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A CONSIDERATION OF THE VARIOUS METHODS OF DRUG ADMINISTRATION.

POST-GRADUATE LECTURE DELIVERED AT THE WELLCOME
MUSEUM OF MEDICAL SCIENCE.

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IT has occasionally been fashionable in the past to belittle the value of "drug treatment." A famous physician once said that he could well dispense with all the drugs in the British Pharmacopœia, provided that he could keep magnesium sulphate. This was a surprising statement, for even in those days the value of mercury in the treatment of syphilis and of quinine in "ague" was acknowledged by all. It is possible that his

attitude was more in the nature of a protest against that blind faith in a bottle of medicine which was tending to sink the reputation of the physician in the mystic potency of his bottled prescription.

At the present time such an attitude would be inconceivable in the light of recent advances in medicinal treatment. We have only to think of the prognostic revolution which has been brought about in such diseases as kala-azar, the black death of India; in bilharziasis, the curse of Egypt; in syphilis, in diabetes, in pernicious anæmia, in diphtheria, in cretinism, and a host of other diseases. We even find drug treatments waging warfare with the surgeon in his stronghold of the upper abdomen, and triumphantly proclaiming their victories over gastric and duodenal ulceration. It is whispered that the exponents of radical

treatment have given a not unwilling ear to such blandishments when called upon to make the great decision on their own behalf. There must be an explanation for such progress, and it seems to me that we can find it in the greater care that is now taken with regard to a correct technique of administration. Cushny says: "The effect of a remedy is often determined, very largely, by the method in which it is administered. A substance may be quite inactive when given by one route, and fatal when administered by some other method."

Let me give some illustrations of this most important therapeutic truth. In the first place, the wise physician has realized the important part played by suggestion in successful treatment. I think of a physician of the old school—some called him a homœopathist—who was famous throughout London for the results he obtained. I can hear him now: "I will give you something that will do you good, it will. . . ." and then the patient knew exactly what would happen. Many have objected to such methods, but surely they constitute one of the techniques of successful administration—suggestion combined with the correct remedy.

We must leave, however, this side of the problem and pass to more obvious examples. *Adrenalin*, if given by the mouth, is oxidized and rendered useless. If given hypodermically, it constricts blood-vessels and is only slowly absorbed. It is, however, used successfully by this route in the treatment of asthma. For shock, it must be given intravenously in order to induce contraction of the abdominal blood-vessels and raise the blood-pressure. If applied locally it produces ischæmia and, when given with a toxic substance may act as a safeguard by reducing absorption.

Insulin is another good example. This substance is destroyed by the enzymes of the stomach and must be given by injection.

There would be a manifest advantage in oral administration in such a case, and a

drug, synthalin, has been tried, but has proved to be slow in action and relatively ineffective. It is for this reason that ephedrine has become so popular. People with chronic diseases, such as diabetes and asthma, do not want to depend upon repeated injections. The asthmatics are more fortunate than the diabetics, for in ephedrine they have a substance which can be taken by the mouth and which is effective in certain number of cases. It is an alkaloid which is obtained from a Chinese drug, *M. Huang*, and is closely related to adrenalin. It is more stable, however, and its activity is not destroyed by boiling.

Among our examples we can include *salvarsan* and the various allied drugs used in the treatment of syphilis and yaws. Here we have a trivalent organic arsenic compound, which is not available for oral administration owing to the fact that, given by the mouth, it becomes organic arsenoxide, the cause of many of the troubles that arose in early days with impure preparations. As a result, injection into muscles was tried, but the drug was deposited locally, caused pain and swelling and was very slowly absorbed. The intravenous method is now used; it acts very rapidly—a few hours—and the drug is mostly excreted in three days. It is for this reason that, in syphilis, mercury is used as well, the insoluble salts being injected intramuscularly so that the action of the mercury is prolonged. Here we have an excellent example of how the different methods of administration may be used to accomplish definite objects; a prognostic revolution has occurred, we have salvation without salivation.

