormal conditions, exercise an important influence on that organ, by removing deleterious matters from the intestinal canal and by draining the portal system. We concede, then, that by the discovery of the depressant effect on hepatic action of purely intestinal purgatives, we have furnished the physician with a fact which will not fail to be of no little service in rational therapeutics.

In the above connection, it is necessary that allusion should again be made to the action of ammonium-chloride; for, in our second series of experiments (this JOURNAL, 1877), the clinical evidence regarding the effect of this substance in hepatic affections was too cursorily passed by, owing to the want of a valuable paper by Dr. Stewart of Brecon ("On Chloride of Ammonium in the Treatment of Hepatic Disease", *Philadelphia Medical Times*, January 1878, p. 316).† The large experience in the treatment of hepatic affections acquired by that physician in India has led him to regard ammonium-chloride as an invaluable agent in the treatment of active hepatic congestion, chronic hepatitis, and in "torpor of the liver", associated with congestion of the organ

and lithæmia. Many such cases he has seen cured by from ten to twenty-grain doses, given twice or thrice daily, with attention to diet, rest, and such other general indications. The drug produces diuresis, a sensation of warmth in the epigastrium, that gradually extends over the whole body, and ends in diaphoresis, exhilaration of the nervous system, and in an undoubted effect on the liver, as shown, not only by gradual disappearance of the symptoms referable to hepatic congestion, but by other and more immediate signs, "peculiarly and directly referable to the liver and related parts". Thus, within five minutes or half an hour after a dose of the salt, the patient may experience one or more "shocks" as of "something giving way", or a "pricking" or "gnawing" sensation in the hepatic region. In addition to these, a full dose increases intestinal peristalsis, "as evidenced by the twisting and other movements experienced in the situation of the duodenum, or all over the abdomen, and which, at times, are more sensibly felt in the situation of the umbilicus, or in the inguinal region. The abdominal muscles may also be thrown into tonic contractions, which are perceptible at times to both sight and touch." In "torpor of the liver" and functional derangements attended by lithæmia (Murchison), associated with congestion of the liver, want of sleep and depression of spirits, patients are benefited in a remarkable manner by a course of ammonium-chloride, with careful attention to diet and regimen. In such cases, he has known a few twenty-grain doses of the salt remove symptoms of disordered liver, restore sleep, and revive the drooping spirits, after the failure of other remedies. Dr. Stewart nowhere says that he ever observed any cholagogue effect from this remedy. In two experiments (27 and 28 of our Second Series of this JOURNAL, 1877) we proved that, in the dog, ammonium-chloride induces watery purgation, with slightly increased redness of the intestinal mucous membrane. The secretion of bile is not increased, but, on the contrary, more or less diminished. This we ascribed to the purgative effect. In proportion to the body-weight, the doses we gave to the dog were greater than those given to man; and, therefore, it need not be expected that, in the doses recommended by Dr. Stewart, a purgative effect should be observed in man. Our experiments supplement Dr. Stewart's observations, and plainly narrow the range of speculation in searching for a rational theory of the action of the drug in hepatic congestion. The notion that it excites the hepatic cells to secrete more bile ("by some it is considered cholagogue", Garrod's *Materia Medica*, 1874, p. 51), may in all probability be set aside and some other theory of its action sought for.

Before leaving the subject of the effect of purgation on hepatic action, we would very specially dwell upon the important practical indication to be derived from the fact that the secretion of bile is lessened by an intestinal purge. Thus it was pointed out in the experiments with podophyllin (First Series, this JOURNAL, 1875), that, if a large dose be given, the excitement of the intestinal glands is excessive, but the secretion of bile, instead of rising, may only fall; and it may often be noticed in other of our experiments, that when a substance is a powerful intestinal as well as hepatic stimulant, the secretion of bile—though increased at first—soon falls as the drug finds its way down the intestine and implicates a greater and greater number of Lieberkühn's glands. It follows, that stimulation of the liver may be most certainly induced by hepatic stimulants, which are either not at all, or to only a slight extent, intestinal stimulants. Although, for the purpose of getting rid of biliary matter, it is important that it be removed from the intestine as well as secreted by the liver, yet hepatic should, as far as possible, precede the intestinal excitement, in order that the latter may not interfere with the former, but merely remove its results. We know of no means by which these indications may be fulfilled more efficiently and agreeably, than by giving a dose of euonymin, a powerful hepatic but feeble intestinal stimulant; and following it in the morning by an ordinary saline aperient. The former excites the liver, while the latter, after the hepatic excitement is over, speedily removes its effects. In this connection, very much indeed has come out of this research, of which the thoughtful physician will quickly avail himself in framing a system of rational hepatic therapeutics.