Once again, a preparation which could be used by the mouth would be invaluable. *Stovarsol* has been tried, and merits further trial. It is said to have prophylactic value in syphilis, and has been proved to be of value in chronic malaria.

The neo-compounds, *neosalvarsan*, *neokharsivan*, &c., are less toxic, more rapidly

excreted, more easily prepared for injection, and can be given intramuscularly, but the intravenous route is generally preferred.

In this group also we have *tryparsamide*—a pentavalent arsenical compound—which has little action in syphilis, but has proved invaluable in the treatment of sleeping sickness.

In *antimony* we have another outstanding example of the importance of the mode of administration. Antimony may be regarded as a drug with a past and a future. It has eaten husks in a far country and returned to become a useful citizen. In the seventeenth century it was much prescribed and did harm; so much so, that the graduates of Heidelberg were required to take an oath never to use it. When taken by the mouth it is an emetic, expectorant and very depressing. If it is rubbed into the skin a crop of pustules occurs. This does not seem much recommendation, but antimony ointment applied in this way has been used with success in the treatment of lumbago, and also in the treatment of oriental sore. As the inorganic antimony preparations cause vomiting and the organic may be decomposed in the stomach, injection was tried. Hypodermic and intramuscular injections are impossible, owing to the intense pain, suppuration and sloughing which may occur. Intravenous injection is safe and effective provided care is taken that all the solution passes into the vein. So we have worked, by devious routes, to a state of great reliance on this drug in two very important diseases—bilharziasis and kala-azar.

The pentavalent organic compounds are chiefly used for kala-azar—stibamine glucoside, urea stibamine and v. Heyden 693.¹

One could go on indefinitely illustrating this statement of Cushny's with regard to the importance of the method of administration.

Iodine applied to the skin is antiseptic; taken internally it can stop vomiting.

Chloroform by the lungs is anæsthetic; in small doses, by the mouth, it is a carminative.

Olive oil, by the rectum, opens the bowels and, by the mouth, reduces gastric acidity.

Certain substances taken by one route may be inactive, whereas by another route they may be fatal. Peptone is a good example, and in snake venom we have a practical and dramatic demonstration of this fact. Adult animals can swallow many times the fatal injection dose. We have all read stories of the hero sucking venom from the heroine's arm, with no ill-effects beyond those incidental to matrimony. A rabbit can swallow 600 times as much poison as it can tolerate when injected. The ptyalin of the digestive juice destroys venom *in vitro* and evidently has a similar action *in vivo*. We must always remember the possibility of the hydrochloric acid or digestive juices of the stomach altering the action of a drug.

We can now rapidly survey the various *methods of drug administration* in use at the present time. Roughly speaking, the drug may gain admission through the unbroken skin or mucous membrane, through the alveoli of the lungs, or by injection into any selected organ or tissue.

We give drugs by the mouth—local application, ingestion, inhalation; by the rectum; by the skin—inunction, ionic medication; by subcutaneous injection; by intramuscular injection; by intravenous injection; by deep injection—lungs, liver, spine, &c. And each of these methods has its appropriate indications and mode of application. To enter into the technique of these various methods is beyond the scope of the lecture, but each will now be reviewed in somewhat greater detail.

By the Mouth. Ingestion.—Medicinal preparations are taken by the mouth, either for their direct action upon the alimentary system, upon some parasite which has invaded that system; or for their general

¹ Antimosan (trivalent) can be administered intramuscularly; also Neostibosan (v. Heyden 693b).

action after absorption. The modern method is to administer a drug in the most pleasant manner possible, and it is well to remember that insoluble salts have very little taste, hence the use of quinine tannate and euquinine. In the bad old days of Gregory's powder nobody studied the taste of the victim, and children were expected to swallow half a pint of the nauseous stuff without complaint. Now we have flown to the other extreme, and aperients are dispensed so attractively that it is only a benevolent Providence which prevents serious accidents. The story of a greedy Indian colonel who, before the very eyes of his horrified hostess, gorged himself on Tamar Indiens in a full appreciation of their delectable properties and ignorance of their medicinal action, may rank with the cautionary tales of Hilaire Belloc.