METHODS OF THERAPEUTICAL RESEARCH.

Every competent person, whose mind is not blinded by the clouds of misguided prejudice which have so seriously hindered the progress of scientific medicine within the last few years, will admit that, by the above research, we have furnished for the first time those precise experimental data, without which the construction of a rational system of hepatic therapeutics were altogether impossible. For the benefit, however, of those who neither comprehend the reason why our knowledge of the actions of medicines so lags behind, nor the means by which it may with certainty be advanced, we may offer the following observations.

* Concluded from p. 179 of last number.

† Dr. Stewart has also published some results of his experience in the BRITISH MEDICAL JOURNAL of 28th September, 1878.

There are *two* methods by which the actions of medicinal agents are investigated; the *clinical* and the *physiological*. By the clinical method, experiments are made with drugs on man and animals in a state of disease; while, by the physiological method, experiments are made with drugs on animals, and sometimes on the human subject, in a state of health. The clinical mode of procedure is as old as medicine itself, but the physiological is of comparatively recent date, and has grown out of the fact that clinical experience has, in very many instances, failed to supply us with that full and precise information which a scientific system of therapeutics requires. It must be admitted that even a few of our medical brethren, who were educated in times when medical education was far less scientific than it happily now is, are slow to recognise the principle, that the actions of medicinal agents in diseased conditions cannot be rightly understood unless we also know their effects on a healthy condition of the bodily system; and are somewhat tardy in recognising the necessity for arriving at precise knowledge by experimenting with drugs on animals in such a manner that the complex bodily system may be, as it were, to some extent unravelled. By experimental methods, inapplicable to the human subject, various bodily organs may be made the subject of special investigations, and may be more or less relieved from the influence of various factors, which would otherwise so complicate the case, that precise knowledge could not be arrived at. No more apt illustration of this could be found than that afforded by the results of the clinical experience of the action of drugs on the liver. The clinical observer has had no difficulty in knowing when a drug excites the sweat-glands, the salivary glands, or the kidneys; but, in the case of the liver, he is so embarrassed that, although he has correctly pointed out a number of agents that increase the *discharge* of bile, he has doubts regarding others that certainly have this effect; and in no case has he been able to say whether or not any cholagogue agent stimulates the liver to *produce* more bile, or merely brings about the expulsion of that already formed. The explanation is easy; the bile, when it enters the alimentary canal, mingles with other secretions, and with alimentary substances, whose quantities are variable. The clinical observer has no means of judging of the amount of bile *secreted*, other than the extremely rough and indefinite method of observing the colour of the dejections; hence it is that, when a purgative agent is administered and the intestinal glands pour forth their watery secretion and dilute the intestinal contents, it becomes difficult—often, indeed, impossible—to say whether or not the discharge of bile is increased, diminished, or unchanged. On this account, the clinical observer did not detect the fact first demonstrated by these experiments—that if a purgative agent, such as magnesium-sulphate or castor-oil, stimulate the intestinal glands, but not the liver, it actually *diminishes* the production of bile. In the cases of sodium-sulphate, sodium-phosphate, and various other drugs, he scarcely knew what conclusion to arrive at, although it is now certain that these agents are important stimulants of the liver, as well as of the intestinal glands. Again, the colour of the medicinal agent may resemble that of the bile, and hence, in the case of so common a substance as rhubarb, the clinical observer is unable to say definitely whether or not it occasions an increased discharge of bile. But, by our exact physiological method, we prove that, in the dog, it certainly stimulates the liver; and on that account, it probably has a similar action in man. Again, where a substance excites the liver to produce more bile, but does not excite Lieberkühn's glands to, as it were, wash out the bile poured into the intestinal canal, the physician has, in the case of benzoic acid and its compounds, sodium-salicylate, and other drugs, failed to observe that the substance is a cholagogue.

To superficial minds, it may, perhaps, seem no very great matter to determine whether a cholagogue merely occasions a discharge of accumulated bile, or actually increases its secretion; but all who really comprehend the serious defects of our therapeutical knowledge, and the benefits that accrue to pathology from an accurate knowledge of the actions of drugs, will not fail to perceive the necessity for a definite answer to, at all events, the latter part of the above question. If any proof of this be necessary, the following fact will suffice. We inquired of an experienced Indian physician how he accounted for the appearance of a large quantity of bile in the dejections, after the administration of sixty grains of ipecacuan in cases of dysentery. He at once replied, "My theory is, that the ipecacuan relieves a spasm of the bile-ducts, and thus allows the pent-up bile to escape". But having found that this dose of ipecacuan, when given to a healthy dog (Second Series, this JOURNAL, 1877), never fails to greatly excite the liver to produce more bile, will anyone *now* hesitate to believe that in dysentery, ipecacuan acts on the liver in a similar manner, and that the increased discharge of bile is due to its increased *production*, and not to the relief of spasm of the bile-ducts, of whose existence there is no evidence whatever? Thus, by our physiological experiments, important light is

thrown upon the *modus operandi* of a drug 'in a very serious disease, and we come one step nearer to a knowledge of the pathology of that disease; for, once we know the action of a drug in a healthy state of the body, and find that a diseased state is cured by that action, our knowledge of the nature of the diseased state is necessarily advanced. Recently, we had occasion to see a lady who had for some years suffered greatly from attacks of indigestion, headaches, burning heat between the shoulders, and general *malaise*, for which she had been largely and variously treated, with very indifferent success. Nothing that she had ever taken yielded so much and so speedy relief as two doses of euonymin (one-and-a-half grain), taken at night. Having shown that this substance is a powerful stimulant of the liver, and scarcely at all of the intestinal canal, we were, by means of this "medicine diagnosis", easily led to believe that she was suffering from an affection of the liver, that was cured for the time by increasing the secretion of bile. Thus, by a study of the physiological actions of drugs, not only therapeutics, but also pathology, advance.

Of necessity, the influence of a drug on a diseased condition is the ultimatum of pharmacology; and every experiment upon a healthy bodily system, whether of man or animal, is merely ancillary to experiments with the drug in disease. If we discover that a drug stimulates the healthy liver of a dog, we do not infer that it *must* also stimulate the human liver in health, and still less do we conclude that it *must* have this action in disease. The experiments on the healthy liver of the dog, on the normal and on the abnormal human liver, are *three* sets of experiments, *closely related, but still distinct*. The facts derived from any one of the three cannot be substituted for those of the other two; each set of facts has its own proper place, and must be carefully kept there. When, therefore, we show by our method of experiment that such a drug as sodium-benzoate or sodium-salicylate powerfully excites the liver of the dog, we do not for a moment say to the clinical observer, "You will find that these things have a similar action in man"; but what we do say is merely this, "Experiment with these drugs in man, and tell us whether or not you find that they stimulate the human as well as the dog's liver; and tell us also for what diseased states you find the employment of this or that hepatic stimulant best adapted". Certainly the clinical experimentalist has a far more difficult task to discharge than the physiological investigator, and he requires all the assistance that the physiological method of research can render him.

Some persons, who are inadequately acquainted with these matters, but who nevertheless show no reticence in expressing their opinions in periodicals intended for the ruin of medical research, have freely attempted to discredit the important results of this research by insisting on the folly of supposing that experiments on the liver of a healthy dog can throw any light on the action of drugs on the diseased human liver. To the ignorant this is a plausible objection; but to us it is only frivolous and absurd. The preceding paragraph explains the position which we assign to our experiments on the dog; and, the more clearly to expose the silly ignorance of our detractors, we have to add that the results of our observations on the liver of healthy dogs are in complete harmony with the results of reliable observations on the human subject, whether in health or in disease. It is true, we have found that calomel is not, while mercuric chloride is, a stimulant of the dog's liver; while, from observation on man, the physician had thought that calomel is a cholagogue, but knew nothing of the effect of mercuric chloride on the liver. Yet the physician really never said that calomel is a *stimulant* of the human liver; he only said that its *administration* is followed by an increased discharge of bile. This question has been fully discussed in our second series (this JOURNAL, 1877), where it is shown that there is *no real discrepancy between our observations and those of the clinical observer in this matter*. And it is to us most gratifying that, while our research furnishes the physician with a great number of new facts with which he has hitherto been totally unacquainted, it gives at the same time striking proof of the accuracy of his observations, made very often under perplexing circumstances.