For convenience of dosage, administration and transport, medicinal preparations are frequently sold in some compact form, either *compressed* or otherwise. Such preparations may be ready to be swallowed, or may require to be crushed or dissolved before administration. Full directions are supplied by the manufacturers of such products, and it is important to follow carefully these directions. There can be no question that for convenience of dosage and transport such a method has manifest advantages. When, however, we come to the question of administration it is not quite so simple. During the war a physician who was treating cases of malaria with quinine found one of his patients who refused to respond; it was obviously a case of a quinine-resistant parasite. Being young and enthusiastic, the physician seized pen and paper to record his experience for the benefit of posterity. The hospital orderly, being a plain man and without guile, examined the patient's stools, where he found most of the quinine exactly as it had been swallowed. The tablets had never been dissolved; they were evidently unsuitable for administration to that particular patient in that particular way.

This danger does not exist if the drug is of good quality, properly prepared and administered according to directions. The advantages of taking medicine in such a form are many, quite apart from palatability—iron can be swallowed without effect on the teeth, special coatings can be used to ensure passage through the stomach when necessary, accuracy of dosage is secured.

Having got the substance down, it either has to be absorbed or not to be absorbed. It is obvious that such remedies as aperient salts, anthelmintics, astringents, amœbicides, &c., must reach their objective in the small bowel. Some do so without any help; for example, the aperient sulphates. Others need some protective coating, keratin, salol or wax, which will pass through the stomach unharmed. Others need special precautions for them to achieve their object, as, for example, thymol or male fern. Here special aperient treatment, both before and after, is required, and certain substances which encourage absorption must be avoided, as, for example, fats and alcohol with thymol. In using alkalis in the treatment of gastric or duodenal ulcers we need local not general action, and sodium bicarbonate, which is readily absorbed, should be used sparingly, giving place to the magnesium and calcium salts.

Rectal medication may have one of four objects in view :—

- (1) General action.
- (2) Local action.
- (3) To wash out the bowel.
- (4) Anæsthesia.

With regard to the last group, ether in olive oil has been used, and recently a substance, "avertin," a tri-brom-ethyl alcohol has been introduced. For a man of 11 stone 10 gm. is said to be readily absorbed and to produce anæsthesia in ten minutes, lasting for two hours or more. There is then thirty-six hours' sleep, after the operation, owing to the production of sodium bromide. To hasten elimination, 5 to 10 gm. of common salt, well diluted, may be

injected into the rectum. This method, in spite of obvious advantages, seems open to the grave objection that it is not readily controlled, and there may be danger of acidosis.

For local action suppositories may be of great use. The late Mr. Harold Barnard used to say, "When in doubt about a rectal condition, try a 2 gr. calomel suppository." Many have had reason to be thankful for that advice.

For general action, quinine may be given to children by this route.

Inhalation.—Here we have a mode of administration which is rapid and can be controlled with moderate accuracy. We have the various anæsthetics—chloroform, ether, nitrous oxide, ethyl chloride, &c. We know that nicotine can act powerfully when inhaled in large quantities. The various asthma inhalations, containing stramonium, &c., are well-known examples, and adrenalin has been administered by this method with success. Oxygen is used as a therapeutic agent under various conditions, more especially in pneumonia. To dilate the blood-vessels and relieve an anginal attack, amyl nitrite is valuable.