Again, our experiments have been frivolously objected to because we introduced drugs directly into the duodenum, while in man they are usually, though not always, given by the mouth. At first glance, this objection seems plausible; for it appears reasonable to suppose that the influence of the gastric juice ought not to be discarded. Had we published a number of results not in harmony with clinical experience, we admit that it would have been permissible to harbour suspicions as to the value of our method; but we shall be glad if any one will point out to us a single misleading result due to our method of administration. Let the hepatic stimulants discovered by us be introduced into the stomach of man, and, if they be not found to be hepatic stimulants in his case, let the fact be made known. In the case of calomel, however, it seemed not unlikely that our method might lead to fallacious results, after we had

made the discovery that corrosive sublimate is a powerful hepatic stimulant; for it seemed not unreasonable to suppose that the free hydrochloric acid of the gastric juice might, by converting a small quantity of calomel into mercuric chloride, render it a hepatic as well as intestinal stimulant. The results of a full investigation of this question were given at the close of the second series of experiments, and they prove that, when calomel is placed in the stomach of the dog, its action is the same as when placed in the duodenum. Having, therefore, established that, in the case of commonly used drugs, their action on the liver is similar, whether directly introduced into the stomach or into the duodenum, we are in a position to predict that, when the dog's liver is excited by a drug directly introduced into its duodenum, that drug will *probably* also be found to stimulate the human liver when taken into the stomach by the mouth.

CONCLUDING OBSERVATIONS.

In our introduction to our first series of experiments, we pointed out what had been ascertained regarding the actions of drugs on the secretion of bile by our predecessors. We showed that, for want of a proper method of experiment, the definite knowledge arrived at was very meagre and to some extent erroneous; and, if the statements in that introduction be compared with our summary of results (p. 177), some idea may be formed of the extent of our labour, which we have striven to render as complete and as free from error as possible. We claim that, by means of a novel and precise method of investigation, we have been the first to place the whole subject of the physiological actions of drugs on the liver upon a sound footing, and thus to lay a real foundation for the rational—that is, scientific—treatment of many diseased conditions of this important organ; and it is gratifying to know that, in consequence of this research, not a few physicians have been led to use the new remedies to which we have specially directed attention. We have, indeed, occasioned by our experiments a considerable amount of pain to a number of dogs; but, considering that our discoveries are calculated to relieve much suffering, not only of men, but also of dogs, for all time to come, we believe that we have spared infinitely more suffering in the future than we have occasioned in the present.

In conclusion, I have to tender my warm thanks to my former pupils M. Vignal and William J. Dodds, M.B., D.Sc., for their valuable assistance in the performance of the experiments, and for their agreeable company during the long and weary hours through which they daily extended. I have cordially to thank the Scientific Grants Committee of the British Medical Association for having entirely defrayed, from the funds of the Association, the very heavy expenses incurred for the materials of the research, and for their energetic and powerful support at a time when the clamour of blind ignorance and silly prejudice seriously menaced and almost arrested the progress of this research. Having personally devoted not less than fourteen hundred hours of severe labour to the accomplishment of this work, and having (as, of course, every medical man thinks himself bound to do for the alleviation of suffering) communicated to all every fact calculated eventually to cure affections so common as those of the liver, it is, to say the least, ungrateful, that a certain section of the public should have rewarded our unselfish efforts to cure their *biliousness* by a flood of scurrilous abuse, because, like most of our medical brethren, we refuse to believe that to be penny-wise and pound-foolish as regards pain is not a policy as shortsighted, as narrow-minded, and as reprehensible here as elsewhere. Though profuse with their ingratitude, I doubt not that one and all of them will be very ready and eager to profit by the results of our labour; for I believe them to be much too recreant and craven-hearted to allow themselves to refuse all medical aid, and thus to push their ill-conditioned logic to its practical issue. Desiring, as I think most of them do, to continue in receipt of all the medical assistance they can obtain, they naturally try to overcome their conscientious scruples by vainly attempting to show that *nothing worth knowing* in medicine has been learned from experiments on animals. It is not difficult, by misrepresentation and by a multiplicity of words, to deceive a public ignorant of the machinery of life and of the processes by which its movements are studied and remedies found for its disorders; but they cannot thus deceive any moderately well informed and right-minded medical practitioner. It would be a just return for their opposition to medical experiments on animals, were medical men to take them at their word, and deny them the benefit of advice that is directly and indirectly based on such experiments. Their not having been already placed in this predicament is entirely due to the long-suffering charity of the medical profession, whose members are slow to refuse to alleviate the sufferings and prolong the lives of even those who misrepresent their motives and throw obstacles in their way. But, if they really wish medical men to continue to minister to their wants, the sooner they