To what extent other routes might be substituted is an interesting problem. The rapidity of action required in angina and asthma offers a clear indication as to route. Anæsthetics are never administered by the stomach, though in the old days alcohol was given before operations with a similar object. There is, however, a story which bears upon this question. Chloroform is CHCl_3 , and carbon tetrachloride, used to destroy hookworms, is closely allied, CCl_4 . All the inmates of a hospital in India, staff and patients, were treated for hookworms with carbon tetrachloride. That night the hospital was visited by burglars, who found everybody fast asleep as the result of their CCl_4 . It is obvious, however, that the degree of anæsthesia could never be controlled with equal accuracy by this method.

Cutaneous Administration.—This is gener-

ally used for its local effect; very few drugs have been administered through the skin for their action after absorption. Mercurial inunction is quite effective, but a very dirty method. Cod-liver oil and insulin have both been tried, but without any useful result. Perhaps of greatest interest is the fact that the ergosterol in a child's skin can be inactivated by sunlight, and thus rickets may be treated or prevented by autogenous medication.

The attempt has repeatedly been made to introduce drugs into the body by ionization. It is probably of little value for tissues more than a few mm. below the surface. Ions migrate slowly, encounter blood-vessels and are carried away, or form compounds with tissue proteins and pass no further. The treatment is mainly restricted to the use of zinc sulphate, iodine, &c., for surface lesions.

Hypodermic administration is used where rapidity of action is indicated as, for example, where morphia is used to allay pain. The benefits of this method of administration are:—

Avoidance of local action on the stomach.
Rapid absorption.

Whole remedy used (if soluble and not precipitated at the point of injection).

Occasionally this method is used for local action, as with cocaine, novocain, and other local anæsthetics.

If the substance is irritant it must be injected into the less sensitive muscular tissue; hence, we have *intramuscular injection*. Two familiar examples of the use of this method will occur at once:—

(1) Mercury. Soluble salts are absorbed too rapidly and cause pain. The insoluble salts and metallic mercury are therefore used. These are absorbed slowly.

(2) Quinine, injected into the gluteal muscles. A stout platinum iridium needle is used. The solution is freshly prepared and boiled. Strict asepsis is essential, because there is always some muscle necrosis and a good focus for infection is formed. In the

Sixteenth Annual Report of the Medical Department of the United Fruit Company, de la Torre states that he has given 9,000 intramuscular injections of quinine with excellent therapeutic results (1 gm. daily for four to six days, then twice a week for three weeks). As Manson-Bahr says, "There is no need to make a pin-cushion of your patient." De la Torre recommends a massage ride on horseback after each injection, and states that in his series only four abscesses were seen.

There has been some talk of danger of tetanus from quinine injections. It is well to remember that in trying to sterilize a syringe, (1) cold alcohol does not kill spores; (2) boiling water does not kill spores; (3) boiling oil does not kill spores; though each of these methods will probably kill most of the common organisms. To kill spores the syringe should be boiled in 5 per cent. carbolic acid for ten minutes, or suspended in a plugged test tube and autoclaved.

Deep injections are occasionally of use. Emetine may be injected for liver abscess; injections into the spinal column are used to produce anæsthesia for major operations; injections may be made into lung cavities; iodized oil into the trachea for diagnostic purposes; and alcohol into the ganglion of the trigeminal nerve. In every case of deep injection the action is primarily a local one.

Intravenous injections are more and more employed at the present time. This method of administering drugs was first tried by Sir Christopher Wren in the spare moments left over from architecture and astronomy. It is scarcely strange that it never became really popular in pre-antiseptic days. It has the advantage of exact dosage, rapid action, and complete utilization. Pharmacologists always employ it, when possible, for it is the method of precision. It has the great advantage of producing a maximum concentration in the blood-stream at once; in other methods there may be a delay extending even to twenty-four hours. On

the other hand, it is a minor surgical procedure with definite requirements as to asepsis and technique.

It is therefore essential to have some clear views with regard to the indications for intravenous injections. These may be summarized¹ as follows:—

(1) As an *emergency measure* where rapid action is essential. In such conditions as shock, toxæmia and hæmorrhage—the injection of saline solution, glucose infusions, &c.