lapse into becoming silence the better. Meanwhile, heedless of their ignorance, so contemptible were it not so mischievous, their scurrilous abuse—usually anonymous—and their shameful misrepresentations, we steadily have recourse to those methods of research which every medical man worthy of the title approves, because he knows them to be essential for the advancement of medicine; and the conviction of earnestly doing our utmost to prosper the cause of rational therapeutics—that is, of a scientific practice of the healing art—is to all earnest votaries of medicine a sufficient recompense for labour as honestly unselfish as it is practically unremunerative. And when the dupes of the antiphysiological—that is, of the *antimedical*—apostles awake to a sense of the gross injustice of the present antivivisection agitation, I would suggest that they could not do better than liberally contribute to the endowment of the few—too few—physiological laboratories to be found in the country; for it is not reasonable that, while the public receive the benefit, the heavy expenses of a research such as the above should be defrayed by the practitioners of medicine throughout the country.

REMARKS

ON

ANTISEPTIC MIDWIFERY.*

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THERE is no subject which excites more the interested attention of the profession and of the public than puerperal deaths, yet, unfortunately, there is none regarding which there is more misunderstanding. There seems especially to be great difficulty in accepting the terrible fact of the great mortality of childbearing, a mortality as heavy in private practice as it is in well-managed maternity hospitals.† Puerperal deaths own various causes. Some are traumatic; some are from traumatism; some from simple inflammation; some from textural degeneration; many are from diseases which may be described as more or less accidentally complicating puerperality. But by far the most prevalent and important causes of puerperal deaths are septicaemia and pyaemia. Both these diseases involve or imply inflammatory processes, and both are essentially septic. It is against them that antiseptic midwifery wages war, and already it has achieved great successes. The object of this communication is to increase and diffuse knowledge of this subject, and to stimulate further inquiry into it, with a view to still further development of the beneficent antiseptic methods. Already, more pain is prevented and more life is saved by antiseptic methods than by all the recent combined improvements of midwifery, great though these are; and there is no prospect of preventing pain and saving life half so bright and encouraging as that from the extension and diffusion of them. Midwifery has been infected with its present zeal in this department of therapeutics by its sister surgery, and is proud to own the obligation. But, while the mere theory of antiseptics is the same for both surgery and midwifery, there is practically great divergence. Especially, that perfection of antiseptic treatment, which is called Listerian, has not been attained in midwifery. Ingenuity and skill have as yet failed to achieve this result. But there is no room for despair.

Ever since puerperal fever, or, in other words, puerperal septicaemia and pyaemia, were known, they have been accounted for, more or less distinctly and exclusively, by the uterine wound and a ferment or sepsis in the blood. A theory always, and naturally, brings a treatment in its train; and, accordingly, antiseptics have been in use in these diseases ever since the theory was started. In accordance with the modern developments of the antiseptic theory, attention is more and more exclusively directed to the local conditions, and especially the wounds of the uterus, and, in addition, those of the vagina and pudenda. But, formerly, the disease was opposed principally in the blood by treatment directed against the fermentation or sepsis there. This kind of treatment was almost purely hypothetical, and no evidence of any good results from it has ever been obtained. Even now, this department of therapeutics is

* Read to the Medical Society of London.

† Among other papers, see Winckel, *Berichte und Studien*, Band II; McClintock, *BRITISH MEDICAL JOURNAL*, August 10th, 1878, p. 215; Garrigues, *Gynaecological Transactions*, vol. ii, 1877, p. 592; Hecker, *Aesthetisches Intelligenzblatt*, v Serie, No. 1, 1877; Matthews Duncan, *Mortality of Childbed and Maternity Hospitals*; Grünwaldt, *Volkmann's Sammlung*, No. 123; Lusk, *Transactions of International Medical Congress*, Philadelphia, September 1876; Stadfeldt, *Les Maternités, leur Organisation et Administration*; Feigneaux, *Centralblatt für Gynäkologie*, No. 13, 1878.