To combat severe acidosis—saline sodium bicarbonate solution.

In diabetic coma—intravenous insulin.

In very severe tetany—calcium chloride.

In acute circulatory collapse—slow injection of weak solutions of epinephrine in physiological saline solution.

In severe heart failure—strophanthin.

In malignant malaria—quinine.

In very severe diphtheria—antidiphtheritic serum.

(2) When *greater intensity of action* is required than can be obtained by other methods. Many toxic sera, &c., are very slowly absorbed if given subcutaneously or intramuscularly—antistreptococcic serum, antipneumococcic serum, or non-specific proteins to induce protein shock.

(3) When the *volume of the dosage is large*. More than 100 c.c.—saline, glucose solutions &c.

(4) *To avoid irritation or destruction of tissue* at the site of injection. Arsphenamine, antimony, dye-stuffs, colloidal metals, alkalis, &c.

(5) *To secure direct action within the blood-stream* against invading organisms. This is the most obvious indication, and probably the most fallacious. Most agents leave the blood-stream very rapidly.

In this connection the intravenous use of mercurochrome is of special importance.

¹From the Report of the Special Committee appointed by the American Therapeutic Research Committee of the Council on Pharmacy and Chemistry.

Here we have a drug which has been highly praised, and, with equal force, condemned as useless, for the purpose of fighting blood-infections. Dixon says:—

“Experiments made on animals, inoculated with pneumococcus or anthrax, have shown that mercurochrome produces a considerable proportion of cures—50 per cent. or more. These experiments have, however, been disputed. Clinical reports are more definite and impressive. They show that in a large proportion of cases of septicæmia, in which a pure culture of streptococci could be obtained from the blood, intravenous injections of mercurochrome were followed by cure. . . . Young reports 173 cases of septicæmia treated with mercurochrome, with a cure in 63 per cent. of cases.”

I once asked an authority on the subject what he thought of this group, i.e., direct action on organisms in the blood-stream. His answer was short and to the point, but it was not encouraging.

In these five groups we have certain definite indications which may guide us in our selection of the method of administration.

From this summary you will, I think, be able to appreciate the enormous importance which attaches to a correct method of drug administration.

SOME CLINICAL ASPECTS OF ARTERIAL PRESSURE.

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I ESTEEM it a great privilege to have been asked to give a short address on “Arterial Pressure,” a subject which, by reason of its

widespread ramifications and recent developments, becomes of ever-increasing interest and importance, and I trust that you will prefer a practical issue, such as that which I have chosen, to a more profound or abstract theme. The more we study arterial pressure, the more we find it of the greatest service in daily practice. The aspects of it are, however, so manifold that I cannot do more than to attempt a brief synopsis of the most salient features.

DEFINITIONS OF BLOOD-PRESSURE.

At the outset it is essential to have a clear understanding of the terms that we employ. What, then, do we mean when we speak of “blood-pressure”? In the *physiological* sense not only does this term include arterial pressure, but also pressures which are intra-auricular, intra-ventricular, capillary and venous. In the *physical* sense blood-pressure is that pressure which the blood exerts at a given instant upon a given point of the circulatory system. In the *clinical* sense “blood-pressure” is loosely used in everyday language as implying solely arterial pressure, and sphygmomanometric readings, expressed as a set of figures representing the height in millimetres of a column of mercury or the equivalent in instruments calibrated from that source, constitute the generally accepted measure. In the *pathological* sense we have to deal with arterial pressures which may be either abnormally high or abnormally low.

MEASUREMENTS OF ARTERIAL PRESSURE.

We measure arterial pressure with instruments, primarily to assess the efficiency or otherwise of the circulation, so as to gain an estimate of the nature of each problem with which we have to deal, and secondarily to glean other indications which are both psychical and physical. Personally, I find no instrument so reliable as an accurately-constructed mercurial manometer, such as the “Baumanometer,” though general prac-